



The Nature of Cancer


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Tissue Autonomy and Versatility

- Cells in the body have vast autonomy and versatility.
- Cells carry a complete genome with more information than the cells will ever require.
- Morphogenesis – the biological process that causes an organism or cell to develop its shape.
 - It is one of three fundamental aspects of developmental biology along with the control of cell growth and cellular differentiation.
 - Morphogenesis makes possible the maintenance of adult tissues throughout the life span.
 - Such maintenance may involve the repair of wounds and the replacement of cells.

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- ➔ The genomic sequences are subject to corruption by various mechanisms that alter the structure and information of the genome.
 - ➔ This results in mutated genes with abnormal phenotypes which is usually incompatible with normal cell structure and physiology.
 - ➔ The most profound thing to occur is marked changes in cell growth patterns that don't follow the rules of normal cell growth and maintenance.
 - ➔ Even though the body has extraordinary means of combating this, the cancer cells somehow seem to thrive and grow.

The cancer cells have a completely different agenda than the rest of the cell.

- They only have one agenda, which is to make more copies of themselves!!



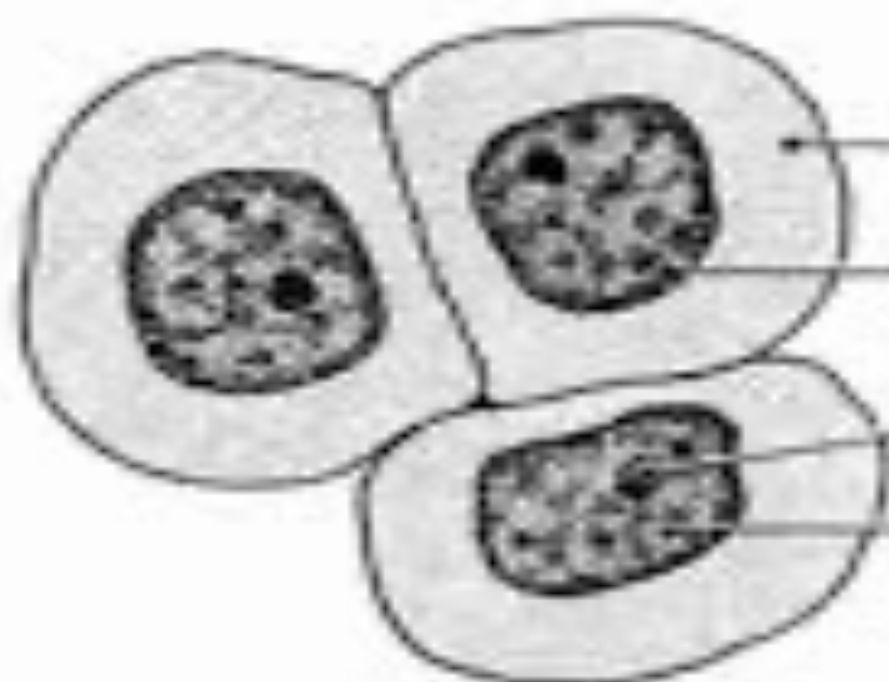


**NO
STOPPING
ANY
TIME**



Normal and Cancer Cells Structure

Normal



Cytoplasm

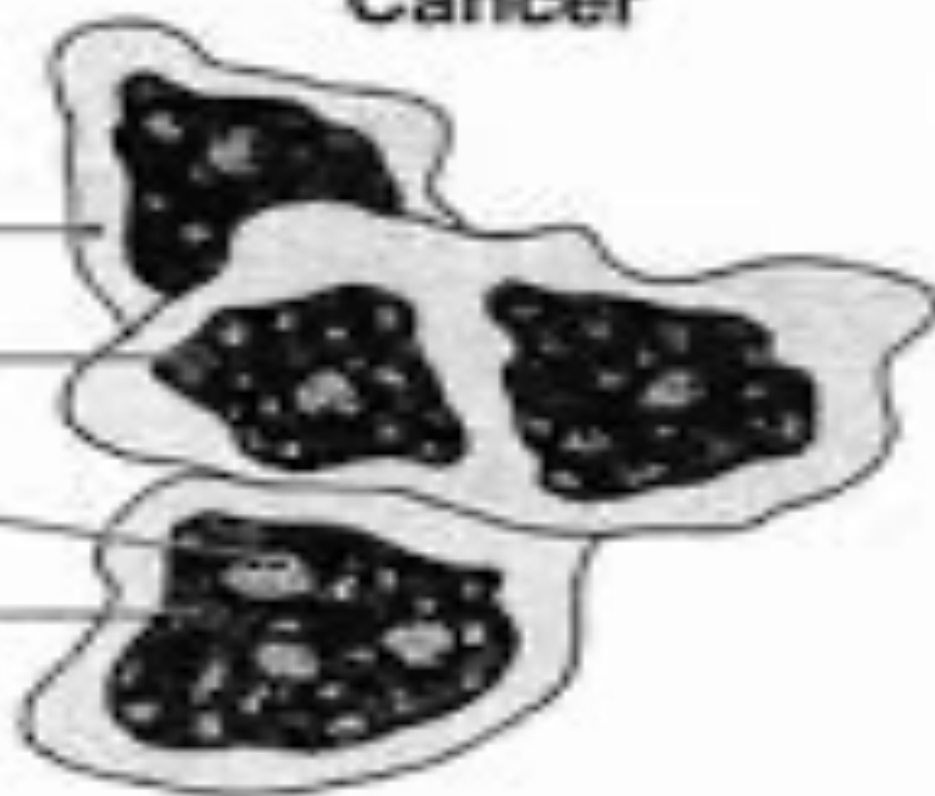
Nucleus

Nucleolus

Chromatin

- Large cytoplasm
- Single nucleus
- Single nucleolus
- Fine chromatin

Cancer





- Small cytoplasm
- Multiple nuclei
- Multiple and large nucleoli
- Coarse chromatin



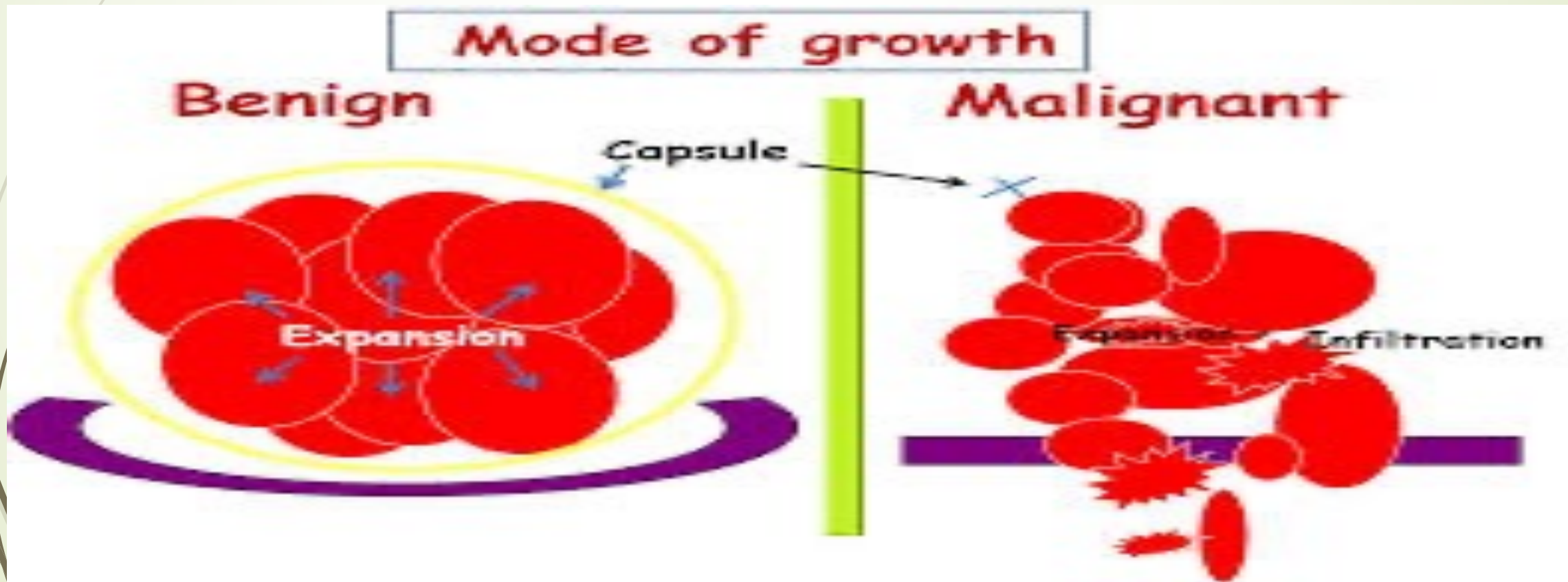
Tumors arise from normal tissues

- We often portray tumors as foreign bodies that have taken root in the body of an afflicted patient.
- Actually, tumors are often derived from normal tissue and not a result of an outside influence.
- Tumors seem to be capable of moving in the body to distant anatomical sites from where they started.
- These new settlements are called metastases.
- The primary tumor is where it all started.

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- Detailed examination of the organization of cells within tumor masses shows that tissue architecture was less organized and structured than the architecture of nearby normal tissues.
 - **IE, cancer cells came to be viewed as a disease of malfunctioning cells that have a mind of their own.**
 - Histologically, tumors fall into two broad categories depending on their degree of growth.

Benign tumors grow locally without invading adjacent tissues.

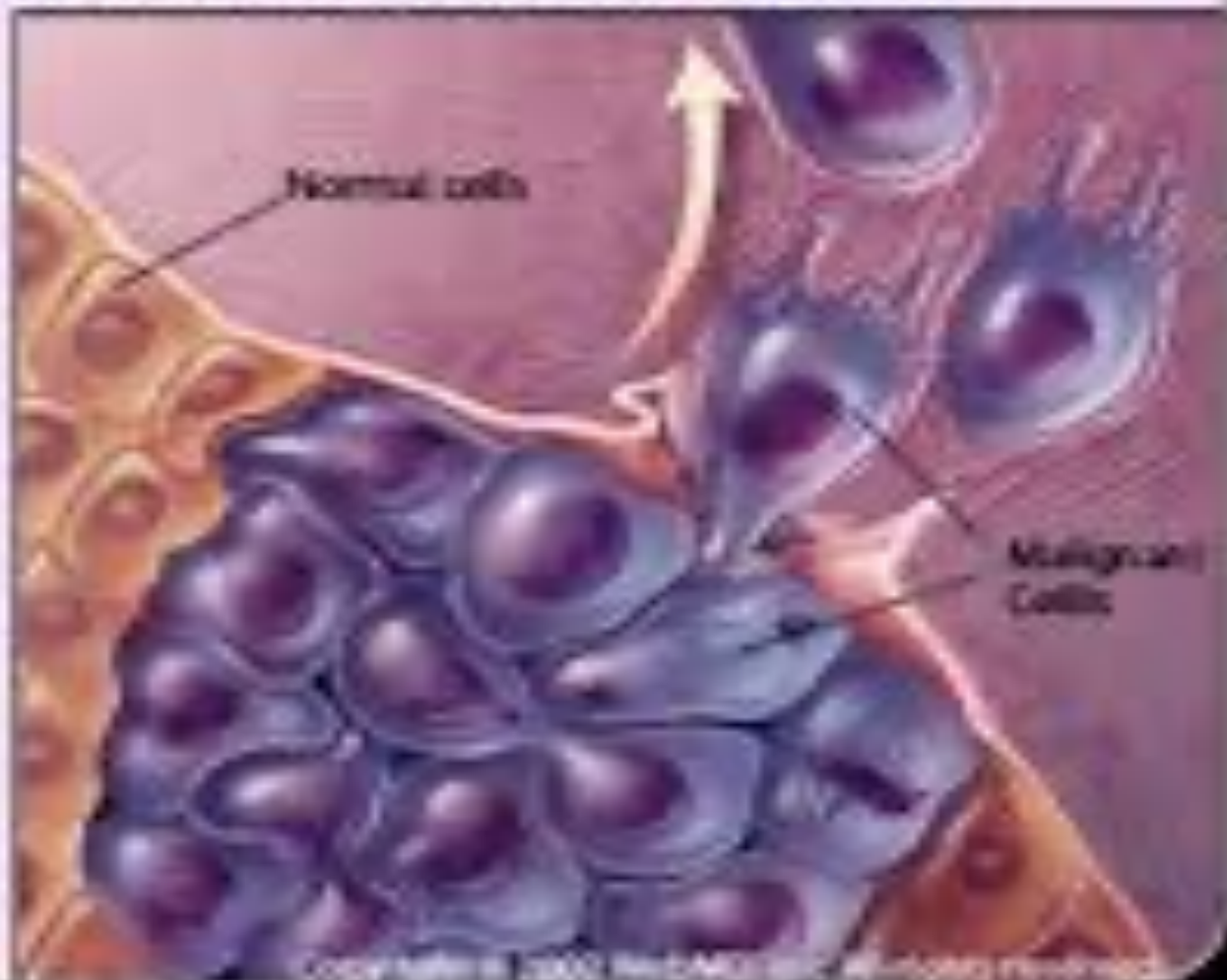
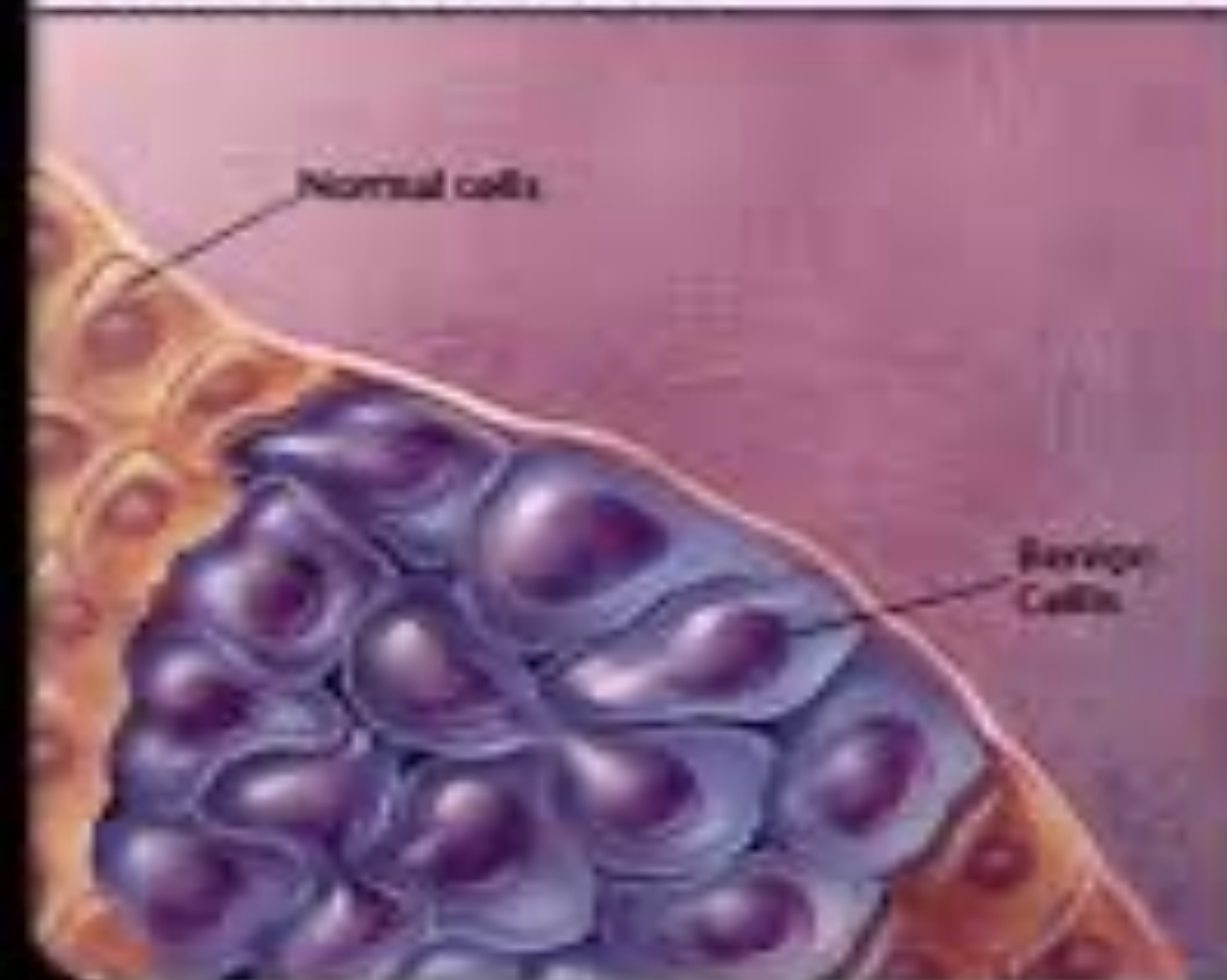
- Malignant tumors invade nearby tissues and spawn metastasis.
- Malignant tumors do not have to travel far, they only need to cross into another body system.



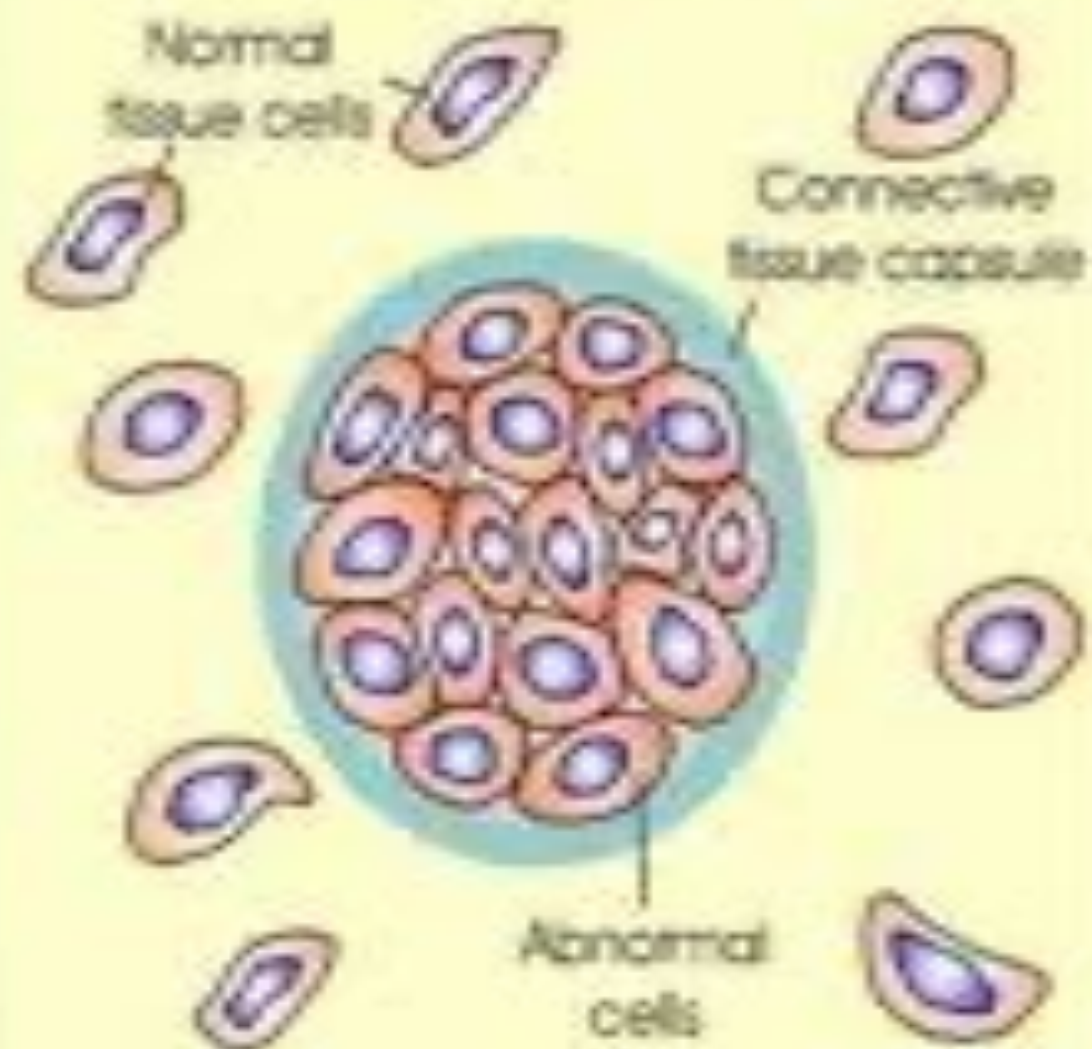
Benign vs. Malignant Tumors

Benign (not cancer) tumor cells grow only locally and cannot spread by invasion or metastasis.

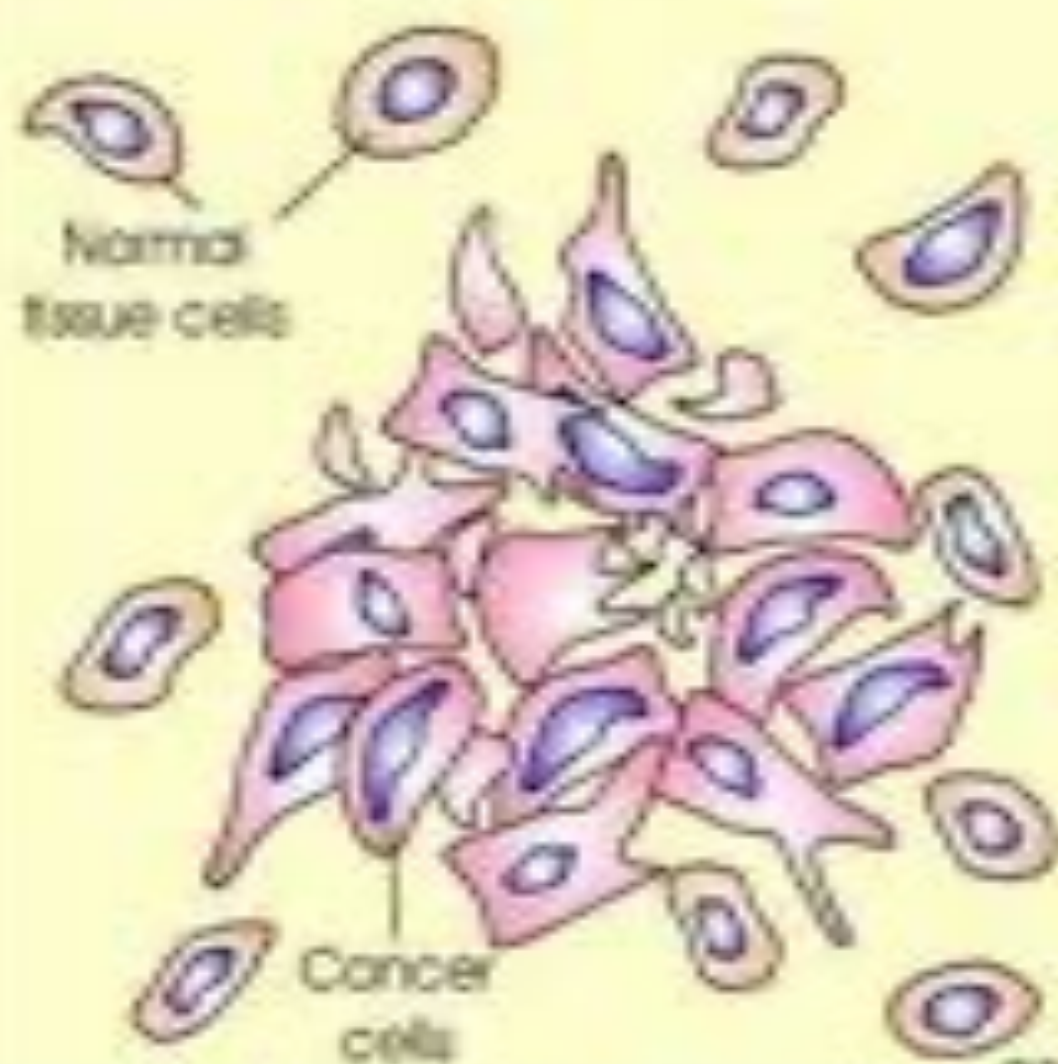
Malignant (cancer) cells invade neighboring tissues, enter blood vessels, and metastasize to different sites.



Benign Growth



Malignant Tumor




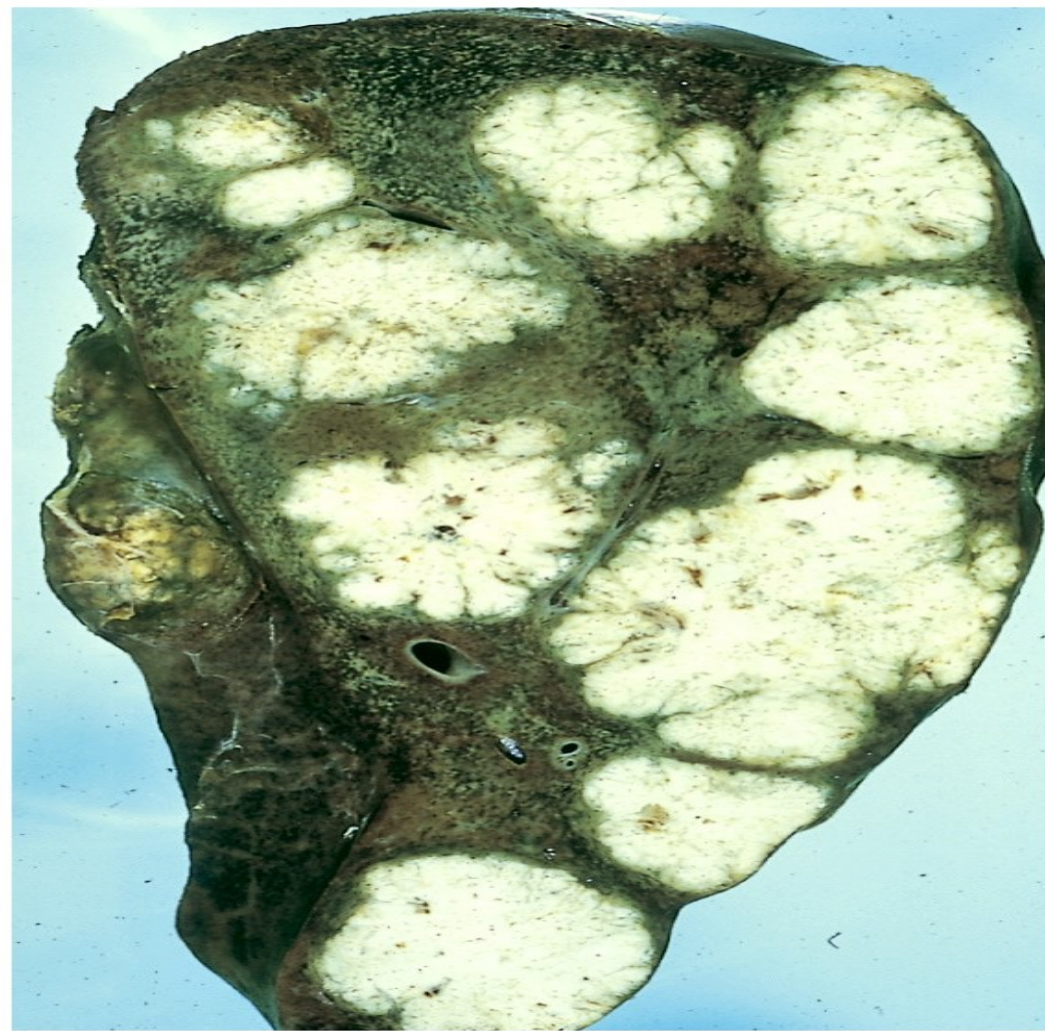
Benign

- Slow growing,
- capsulated,
- Non-invasive
- do not metastasize,
- well differentiated,
- suffix "oma" eg. Fibroma.

Malignant:

- Fast growing,
- non capsulated,
- Invasive & Infiltrate
- Metastasize.
- poorly differentiated,
- Suffix "Carcinoma" or "Sarcoma"

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- The great majority of primary tumors in humans are benign and are harmless to the hosts.
 - But remember that even though they may be “harmless”, they still are occupying space and may cause pressure on nearby organs.
 - Some benign tumors can cause clinical problems by releasing high levels of hormones which create physiologic imbalance.
 - Thyroid adenomas may cause an increase of thyroid hormone
 - Pituitary tumor may cause an increase of growth hormone.
 - Deaths from benign tumors are extremely rare.
 - 90% of cancer deaths are from metastasis.




L) White metastasis noted in the liver from the colon.

R) Spotty melanoma cells noted in left lung and metastasis melanoma noted in the right lung above.

Breast cancer often metastasizes to the brain



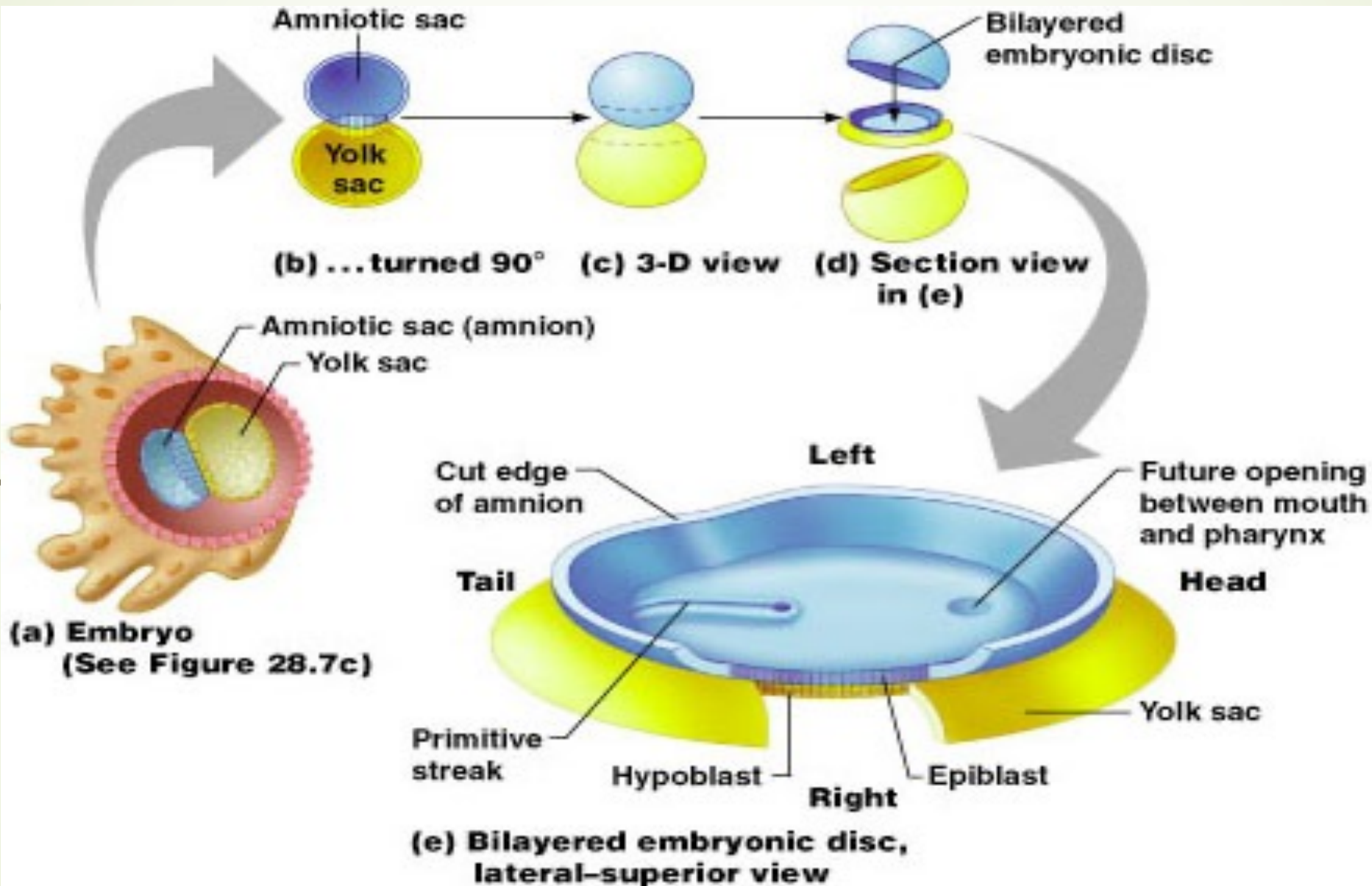


Sometimes tumors will spread along tissues that are of similar embryological origin.

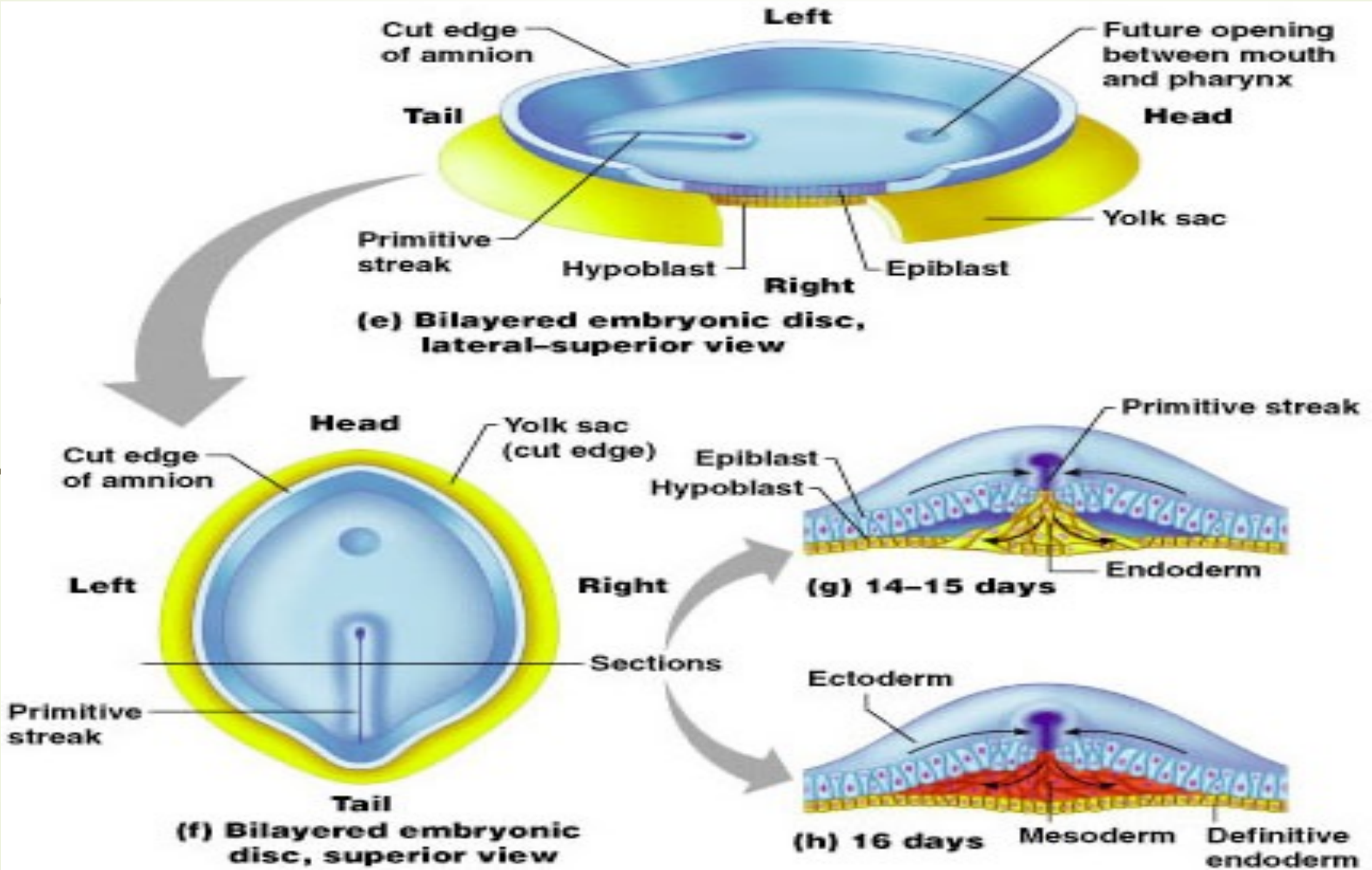
Primary Germ Layers

- Serve as primitive tissues from which all body organs will derive
- **Ectoderm** – forms structures of the nervous system and skin epidermis
- **Endoderm** – forms epithelial linings of the digestive, respiratory, and urogenital systems
- **Mesoderm** – forms all other tissues
- Endoderm and ectoderm are securely joined and are considered epithelia

Primary Germ Layers



Primary Germ Layers





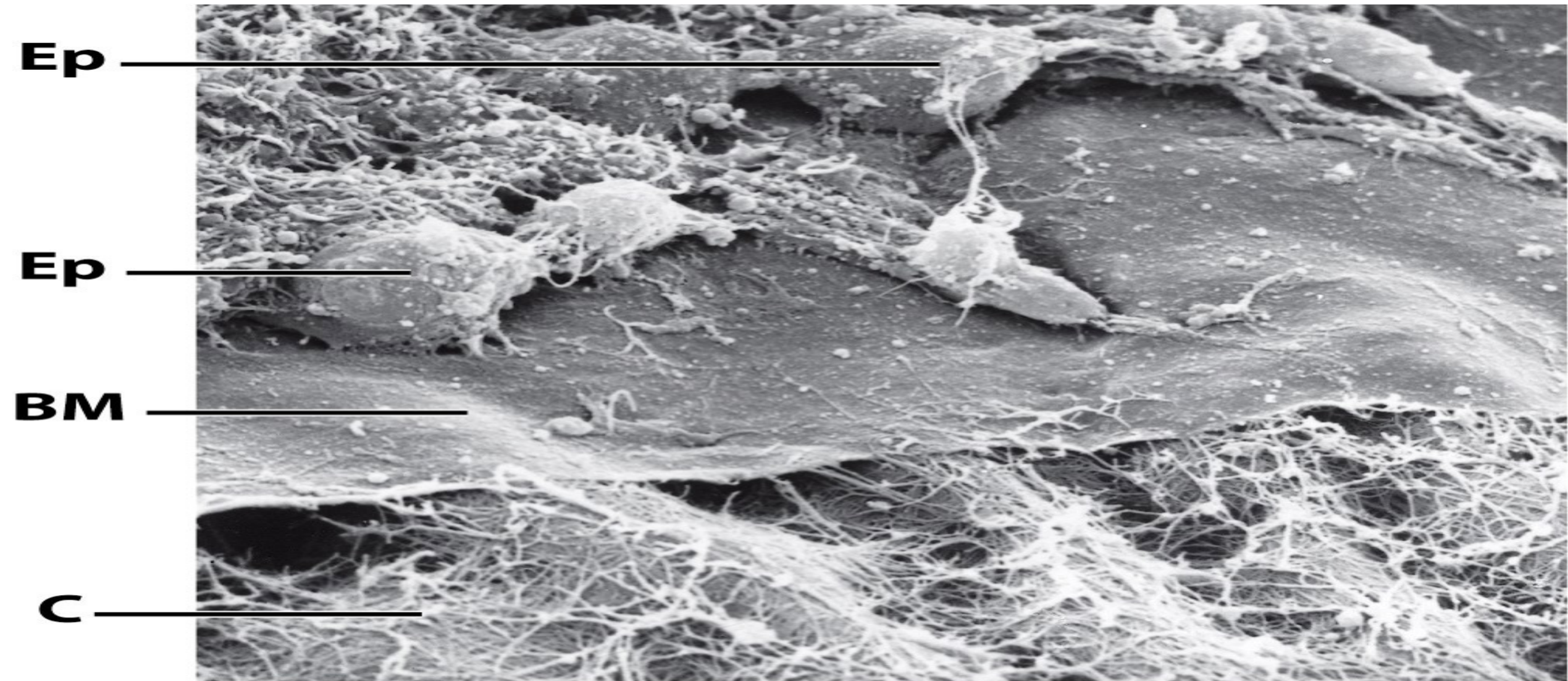
Tumors arise from many specialized cell types throughout the body

- The majority of human tumors arise in the epithelial tissue, which are sheets of cells that line the body cavities, channels and skin.
- Underneath all the epithelial cells is a basement membrane or basal lamina which separates the epithelial cells from the underlying connective tissue or stroma.


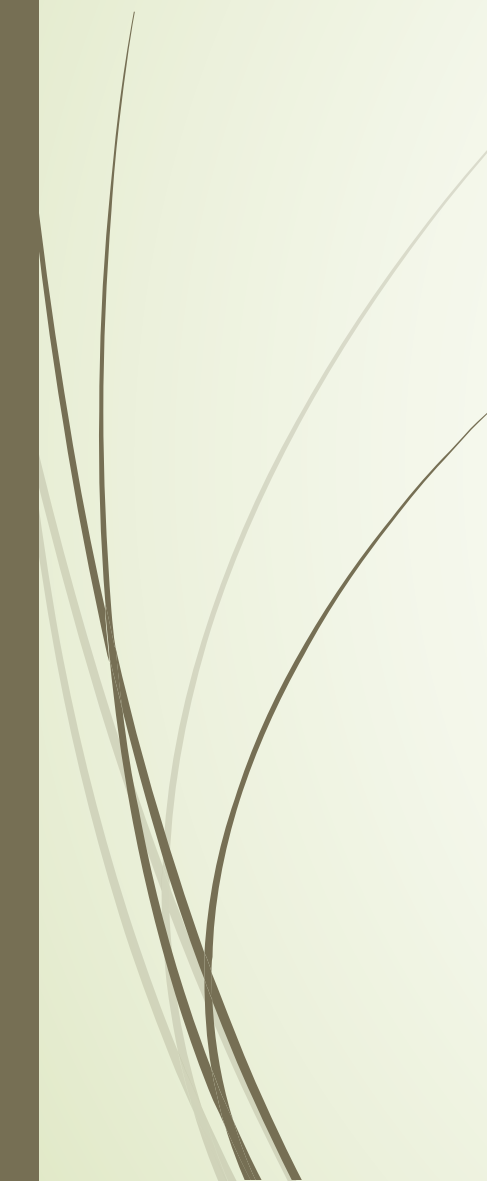
Ep – Epithelia cells tethered to one side of the basement membrane

BM – Basement membrane

C – Collagen fibers of the connective tissue



10 μ m

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- Epithelial tumors are called **carcinomas** and they are responsible for more than 80% of cancer related deaths worldwide.
 - This includes epithelial tumors lining the GI tract, GU, skin and breasts.
 - These tumors fall into two major categories that reflect their biological function.
 - Protective coverings
 - Secreting substances

- Squamous cell carcinomas are tumors of the protective cell coverings and sheaths.
 - For example the epithelial cells lining the esophagus, GI tract or skin.
- Adenocarcinomas are tumors of cells that secrete a substance.
 - For example the epithelial cells of the lungs and mucus membranes.



Carcinomas

(A) Tissue sites of more common types of adenocarcinoma

lung
colon
breast
pancreas
stomach
esophagus
prostate
endometrium
ovary

(B) Tissue sites of more common types of squamous cell carcinoma


skin
nasal cavity
oropharynx
larynx
lung
esophagus
cervix

(C) Other types of carcinoma

small-cell lung carcinoma
large-cell lung carcinoma
hepatocellular carcinoma
renal cell carcinoma
transitional-cell carcinoma (of urinary bladder)

Nonepithelial tumors

- The remaining of malignant tumors arise from nonepithelial tissues throughout the body.
- Other nonepithelial tumors are in three categories:
- 1) Connective tissue tumors are **sarcomas**
 - Only about 1% of tumors are extremely fatal.
 - From fibroblasts that secrete collagen which is the matrix of tendons and skin.
 - From adipocytes which store fat in cytoplasm.
 - From osteoblasts which make bone.
 - From myocytes which make muscle.
 - Various types of connective tissue sarcomas:
 - Osteosarcoma, liposarcoma, leiomyosarcoma, fibrosarcoma, rhabdomyosarcoma, synovial sarcoma, angiosarcoma, chondrosarcoma

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- Other nonepithelial tumors are in three categories:
 - 2) Hematopoietic tumors include cells of the immune system and blood.
 - Example – Leukemia, lymphoma, multiple myeloma, Hodgkin's disease, non-Hodgkin's lymphoma
 - 3) Neuroectodermal tumors
 - Tumors from the central and peripheral nervous systems.
 - While only about 1.3% of all diagnosed cancers, they are responsible for 2.5% of cancer deaths.



Cancers seem to develop progressively

- Between the two extremes of fully normal tissue and highly malignant tissue is a broad spectrum of tissues that progress slowly.
- **Hyperplasia** is when cells deviate by increasing the number of the cells.
 - The enlargement of an organ or tissue caused by an increase in the reproduction rate of its cells.
 - Often as an initial stage in the development of cancer.

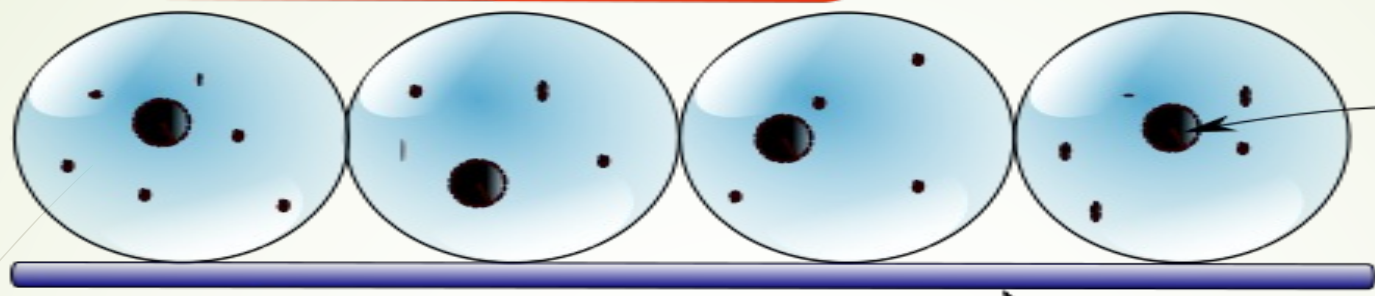
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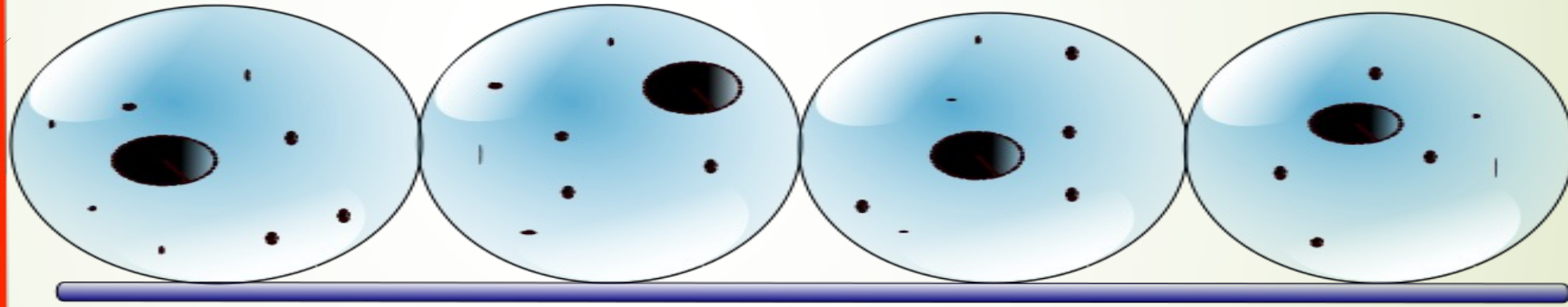
Normal Cells



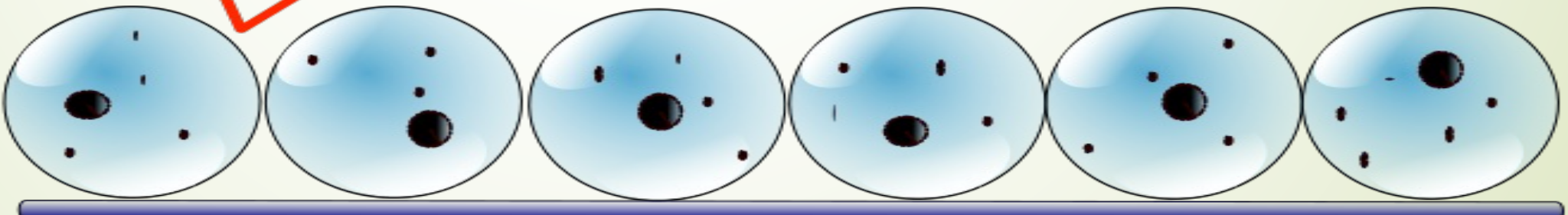
Nucleus

Hypertrophy

Basement Membrane



Hyperplasia



Nucleus

Basement membrane



Normal



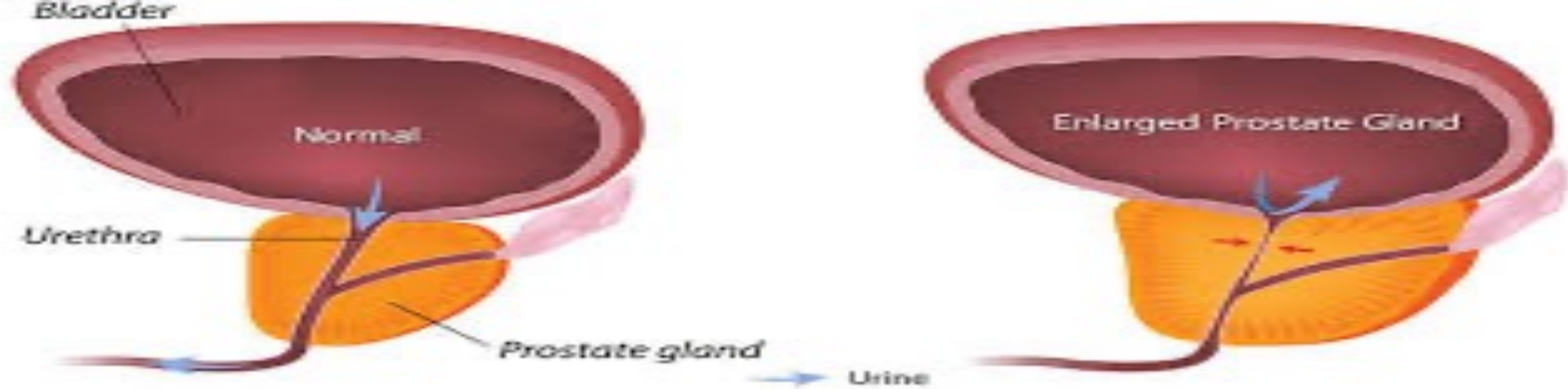
Atrophy



Hypertrophy



Hyperplasia



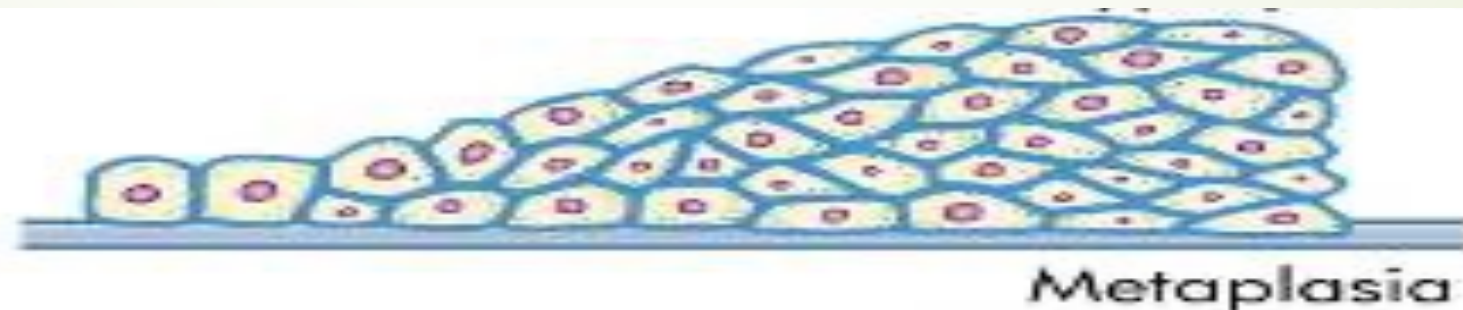
Endometrial hyperplasia



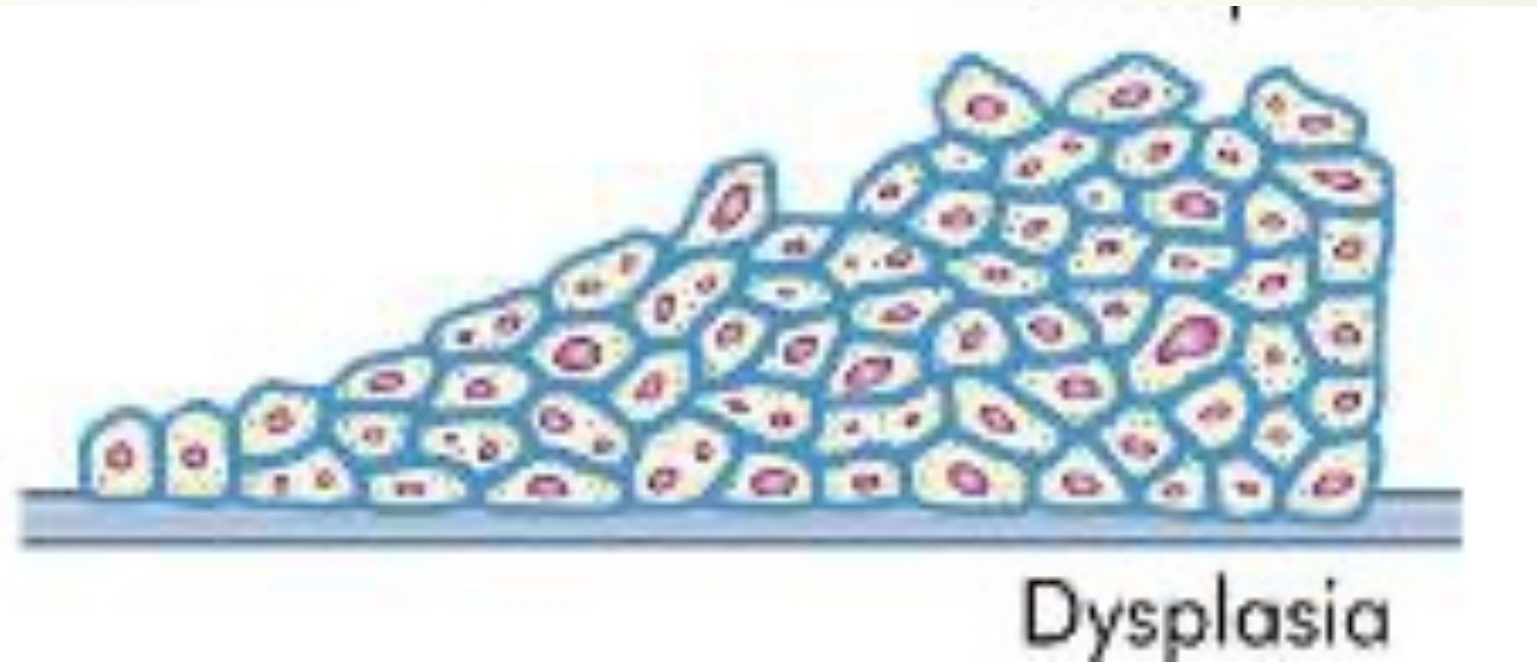
Normal endometrium



- **Metaplasia** is where one type of normal cell is replaced by another type of normal cell.
- If the stimulus that caused metaplasia is removed or ceases, tissues return to their normal pattern of differentiation.
- One example of pathological irritation is cigarette smoke.
- A stone in the bile duct that causes the replacement of the secretory columnar epithelium with stratified squamous epithelium is metaplasia



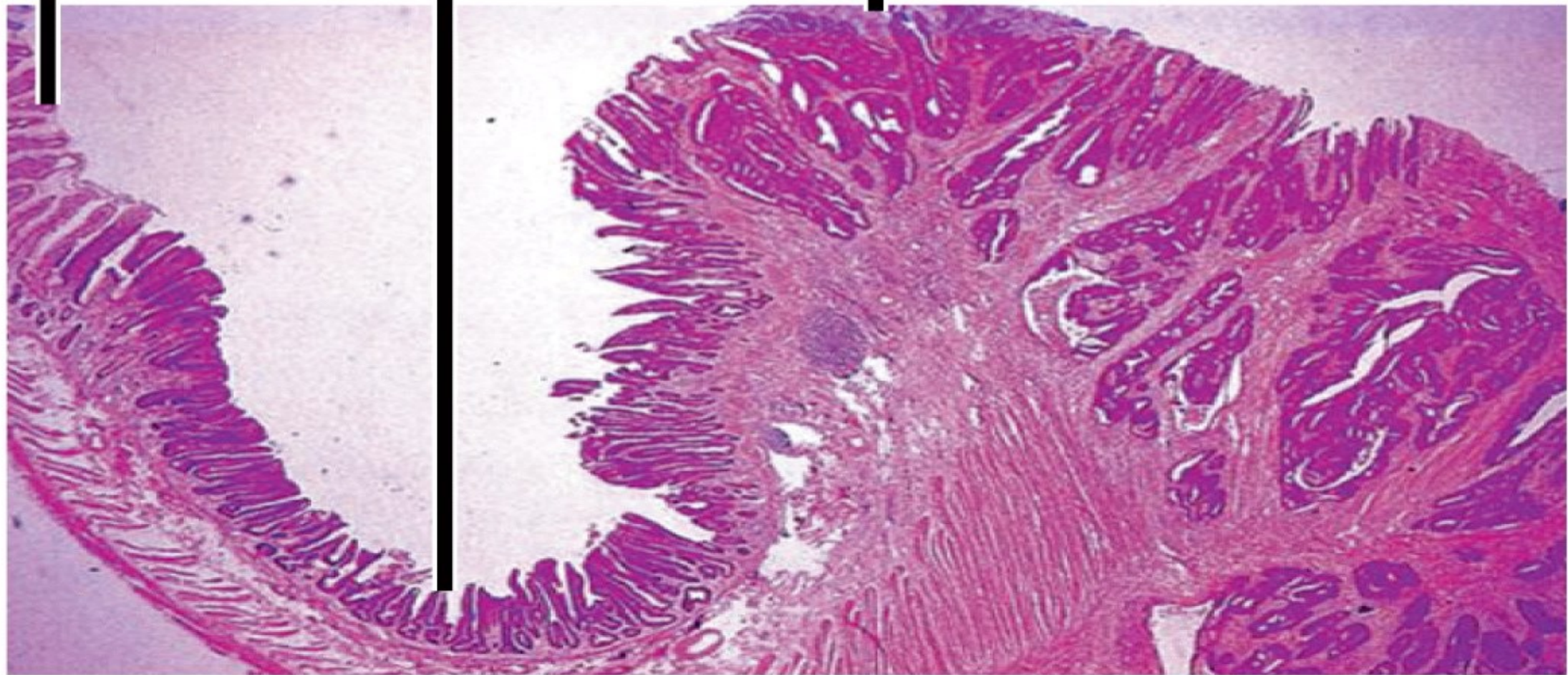
- **Dysplasia** is an abnormality of development.
- This generally consists of an expansion of immature cells, with a corresponding decrease in the number and location of mature cells.
- Dysplasia is often indicative of an early neoplastic process.


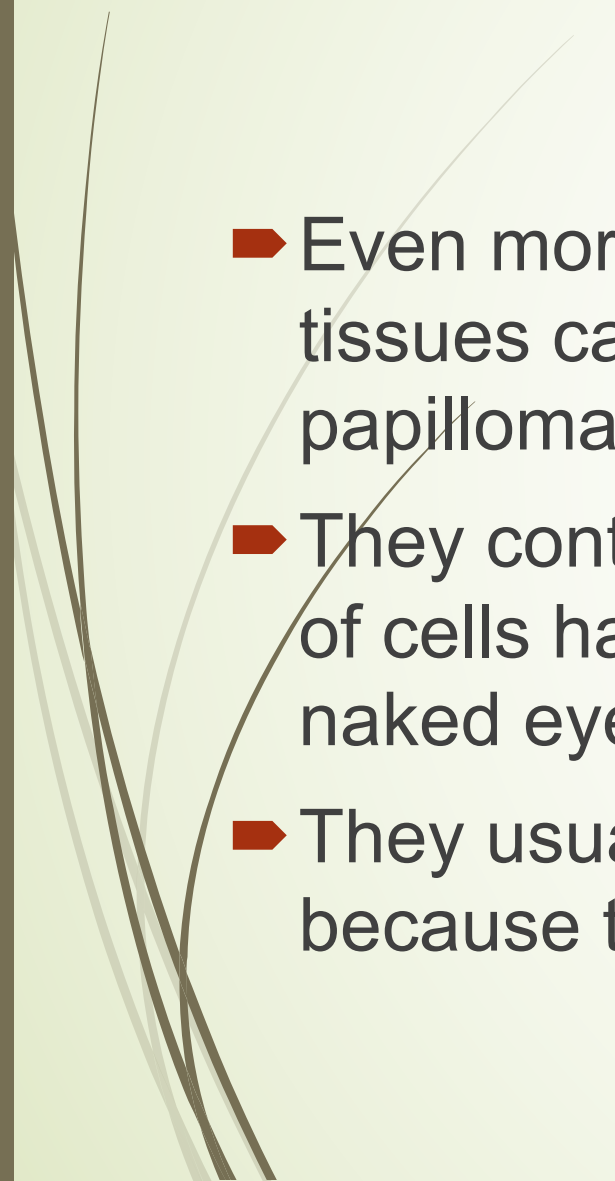



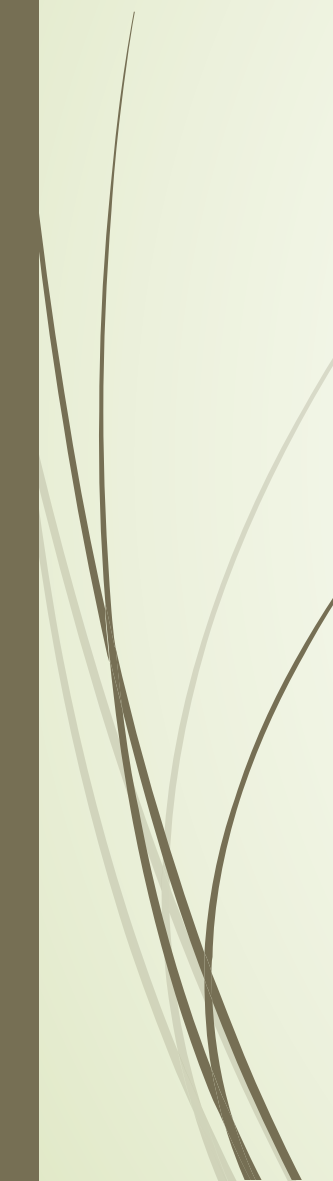
**normal
mucosa**

adenocarcinoma

**dysplastic
mucosa**



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- Even more abnormal are the growths that are seen in epithelial tissues called adenomas, polyps, adenomatous polyps, papillomas.
 - They contain all the cells found in epithelial tissue, but the mass of cells have grown so large that they can be seen with the naked eye. (Macroscopic mass)
 - They usually grow to a certain size and then stop growing because they will not cross the basement membrane.

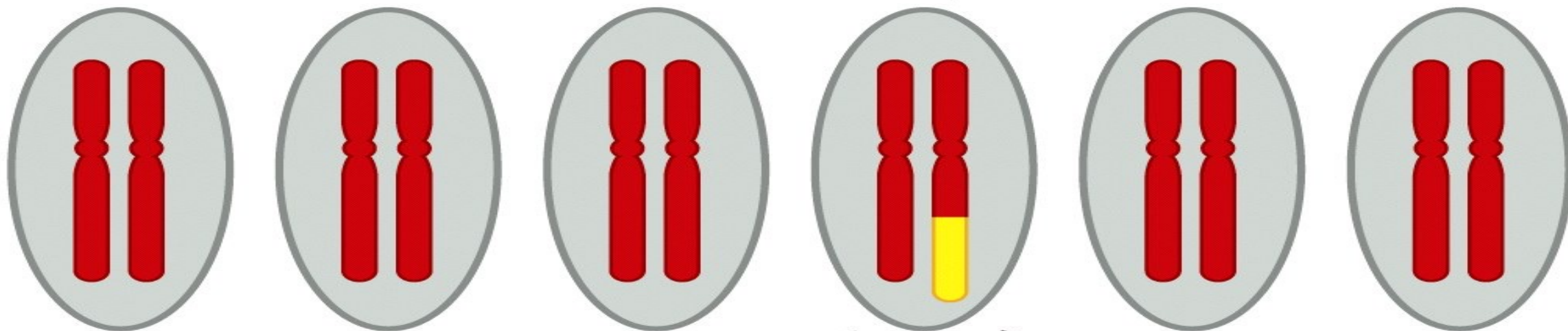
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- A further degree of abnormality is represented by growths that invade underlying tissues.
 - This progressive growth has the substantial potential of becoming life threatening.
 - These growths are called neoplasms (i.e. new tissues)
 - Oncologists and surgeons will often reserve the word cancer only for these neoplastic growths.
 - In cancer research, the word cancer is used to include all types of abnormal growth.

Tumor progression

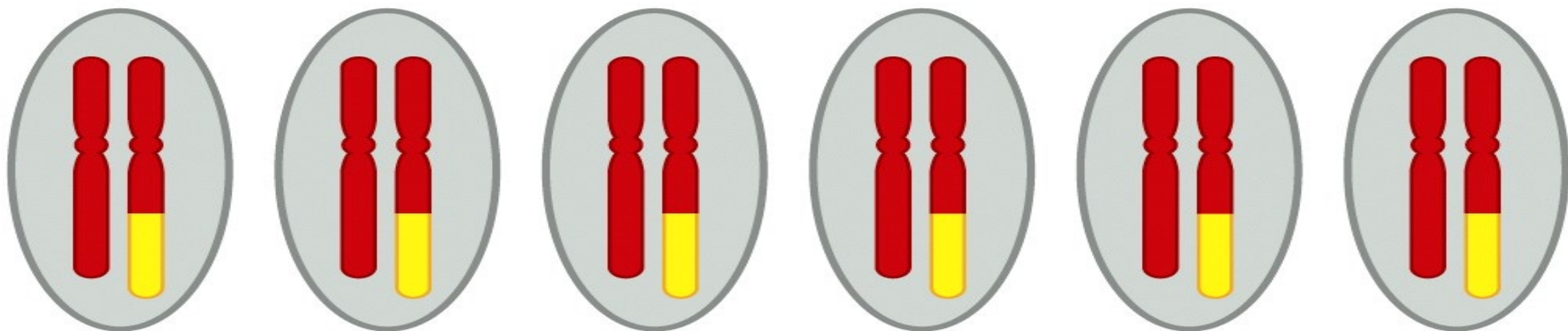
- Tumor progression is when normal tissue evolves progressively into tissue that is highly malignant.



normal tissue




tumor tissue





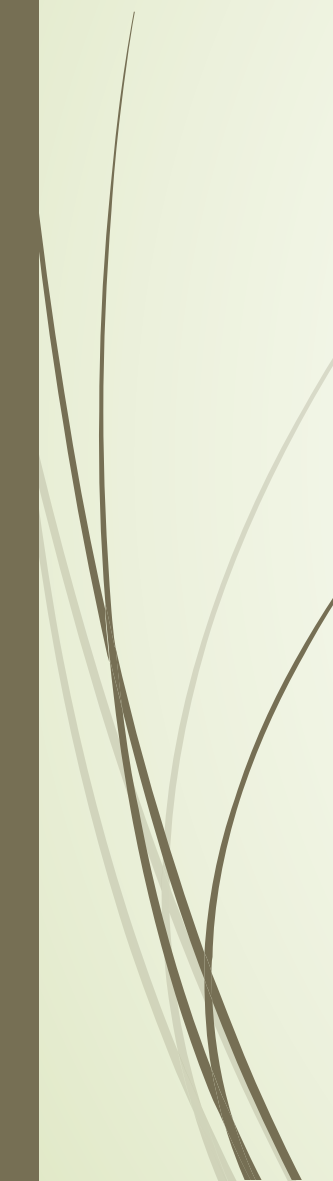


Cancers occur with vastly different frequencies in different populations

- The very nature of cancer suggests that it is a disease of chaos, a breakdown of the normal biological order.
- This disorder comes from malfunctioning of the cells normal homeostatic controls.
- The number of cells produced in a lifetime is incalculable.
- We are killing and replacing cells at a rate of 100,000,000 per second.
- Thus the chance for cancer to strike is fairly large.

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- Since a normal biological process of incessant cell division occurs and could be a risk of cancer, it would seem logical that the incidence and frequencies of cancers around the world would be similar.
 - Actually the incidence and kinds of cancers around the world are dramatically different.
 - Some cancers have a high proportion of tumors that are caused by random, unavoidable accidents of nature.
 - The two contributory factors are heredity and environment.
 - Which is worse? Heredity or Environment?

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- They measured cancer rates in migrant populations and found dramatic increases in different environments
 - Japanese experience stomach cancer 6-8 X more than the USA. When they immigrated to the USA, within one generation their stomach cancer rates was the same as the population.
 - Breast cancer in China is 1/6 of what it is in the USA or Northern Europe. When they immigrate to the USA, normal breast cancer rates (1:7) are normally seen in a few decades.
 - Seventh-Day Adventists incidence and death from cancer is half of the normal population.

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- **Etiology** is the cause of cancer
 - The great majority of cancers are caused by factors or agents that are external to the body, enter the body, and somehow attack and corrupt tissues.
 - It is estimated that avoidance of cancer-causing factors in diet and lifestyle may result in a 50% reduction of dying from cancer in the west.
 - This would reduce cancer mortality to 10% of the population.
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Geographic variation in cancer incidence and death rates

Countries showing highest and lowest incidence of specific types of cancer^a

Cancer site	Country of highest risk	Country of lowest risk	Relative risk H/L ^b
Skin (melanoma)	Australia (Queensland)	Japan	155
Lip	Canada (Newfoundland)	Japan	151
Nasopharynx	Hong Kong	United Kingdom	100
Prostate	U.S. (African American)	China	70
Liver	China (Shanghai)	Canada (Nova Scotia)	49
Penis	Brazil	Israel (Ashkenazic)	42
Cervix (uterus)	Brazil	Israel (non-Jews)	28
Stomach	Japan	Kuwait	22
Lung	U.S. (Louisiana, African American)	India (Madras)	19
Pancreas	U.S. (Los Angeles, Korean American)	India	11
Ovary	New Zealand (Polynesian)	Kuwait	8

Geographic variation in cancer incidence and death rates


Geographic areas showing highest and lowest death rates from specific types of cancer^c

Cancer site	Area of highest risk	Area of lowest risk	Relative risk H/L ^b
Lung, male	Eastern Europe	West Africa	33
Esophagus	Southern Africa	West Africa	16
Colon, male	Australia, New Zealand	Middle Africa	15
Breast, female	Northern Europe	China	6



Cancer risks seem to be increased with certain lifestyles


- Evidence that certain kinds of cancers are associated with certain lifestyles have been observed for hundreds of years.
- 1761 English Physician John Hill noted the connection between nasal cancer and tobacco snuff.
- 1775 Surgeon Percivall Pott found that a substantial number of scrotal cancers was found in young teenager chimney sweeps.
- 1839 Italian Physician noted breast cancer rates were 6X more in nuns than the general population.
 - This was related to celibacy and never having given birth.

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- By 1850 they were documenting high lung cancer rates in miners.
 - 1910 they were finding a connection between cancer and the recent discovery of x-rays.
 - By 1950 epidemiologists found that heavy cigarette smokers carried a 20X risk.



Specific chemical and physical agents can induce cancer

- By 1940, British chemists had identified several of the components of coal tar that was carcinogenic.
- Some of these same compound condensates have been found in cigarette smoke as well.
- This suggests that certain chemicals can enter the body and disturb the tissues and cells and ultimately provoke the emergence of a tumor.

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- By the late 1940's, they were able to identify a series of several carcinogenic chemicals that were used in WWI for warfare, such as mustard gas.
 - X-rays have been found to be carcinogenic because radiation is able to mutate the genes of cells, creating malignant growth patterns.

Carcinogens found in a normal diet

Foodstuff	Compound	Concentration in foodstuff
Black pepper	piperine	100 mg/g
Common mushroom	agaritine	3 mg/g
Celery ^b	furocoumarins, psoralens	1 µg/g, 0.8 µg/g
Rhubarb	anthraquinones	varies
Cocoa powder	theobromine	20 mg/g
Mustard, horseradish	allyl isothiocyanate	varies
Alfalfa sprouts	canavanine ^c	15 mg/g
Burnt materials ^d	large number	varies
Coffee	caffeic acid	11.6 mg/g

^aAmes has cited 37 naturally occurring compounds that have registered as carcinogens in laboratory animals; one or more have been found in each of the following foodstuffs:

absinthe, allspice, anise, apple, apricot, banana, basil, beet, broccoli, Brussels sprouts, cabbage, cantaloupe, caraway, cardamom, carrot, cauliflower, celery, cherries, chili pepper, chocolate, cinnamon, cloves, coffee, collard greens, comfrey herb tea, coriander, corn, currants, dill, eggplant, endive, fennel, garlic, grapefruit, grapes, guava, honey, honeydew melon, horseradish, kale, lemon, lentils, lettuce, licorice, lime, mace, mango, marjoram, mint, mushrooms, mustard, nutmeg, onion, orange, paprika, parsley, parsnip, peach, pear, peas, black pepper, pineapple, plum, potato, radish, raspberries, rhubarb, rosemary, rutabaga, sage, savory, sesame seeds, soybean, star anise, tarragon, tea, thyme, tomato, turmeric, and turnip

^bThe levels of these can increase 100-fold in diseased plants.

^cCanavanine is indirectly genotoxic because of oxygen radicals that are released, perhaps during the inflammatory reactions associated with elimination of canavanine-containing proteins.

^dOn average, several grams of burnt material are consumed daily in the form of bread crusts, burnt toast, and burnt surfaces of meats cooked at high temperature.

Risk of lung cancer as a function of number of cigarettes per day

	Lifelong nonsmoker	Smokers			
Most recent number of cigarettes smoked (by subjects) per day before onset of disease	—	$\geq 1, < 5$	$\geq 5, < 15$	$\geq 15, < 25$	≥ 25
Relative risk	1	8	12	14	27

^aThe relative risk indicates the risk of contracting lung cancer compared with that of a nonsmoker, which is set at 1. (From R. Doll and A.B. Hill, *BMJ* 2:739–748, 1950.)

Known or suspected causes of human cancers

Environmental and lifestyle factors known or suspected to be etiologic for human cancers in the United States^a

Type	% of total cases ^b
Cancers due to occupational exposures	1–2
Lifestyle cancers	
Tobacco-related (sites: e.g., lung, bladder, kidney)	34
Diet (low in vegetables, high in nitrates, salt) (sites: e.g., stomach, esophagus)	5
Diet (high fat, lower fiber, broiled/fried foods) (sites: e.g., bowel, pancreas, prostate, breast)	37
Tobacco and alcohol (sites: mouth, throat)	2

Specific carcinogenic agents implicated in the causation of certain cancers^c

Cancer	Exposure
Scrotal carcinomas	chimney smoke condensates
Liver angiosarcoma	vinyl chloride
Acute leukemias	benzene
Nasal adenocarcinoma	hardwood dust
Osteosarcoma	radium
Skin carcinoma	arsenic
Mesothelioma	asbestos
Vaginal carcinoma	diethylstilbestrol
Oral carcinoma	snuff

A microscopic view of a tissue section showing various cells. The cells are stained, with some appearing pink and others grey. The text 'Cells gone Bad' is overlaid on the image. 'Cells' is in a large, dark red serif font, 'gone' is in a smaller, black serif font, and 'Bad' is in a large, black serif font.

Cells
gone
Bad