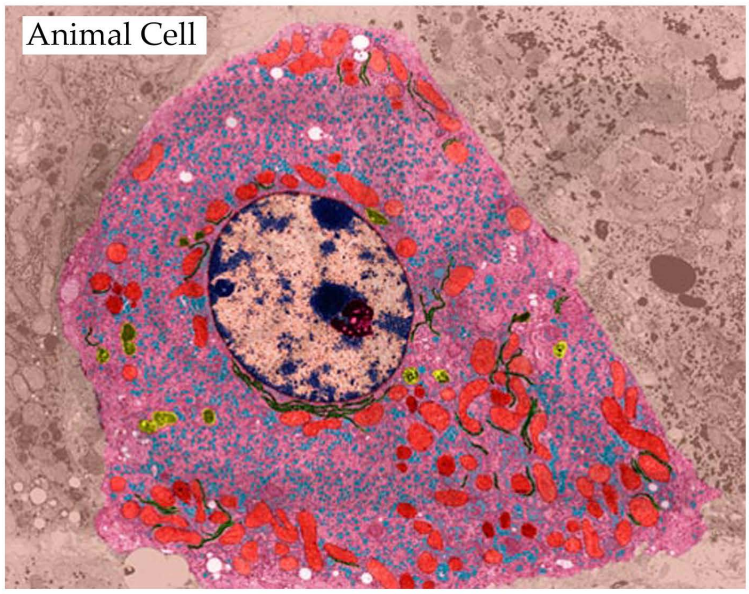
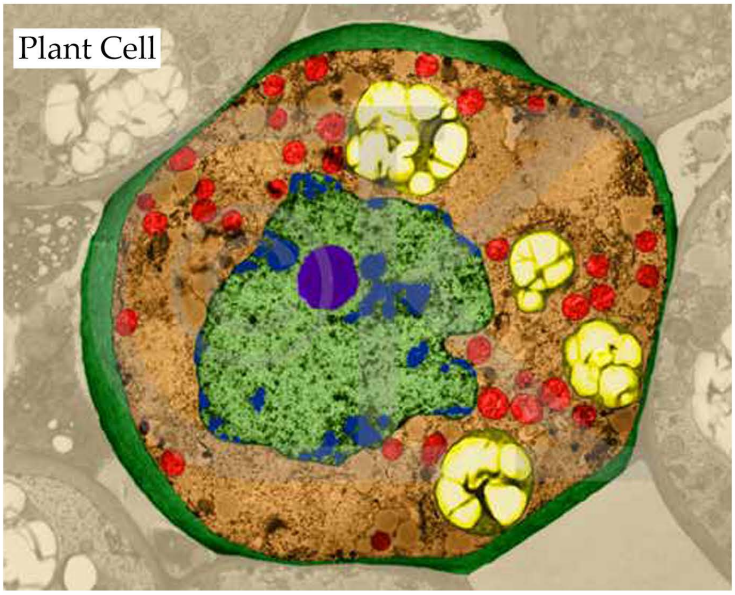
Cell Biology Review

a) The chemical composition of cells…might not be what you'd first think!

CHEMICAL COMPONENT	PERCENT OF TOTAL CELL WEIGHT
DNA	~0.4%
RNA	~0.7%
Carbohydrates	~1%
Inorganic Ions, Salts, etc.	~2%
Lipids	~2%
Proteins	10-15%
Water	80-85%

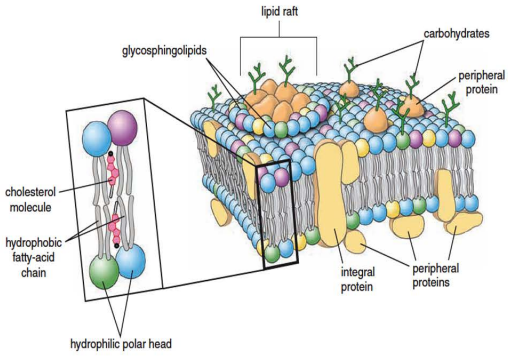
b) Cellular organelles: Their structure and function

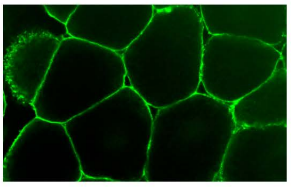




THE MEMBRANE SYSTEM OF THE CELL

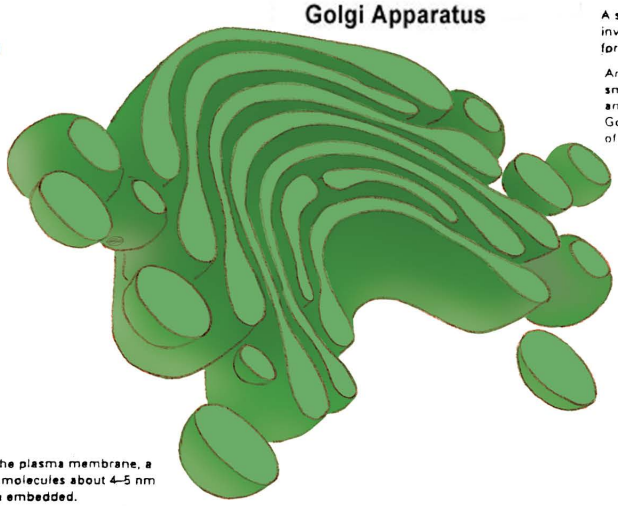
Plasma Membrane Structure





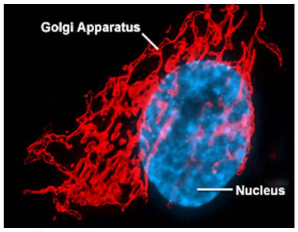
The outer boundary of the cell is the plasma membrane, a continuous sheet of phospholipid molecules about 4–5 nm thick in which various proteins are embedded.

Golgi Apparatus

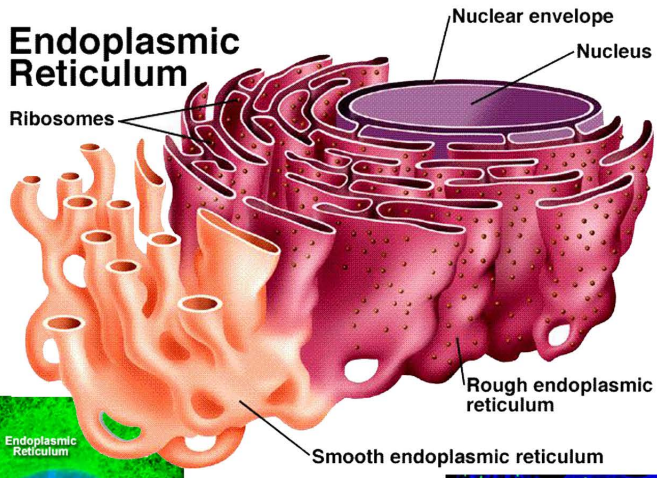


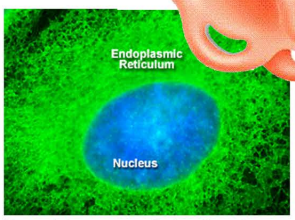
A system of stacked, membrane-bounded, flattened sacs involved in modifying, sorting, and packaging macromolecules for secretion or for delivery to other organelles.

Around the Golgi apparatus are numerous small membrane-bounded vesicles (50 nm and larger) that carry material between the Golgi apparatus and different compartments of the cell.



Endoplasmic Reticulum

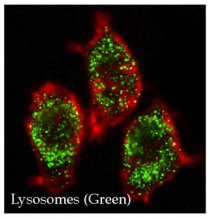


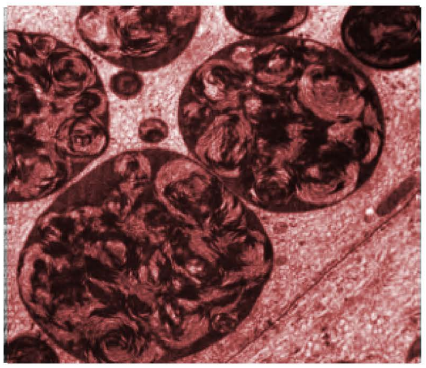


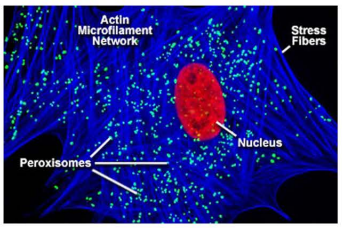
Flattened sheets, sacs, and tubes of membrane extend through the cytoplasm of eucaryotic cells, enclosing a large intracellular space. The ER membrane is in structural continuity with the outer membrane of the nuclear envelope, and it specializes in the synthesis and transport of lipids and membrane proteins.

LYSOSOMES

membrane-bounded vesicles that contain hydrolytic enzymes involved in intracellular digestion

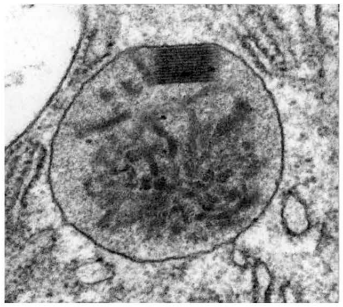




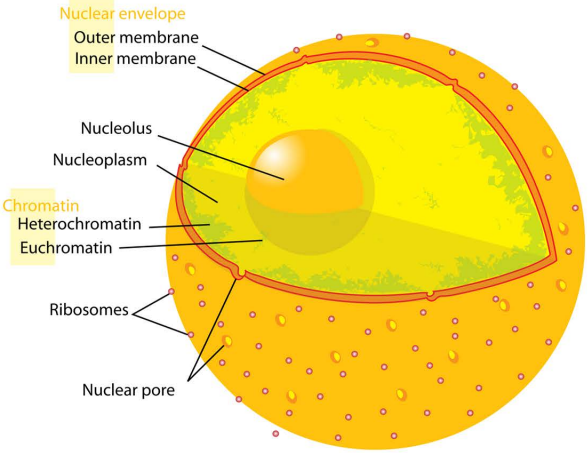


PEROXISOMES

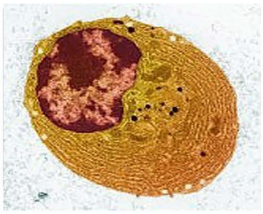
membrane-bounded vesicles containing oxidative enzymes that generate and destroy hydrogen peroxide

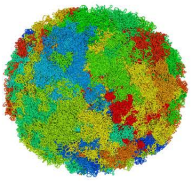


The Cell Nucleus



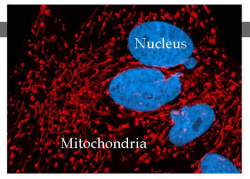
The nucleus is the most conspicuous organelle in the cell. It is separated from the cytoplasm by an envelope consisting of two membranes. All of the chromosomal DNA is held in the nucleus, packed into chromatin fibers by its association with an equal mass of histone proteins. The nuclear contents communicate with the cytosol by means of openings in the nuclear envelope called nuclear pores.

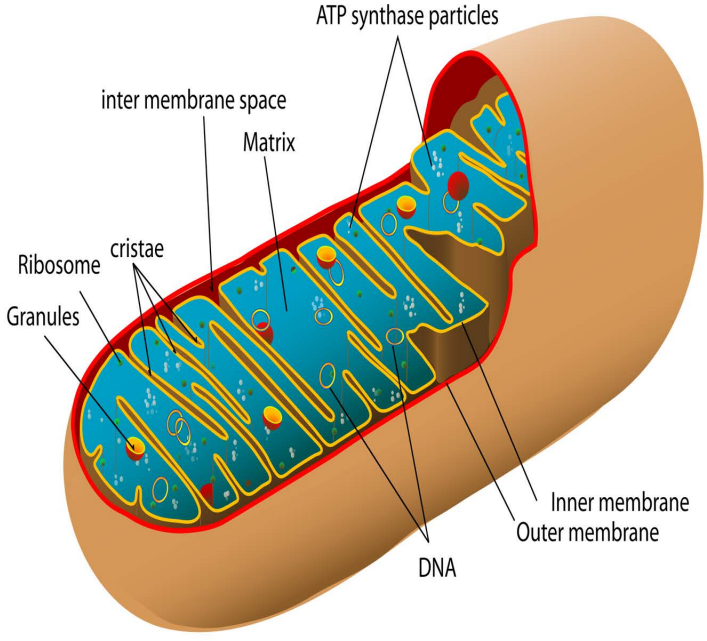




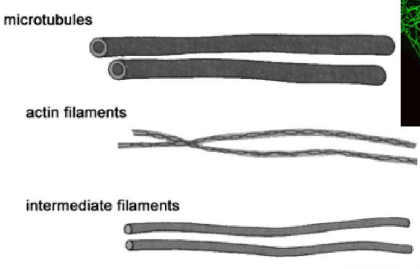
Schematic of unwound chromosomes inside an interphase nucleus

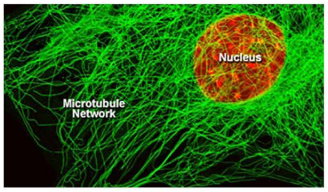
Mitochondria

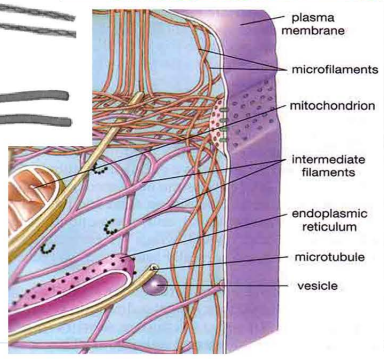




The Cytoskeleton

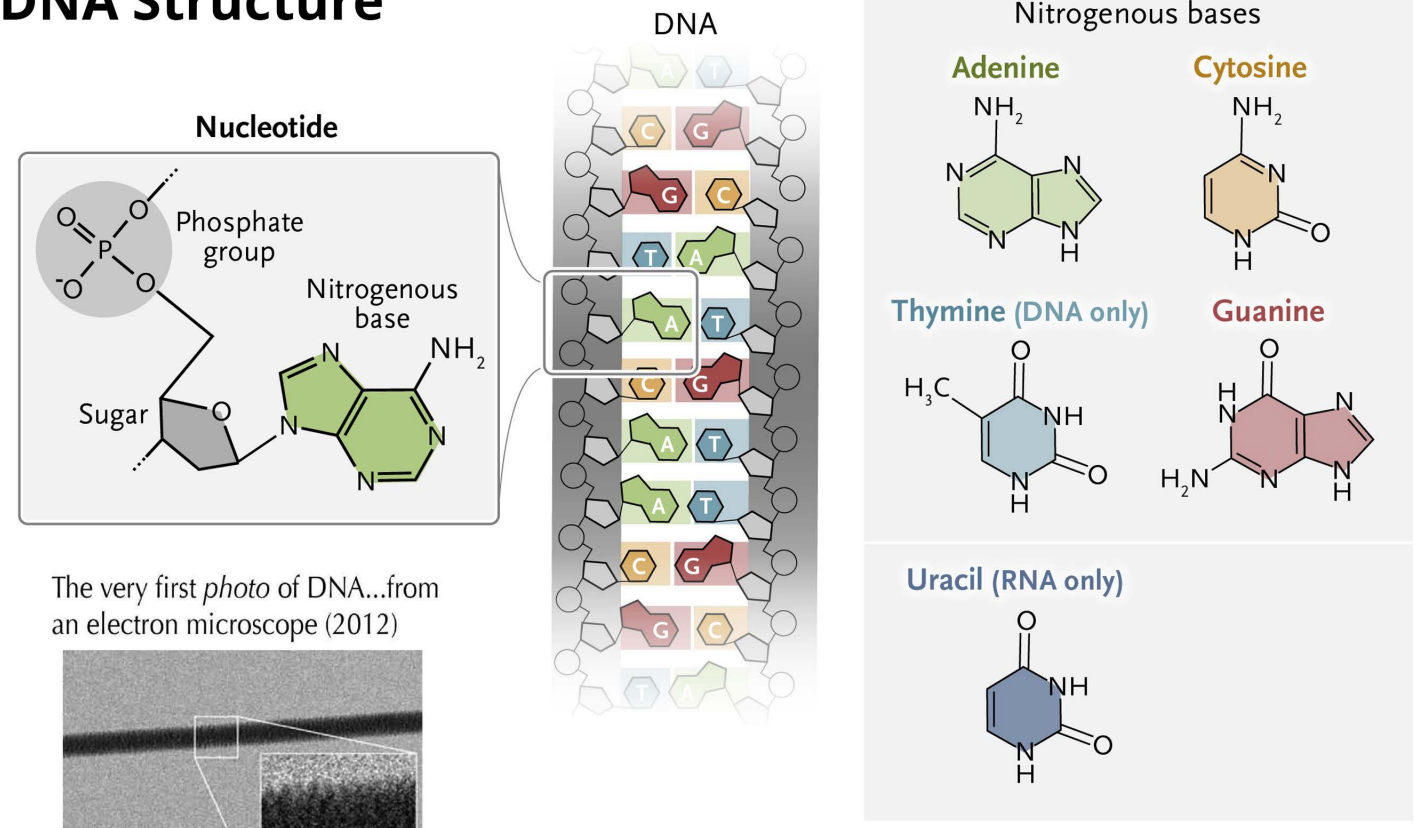




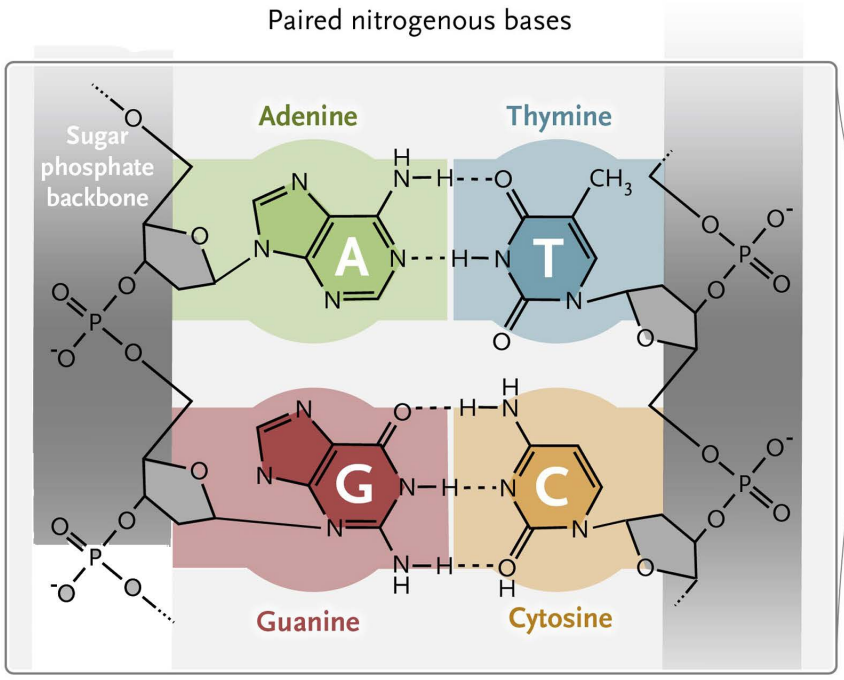


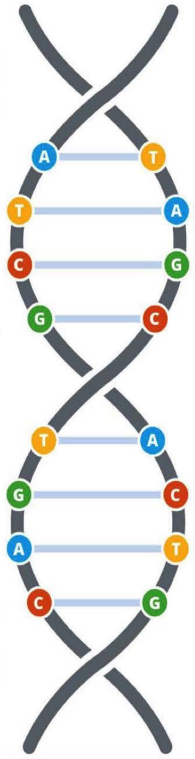
In the cytosol, arrays of protein filaments form networks that give the cell its shape and provide a basis for its movements.

DNA Structure

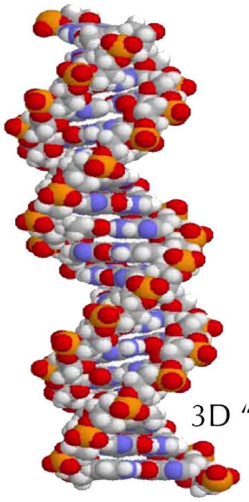


The very first *photo* of DNA...from an electron microscope (2012)



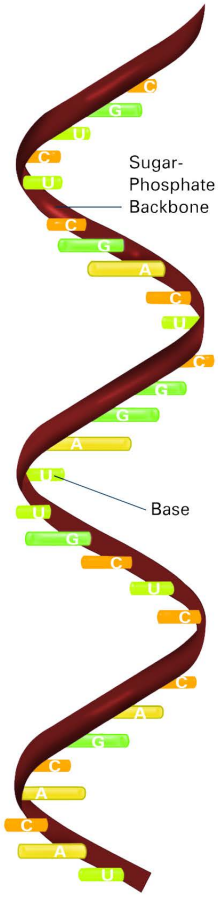


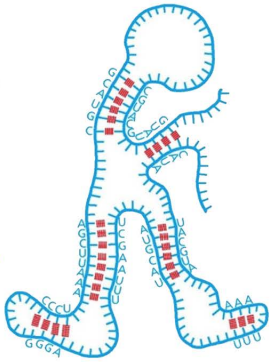
"Double Helix"

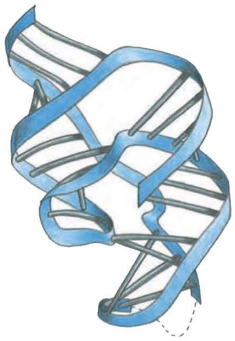


3D "molecular" model of DNA

Messenger RNA

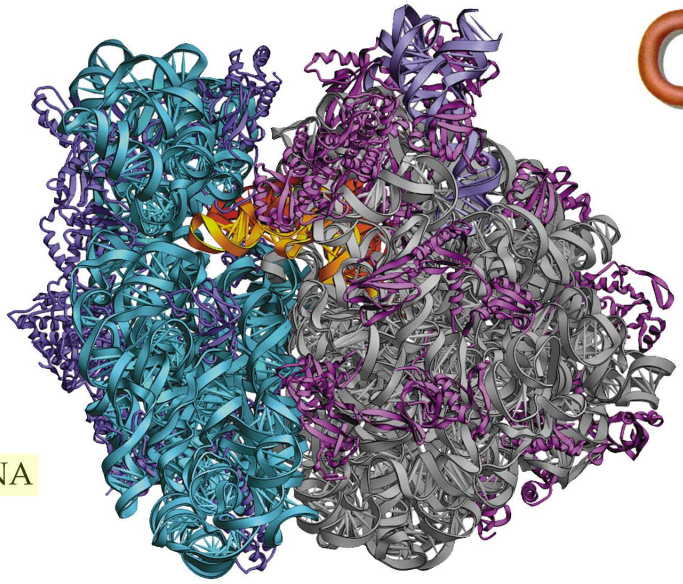




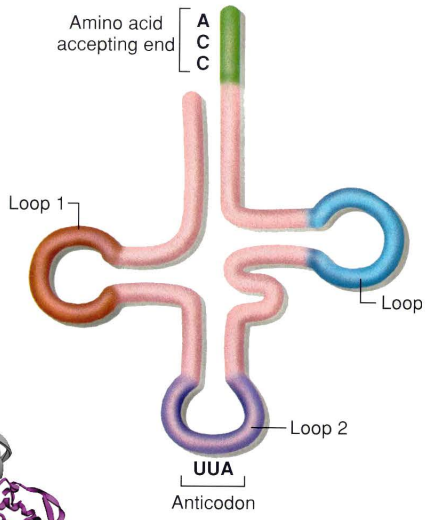


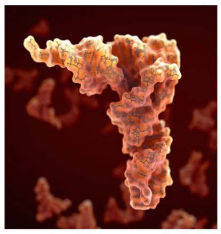
RNA SINGLE STRAND

RNA is single-stranded, but it contains local regions of short complementary base-pairing that can form from a random matching process.



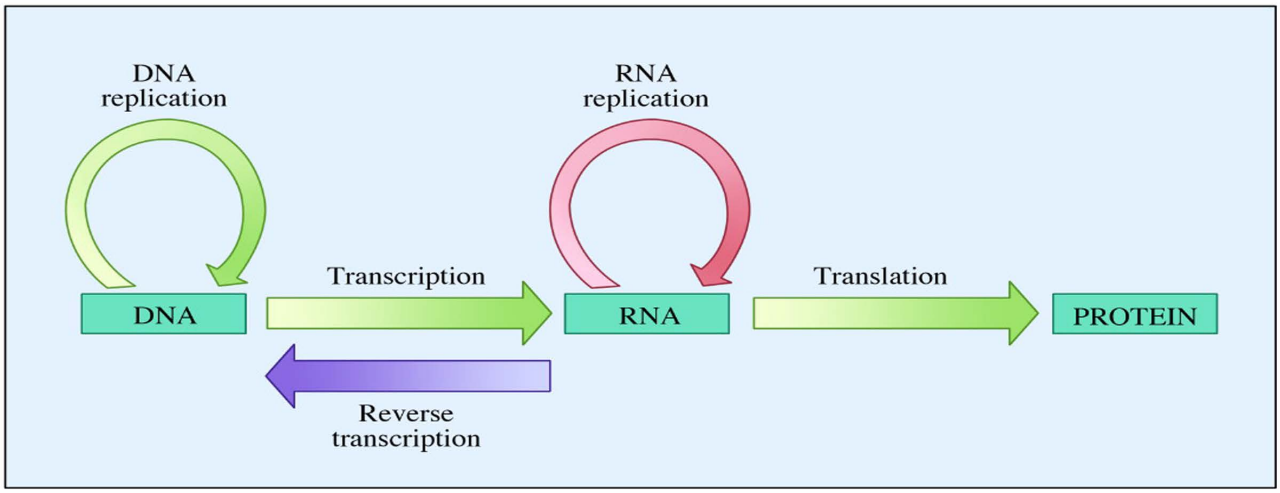
Ribosomal RNA



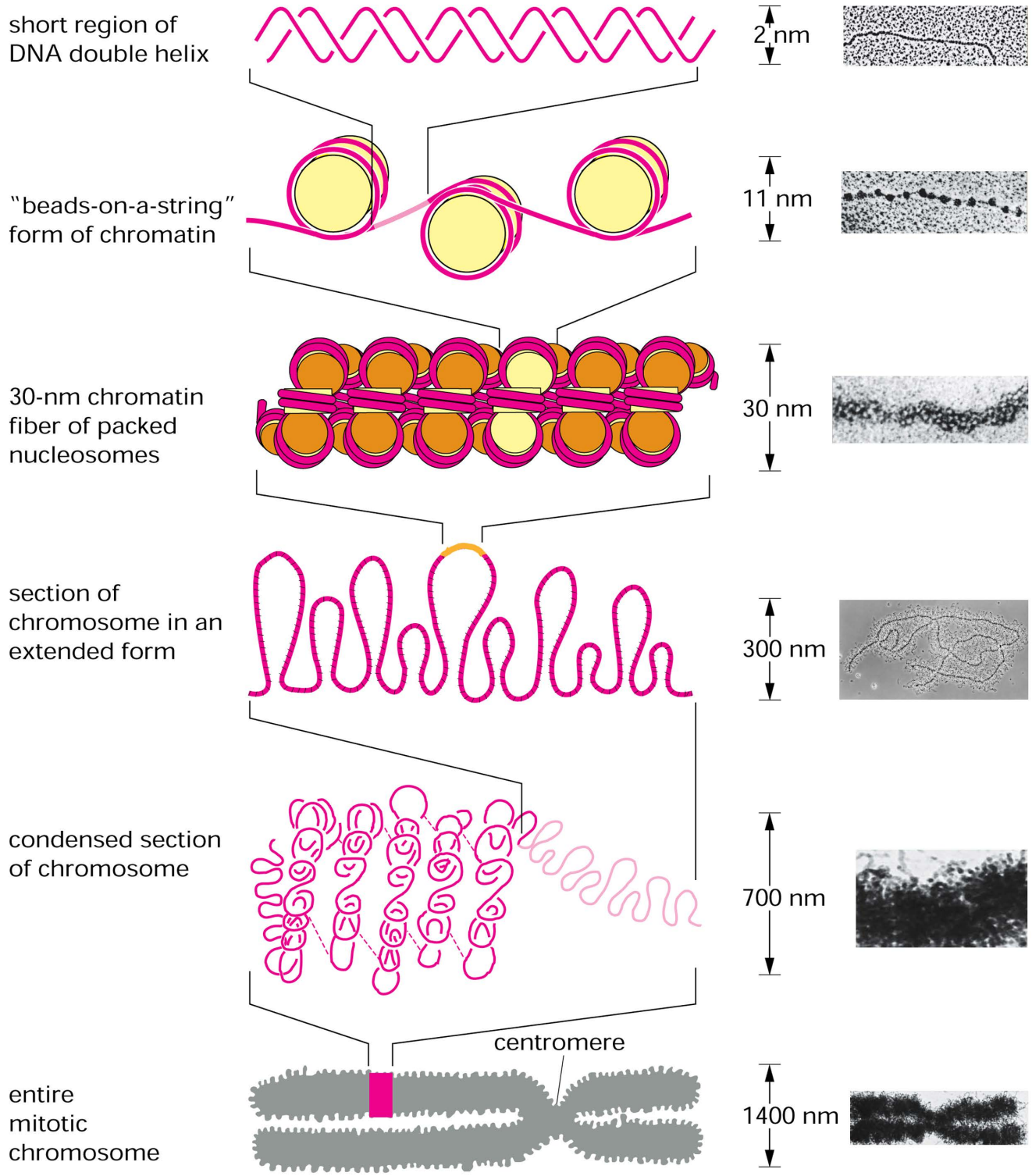


Transfer RNA

The Central Dogma



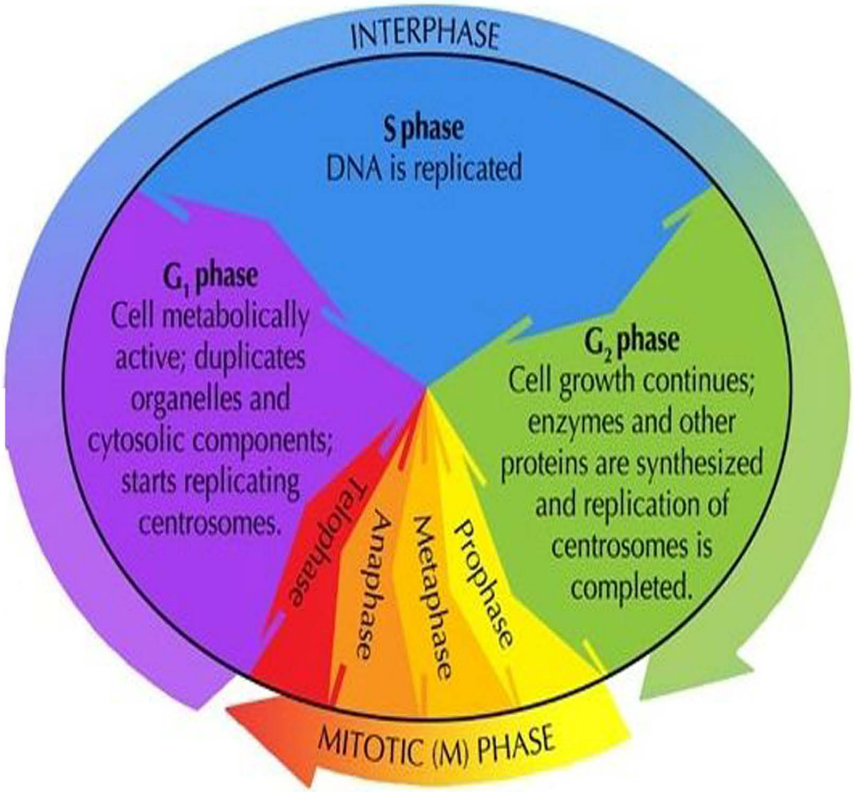
Levels of Chromatin Packing

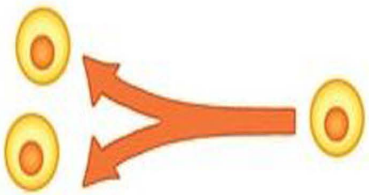


NET RESULT: EACH DNA MOLECULE HAS BEEN PACKAGED INTO A MITOTIC CHROMOSOME THAT IS 50,000x SHORTER THAN ITS EXTENDED LENGTH

3. A review of cell growth characteristics

a) The cell cycle:





1. **the phases of the cell cycle include <u>interphase</u>, a period of cell growth, and <u>mitosis</u>, the period when cell division occurs**...

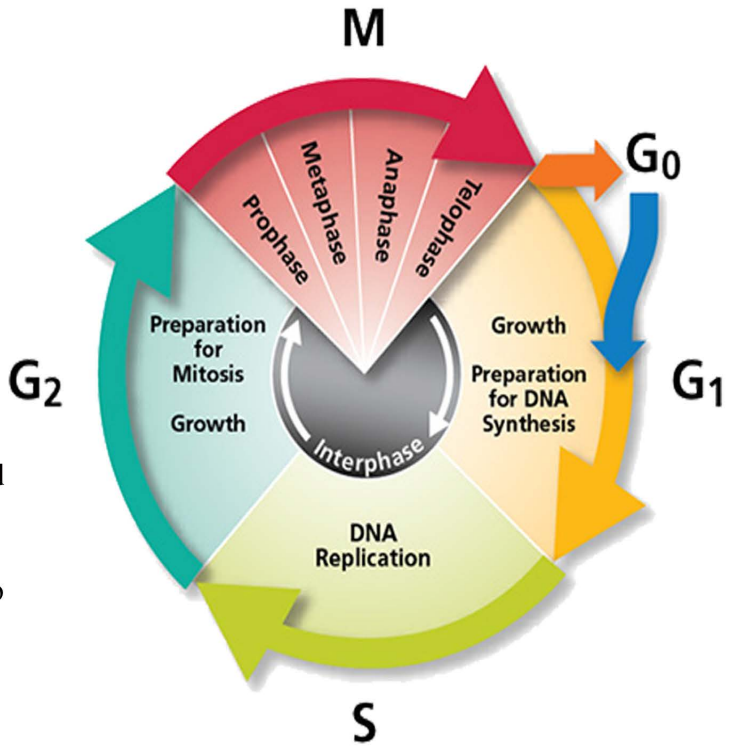
...interphase is further subdivided into three (sub)phases, **S-phase**, when DNA replication occurs, and two "gaps", one before ($\mathbf{G_1}$), and one after ($\mathbf{G_2}$), S-phase.

Mitosis is further subdivided into **prophase**, **metaphase**, **anaphase** and **telophase**

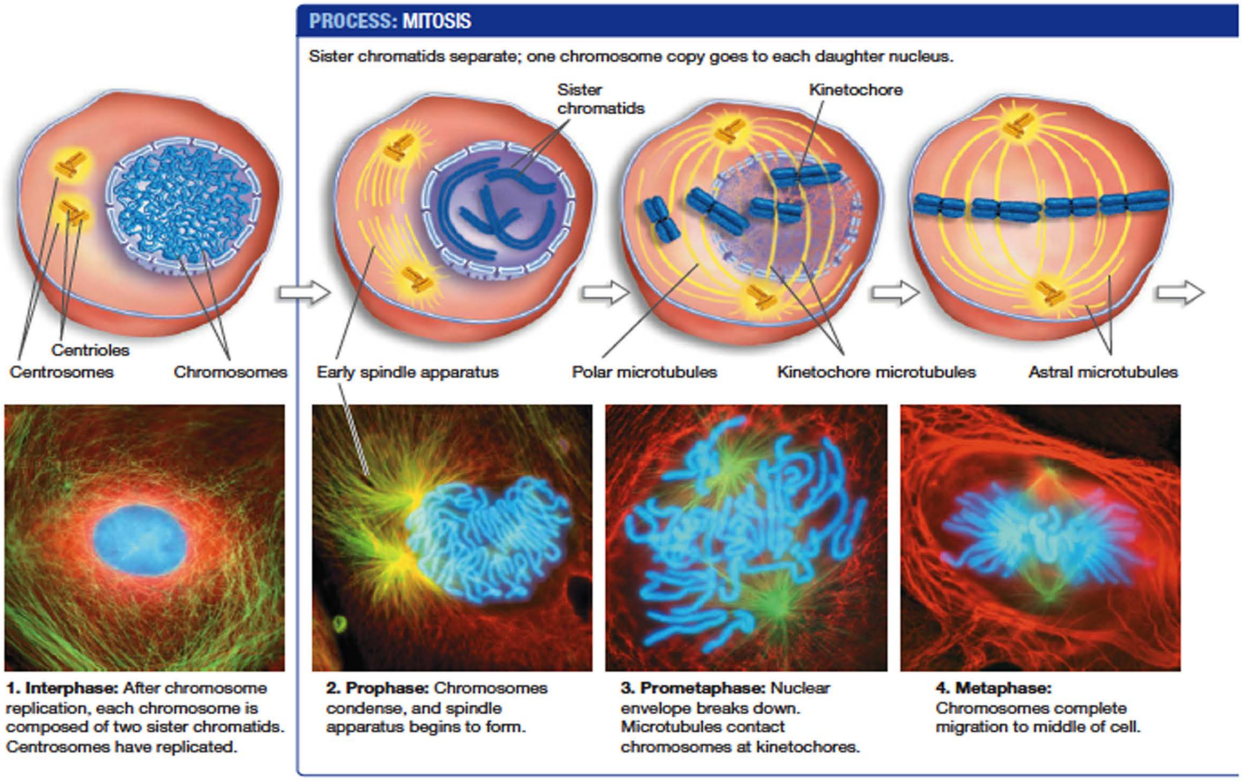
2. However, there's actually *another* phase as well, and that one, called "$\mathbf{G_0}$", applies to cells that have entered a resting state outside of the traditional cell cycle

a. **most cells of the human body are in this resting state where they have become differentiated in order to perform tissue-specific functions**

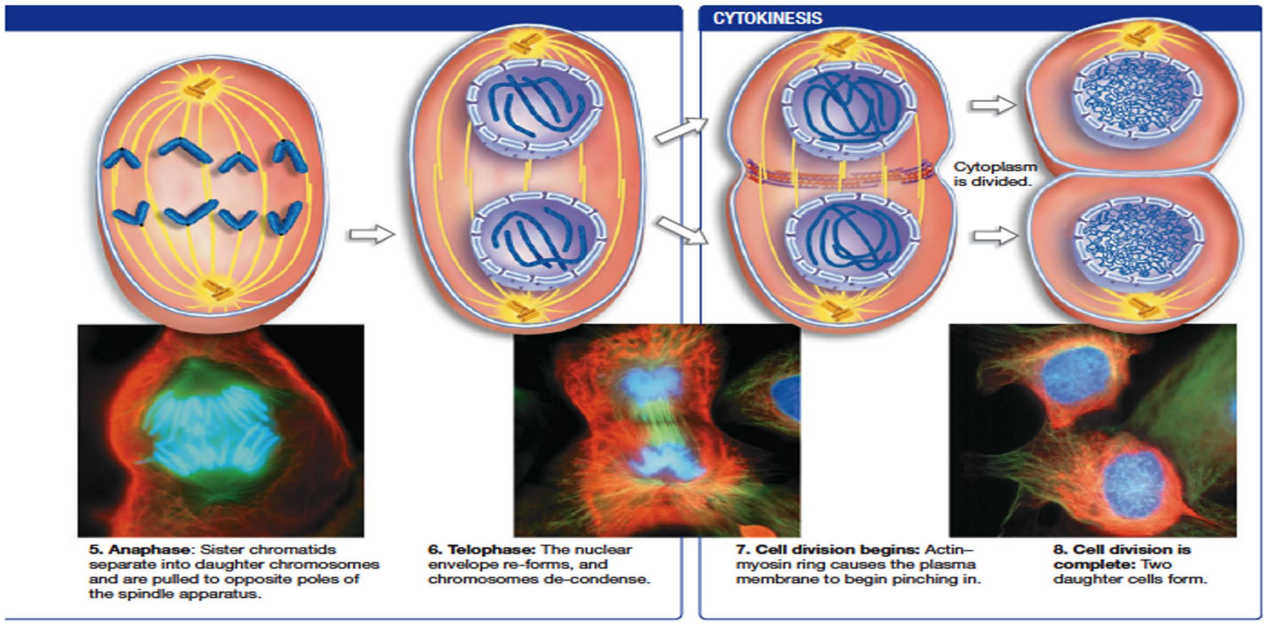
1. ***most*** cells permanently sacrifice the ability to divide when they enter G_0



Mitosis in somatic cells

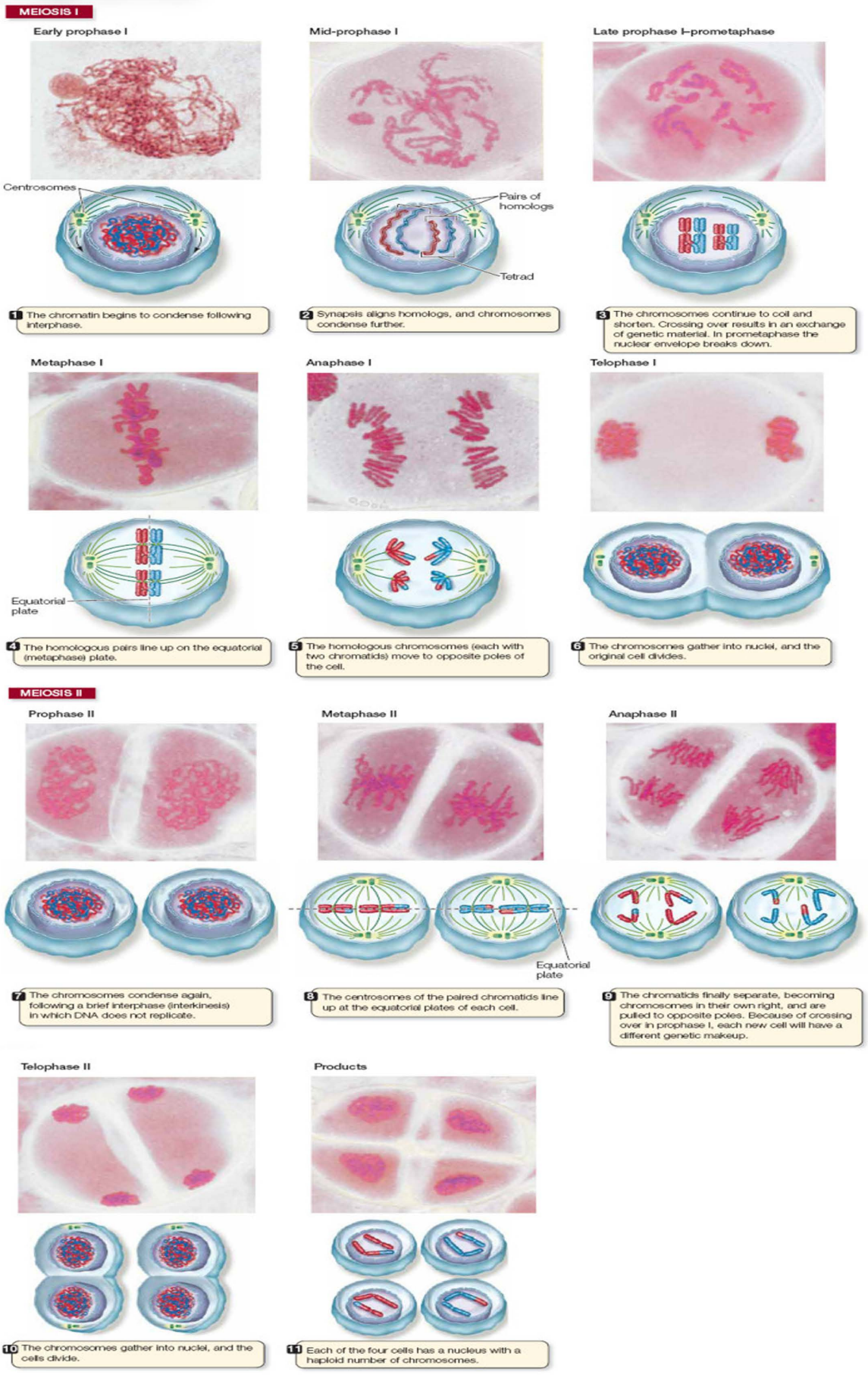


Mitosis and Cytokinesis. In the micrographs, under the drawings, chromosomes are stained blue, microtubules are yellow/green, and intermediate filaments are red.



Credit: NIGMS

Meiosis in germ cells – like two rounds of mitosis…one right after the other



Tissue Biology Review

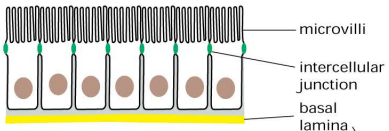
1. A Quick Review of Different Cell and Tissue Types in the Body

a) there are over 200 types of cells in the human body, which are assembled into the different types of tissues, which are assembled into the different organs, which make up the whole organism

EPITHELIA

Epithelial cells form coherent cell sheets called epithelia, which line the inner and outer surfaces of the body. There are many specialized types of epithelia.

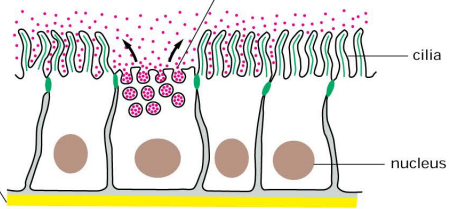
Absorptive cells have numerous hairlike projections called microvilli on their free surface to increase the area for absorption.



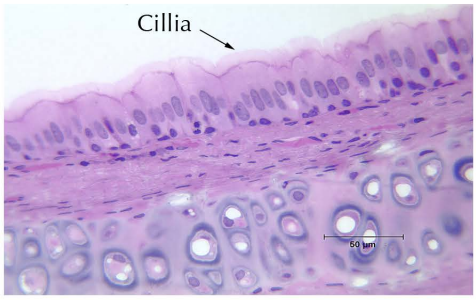
Adjacent epithelial cells are bound together by cell junctions that give the sheet mechanical strength and also make it impermeable to small molecules. The sheet rests on a basal lamina.

Ciliated cells have cilia on their free surface that beat in synchrony to move substances (such as mucus) over the epithelial sheet.

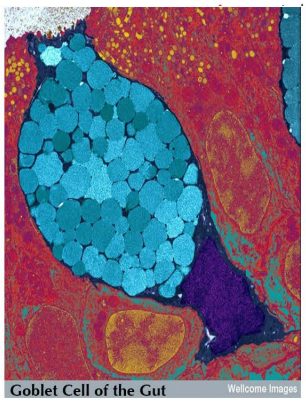
Secretory cells are found in most epithelial layers. These specialized cells secrete substances onto the surface of the cell sheet.



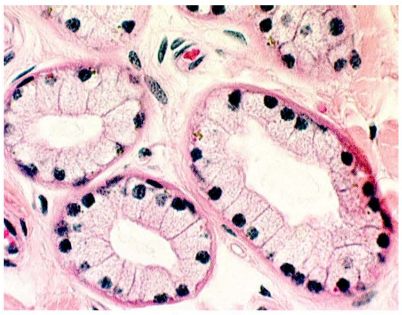
Columnar epithelium of the small intestine



Ciliated cells of the tracheal epithelium



Secretory epithelial cells are often collected together to form a gland that specializes in the secretion of a particular substance. As illustrated, exocrine glands secrete their products (such as tears, mucus, and gastric juices) into ducts. Endocrine glands secrete hormones into the blood.

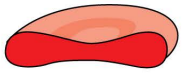


Cross-section through sweat gland

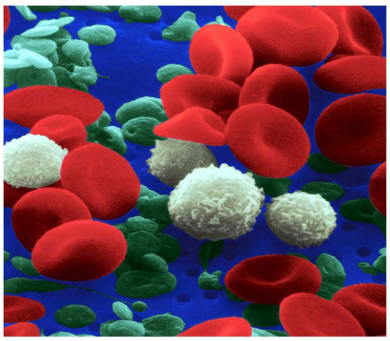
BLOOD

Erythrocytes (red blood cells) are very small cells, and in mammals have no nucleus or internal membranes. When mature they are stuffed full of the oxygen-binding protein hemoglobin.

1 cm^3 of blood contains 5 billion erythrocytes



their normal shape is a biconcave disc

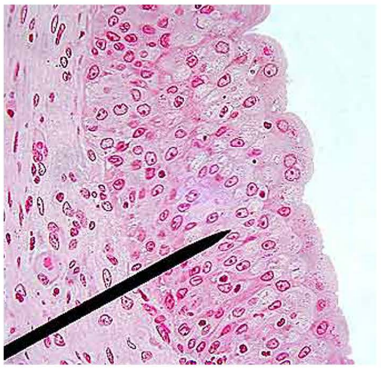


Leucocytes (white blood cells) protect against infections. Blood contains about one leucocyte for every 100 red blood cells. Although leucocytes travel in the circulation, they can pass through the walls of blood vessels to do their work in the surrounding tissues. There are several different kinds, including

lymphocytes—responsible for immune responses such as the production of antibodies.

macrophages and neutrophils—move to sites of infection, where they ingest bacteria and debris.

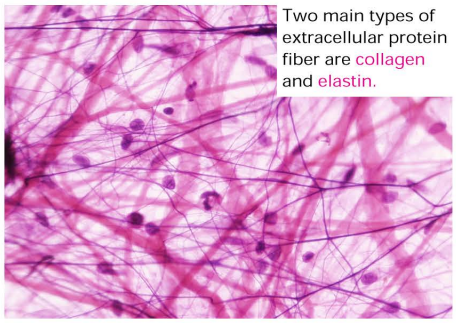
platelets - responsible for blood clotting and scab formation



Transitional epithelium (bladder) is thick and rubbery to allow stretching and contracting.

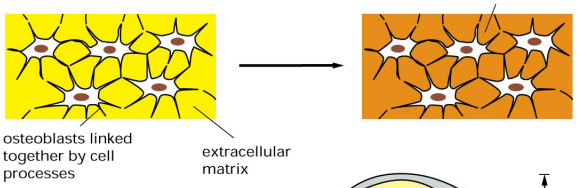
CONNECTIVE TISSUE

The spaces between organs and tissues in the body are filled with connective tissue made principally of a network of tough protein fibers embedded in a polysaccharide gel. This extracellular matrix is secreted mainly by fibroblasts.



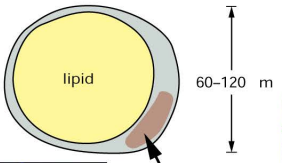
Two main types of extracellular protein fiber are collagen and elastin.

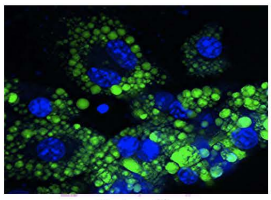
Bone is made by cells called osteoblasts. These secrete an extracellular matrix in which crystals of calcium phosphate are later deposited.



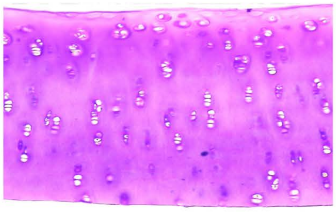
Bone

Fat cells (or adipose cells), among the largest cells in the body, are responsible for the production and storage of fat. The nucleus and cytoplasm are squeezed by a large lipid droplet.



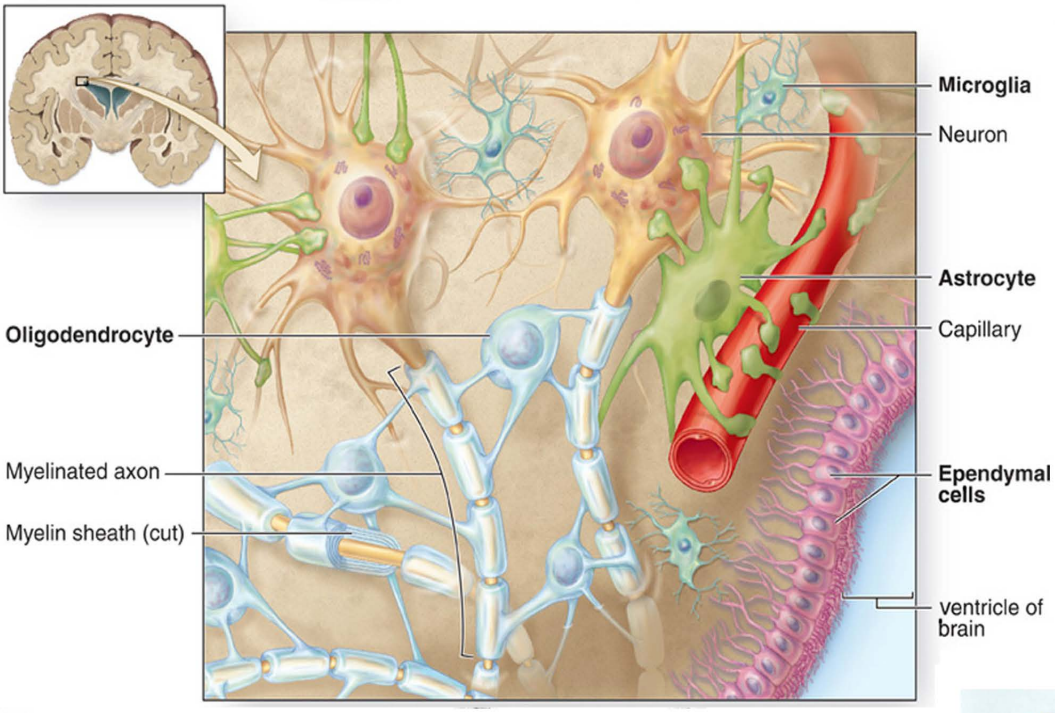


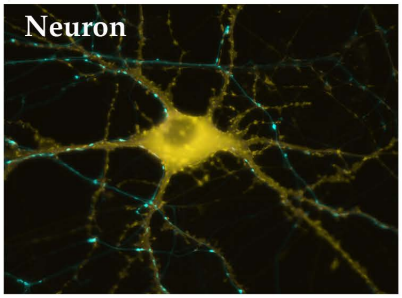
Fat cells

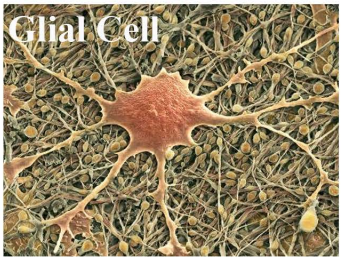


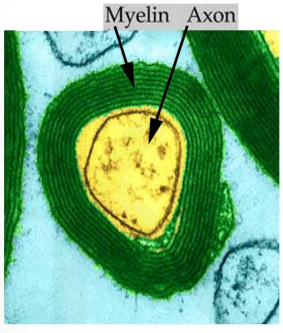
Cartilage

NERVOUS SYSTEM



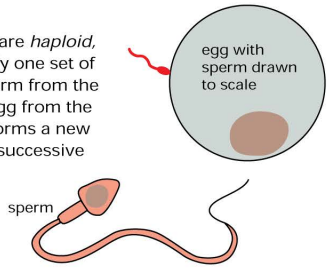


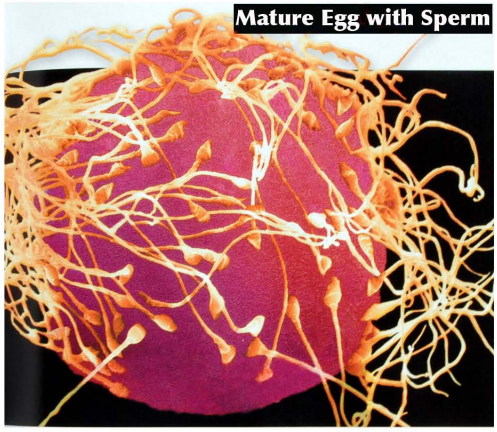




GERM CELLS

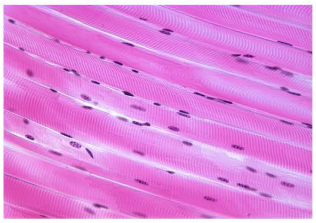
Both sperm and egg are *haploid*, that is, they carry only one set of chromosomes. A sperm from the male fuses with an egg from the female, which then forms a new diploid organism by successive cell divisions.



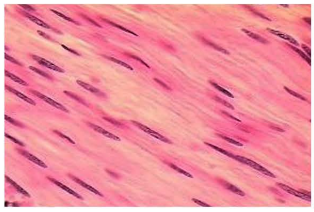


MUSCLE

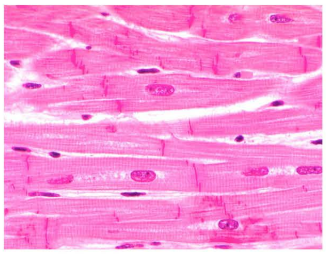
Muscle cells produce mechanical force by their contraction. In vertebrates there are three main types:



skeletal muscle—this moves joints by its strong and rapid contraction. Each muscle is a bundle of muscle fibers, each of which is an enormous multinucleated cell.



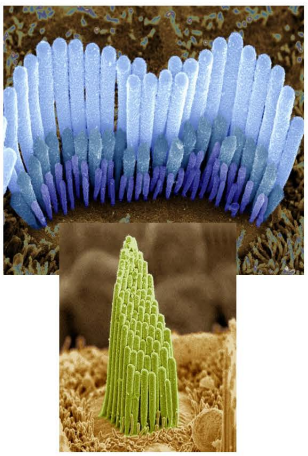
smooth muscle—present in digestive tract, bladder, arteries, and veins. It is composed of thin elongated cells (not striated), each of which has one nucleus.



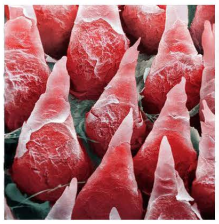
cardiac muscle—intermediate in character between skeletal and smooth muscle. It produces the heart beat. Adjacent cells are linked by electrically conducting junctions that cause the cells to contract in synchrony.

SENSORY CELLS

Among the most strikingly specialized cells in the vertebrate body are those that detect external stimuli. Hair cells of the inner ear are primary detectors of sound. They are modified epithelial cells that carry special microvilli (stereocilia) on their surface. The movement of these in response to sound vibrations causes an electrical signal to pass to the brain.

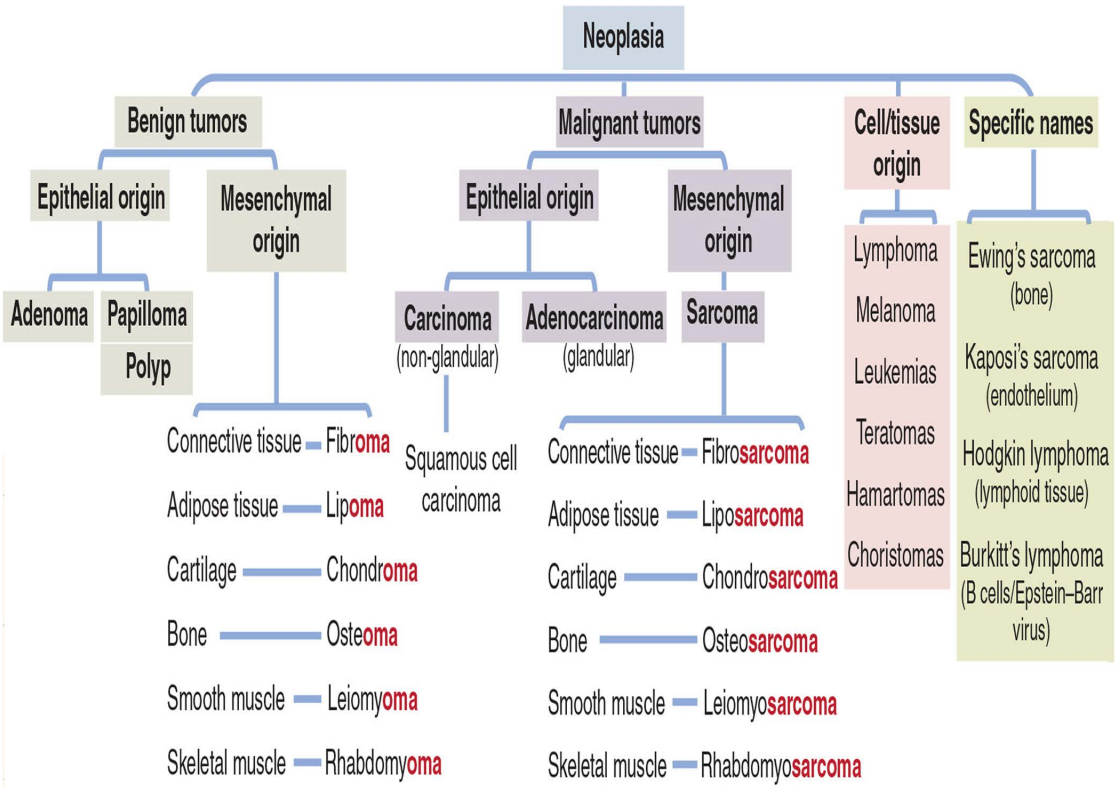


Rods and cones of the retina transmit visual signals to the optic nerve and brain

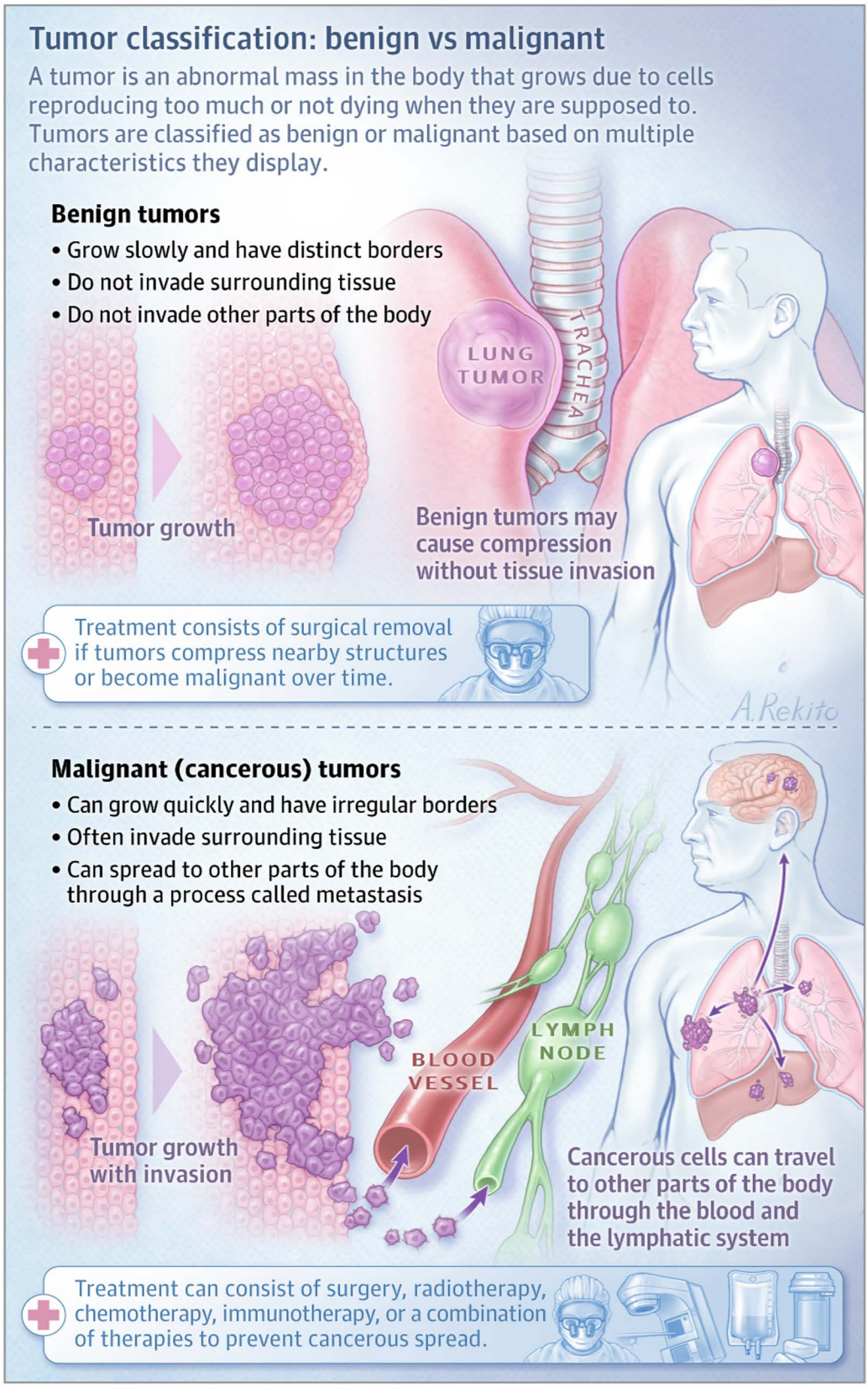


Taste buds are embedded in the epithelium of the tongue

1] *unfortunately, there are also about 200 different types of cancer for every type of human cell....*



What's the difference between a tumor that's benign, and one that's malignant?



Cancer Biology

Just What is Cancer, Anyway?

a) Answer: it depends on who you ask!

As it turns out, no one definition is all-encompassing or entirely satisfactory (i.e., there are exceptions to every definition) to explain all the molecular, cellular, pathological and clinical aspects of the disease

The Oncologist's Definition: A spectrum of many separate diseases, usually of multiple etiologies, that, if left untreated, almost always results in the death of the patient either directly or indirectly

The Pathologist's Definition: A relatively automomous growth of tissue that negatively affects the structure or function of the tissue of origin, and that is also capable of invasive and/or metastatic behavior

The Cell or Molecular Biologist's Definition: A disease of the cell in which the normal mechanisms of cell growth, proliferation, death, differentiation, motility and/or communication are dysregulated secondary to deleterious changes in the cell's DNA (i.e., mutations, deletions, duplications or chromosomal rearrangements), and/or the regulation of the DNA

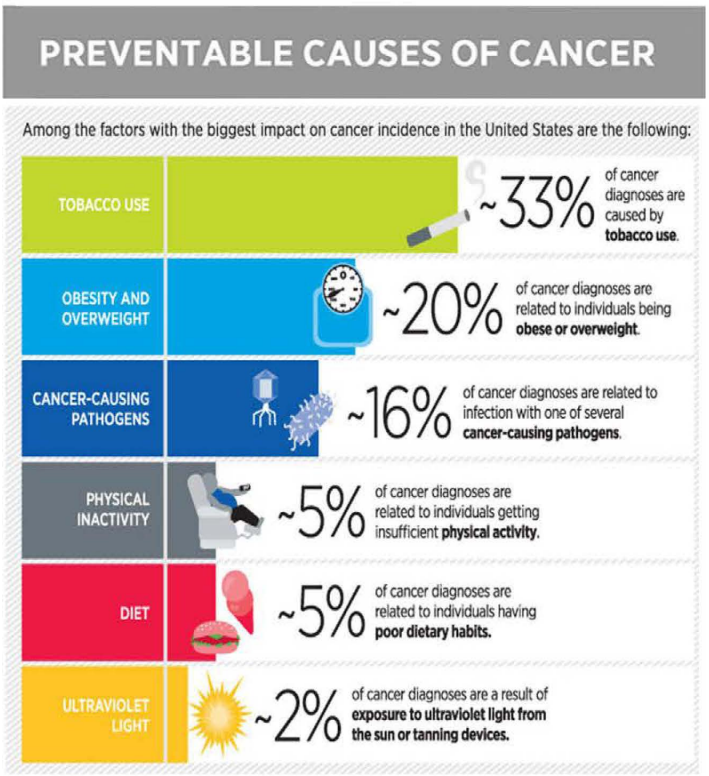
b) **What causes cancer?** Answer: ***Carcinogens*** that (either directly or indirectly) damage the cell's DNA...or sometimes, a ***genetic predisposition*** to cancer, i.e., the individual inherits already-damaged DNA from one or both parents

Types of Carcinogens

Chemical Agents: include both natural and man-made substances (or their metabolites) that either *initiate* cancer (cause the "first hit"), or else *promote* its progression thereafter

Physical Agents: include irritants such as asbestos, along with UV and ionizing radiation; typically, these can act as cancer initiators or promoters (or both)

Infectious Agents: bacteria and viruses that are associated with particular cancers because they either directly alter the DNA of the host cells they infect, or else they cause local irritation/inflammation that can promote cancer



CANCER-CAUSING PATHOGENS

Bacteria

Infectious Agent	Cancer	% of global cancer cases attributable to infection*
Helicobacter pylori	Stomach cancers	32.5

Parasites

Infectious Agent	Cancer	% of global cancer cases attributable to infection*
Clonorchis sinensis	Biliary, gallbladder, and pancreatic cancers	0.1
Opisthorchis viverrini	Biliary, gallbladder, and pancreatic cancers	unknown
Schistosoma haematobium	Bladder cancer	0.3

Viruses

Infectious Agent	Cancer	% of global cancer cases attributable to infection*
Epstein-Barr Virus (EBV)	Hodgkin and certain non-Hodgkin lymphomas,and stomach and nasopharyngeal cancers	5.4
Hepatitis B/C Virus (HBV and HCV)	Hepatocellular carcinoma	29.5
Human Herpes Virus type -8 (HHV-8; also known as Kaposi sarcoma herpes virus)	Kaposi sarcoma and certain forms of lymphoma	2.1
Human Immunodeficiency Virus (HIV)	Kaposi sarcoma and non-Hodgkin lymphoma	unknown
Human Papillomavirus (HPV)	Anal, cervical, head and neck, oral, penile, vaginal, and vulvar cancers	30
Human T-cell Lymphotrophic Virus, type 1 (HTLV-1)	T-cell leukemia and lymphoma	0.1
Merkel Cell Polyomavirus (MCV)	Skin cancer	unknown

INHERITED CANCER RISK

Cancers	Syndrome	Associated Gene(s)
Leukemias and lymphomas	Ataxia telangiectasia	ATM
Basal cell carcinoma	Basal cell nevus syndrome	PTCH1, PTCH2, SUFU
All cancers	Bloom syndrome	BLM
Breast, ovarian, pancreatic, and prostate cancers	Breast-ovarian cancer syndrome	BRCA1, BRCA2
Breast, thyroid, and endometrial cancers	Cowden syndrome	PTEN
Breast and stomach cancers	Diffuse gastric and lobular breast cancer syndrome	CDH1
Colorectal cancer	Familial adenomatous polyposis (FAP)	APC
Melanoma and pancreatic cancer	Familial atypical multiple mole–melanoma syndrome (FAMM)	CDKN2A
Retinal cancer	Familial retinoblastoma	RB1
Leukemia	Fanconi's anemia	FACC, FACA
Kidney cancer and uterine fibroids	Hereditary leiomyomatosis and renal cell cancer	FH
Pancreatic cancer	Hereditary pancreatitis/familial pancreatitis	PRSS1, SPINK1
Leukemias, breast, brain, and soft tissue cancers	Li-Fraumeni syndrome	TP53
Colorectal and endometrial cancers	Lynch syndrome	EPCAM, MLH1, MSH2, MSH6, PMS2
Pancreatic cancers, pituitary adenomas, benign skin, and fat tumors	Multiple endocrine neoplasia 1	MEN1
Thyroid cancer and pheochromacytoma	Multiple endocrine neoplasia 2	RET, NTRK1
Pancreatic, liver, lung, breast, ovarian, uterine, and testicular cancers	Peutz–Jeghers syndrome	STK11/LKB1
Tumors of the spinal cord, cerebellum, retina, adrenals, and kidneys	von Hippel-Lindau syndrome	VHL
Kidney cancer	Wilms' tumor	WT1
Skin cancer	Xeroderma pigmentosum	XPD, XPB, XPA

b) What sorts of genes govern these defective cellular "behaviors" (called phenotypes) that lead to cancer?

1. one class of such genes are called ONCOGENES (their normal counterparts are termed "proto-oncogenes") - these genes are critically involved in embryonic development, but once that is complete, the genes are usually either turned off altogether for the remainder of the organism's life, or else, are very carefully monitored and controlled by the cell in case they start misbehaving

a] **genetically speaking, oncogenes behave in a dominant fashion, that is, even though there are two copies of every gene in a cell, even if only one of them becomes defective, the cancer process can begin**

b] in addition, **the activation of oncogenes causes the cell to GAIN a property or function**, such as for example, the ability to invade surrounding tissues, or evade death under conditions where normal cells would die

c] automotive analogy: the activation of oncogenes is akin to stepping on the gas pedal

Some common oncogenes and the cancers they're associated with

Oncogene	Cancer	Targeted Therapy
p110α	breast, prostate, endometrial, colorectal, cervical, head and neck, gastric, lung	
EGFR	lung, glioma, colorectal, ovarian, breast	gefitinib, erlotinib, cetuximab
ERBB2 (HER2)	breast, gastric, ovarian, bladder	trastuzumab, lapatinib
B-RAF	melanoma, thyroid, colorectal, ovarian	vemurafenib
K-RAS	pancreatic, lung, colorectal, endometrial, ovarian	
H-RAS	bladder	
N-RAS	melanoma, AML	
MYC	lymphomas, colorectal, breast, prostate, melanoma, neuroblastoma, ovarian	
BCR-ABL	CML, ALL, AML	imatinib, dasatinib, nilotinib
IDH1	glioblastoma, AML	
IDH2	glioblastoma, AML	
JAK2	CML, ALL	
KIT	gastrointestinal stromal tumors, AML, melanoma	
MET	kidney, gastric, lung, head and neck, colorectal	
FLT-3	AML	

2. a second class of such genes are called TUMOR SUPPRESSOR GENES - these genes are active throughout the life of the cell and play critically important roles counteracting excessive cell proliferation, promoting the repair of damaged DNA in order to avoid mutations, and encouraging irreparably damaged cells to die rather than risk becoming cancerous

a] **genetically speaking, tumor suppressor genes act in a recessive fashion, i.e., that both cellular copies of the gene have to be damaged or lost in order for the cancer process to begin**

b] **mutation or loss of tumor suppressor genes cause the cell to LOSE a property or function**, such as, no longer being able to repair certain kinds of DNA damage, or no longer being able to halt movement through the cell cycle

c] automotive analogy: tumor suppressor genes normally act like the brake pedal, but if lost, it becomes impossible to stop

Tumor Suppressor	Cancer	Diagnostic	Targeted Therapy
p53	lung, colorectal, bladder, ovarian, head and neck, gastric, breast, prostate	IHC, PCR, sequencing	
PTEN	glioblastoma, melanoma, prostate, breast, endometrial, thyroid, lung, colorectal, AML, CLL	IHC, PCR, sequencing	
$p16^{INK4A}$	melanoma, pancreatic, lung, bladder, head and neck, colorectal, breast	IHC, PCR, sequencing	
$p14^{ARF}$	lung, bladder, head and neck, colorectal, breast	IHC, PCR, sequencing	
BRCA1	breast, ovarian	PCR, sequencing	
BRCA2	breast, ovarian	PCR, sequencing	
LKB1	lung, gastrointestinal, pancreatic, cervical, melanoma	PCR, sequencing	
VHL	kidney, adrenal, hemangioblastoma	PCR, sequencing	
APC	colorectal, gastric	PCR, sequencing	
FBXW7	ALL, bile duct, colorectal, gastric, endometrial, lung, pancreatic, prostate, ovarian	PCR, sequencing	
Rb	retinoblastoma, lung, bladder, esophageal, osteosarcoma, glioma, liver, CML, prostate, breast	IHC, PCR, sequencing	
NF1	neurofibroma, neuroblastoma, glioma, colorectal	PCR, sequencing	
NF2	meningioma, schwannoma, glioma	PCR, sequencing	

Abbreviations: ALL, acute lymphoblastic leukemia; *AML*, acute myelogenous leukemia; *CML*, chronic myeloid leukemia; *FISH*, fluorescent in situ hybridization; *IHC*, immunohistochemistry; *PCR*, polymerase chain reaction.

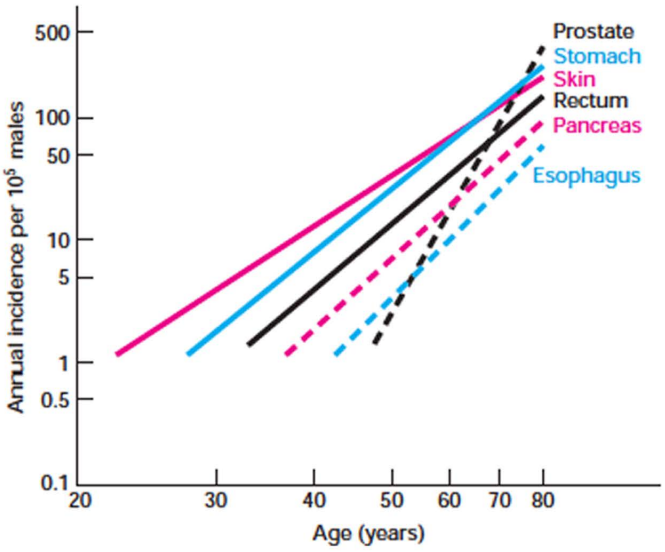
3. ***for most types of malignancies (not without exception), it takes at least a half dozen genes to become defective before the tumor really gets going and is properly termed "cancer"***

a] ***with each additional mutation, the cells acquire more and more cancer-like properties***

b] ***these mutations are (mostly) random, meaning that every cancer is different, technically, from any other cancer – even of the same type – and that the life history of each tumor can vary depending on the order it acquires the different malignant behaviors***

4. the most important point though is that CANCER IS A CONTINUOUSLY-EVOLVING PROCESS, AND IT USUALLY TAKES YEARS TO DECADES FOR ALL THE GENES TO GO BAD AND ALL THE MALIGNANT BEHAVIORS TO DEVELOP

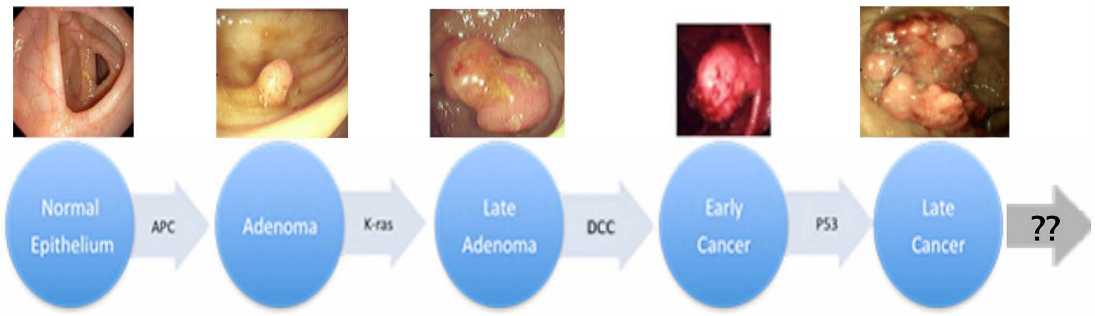
a] this explains why cancer is *usually* a disease of older people

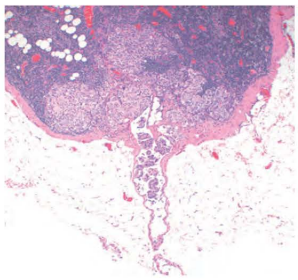


The incidence of human cancers increases as a function of age. The marked increase in the incidence with age is consistent with the multi-hit model of cancer induction. Note that the logarithm of annual incidence is plotted versus the logarithm of age. [From B. Vogelstein and K. Kinzler, 1993, *Trends Genet.* **9**:101.]

b] in cases where cancer occurs earlier in life, it is sometimes the case that the patient has already inherited one or more of the genetic defects from a parent, meaning that it would take less time overall for the rest of the mutations to accumulate and the tumor to develop

c] for several types of cancer, the cancer process (termed "**tumor progression**") can actually be observed at different stages by looking at tissue samples

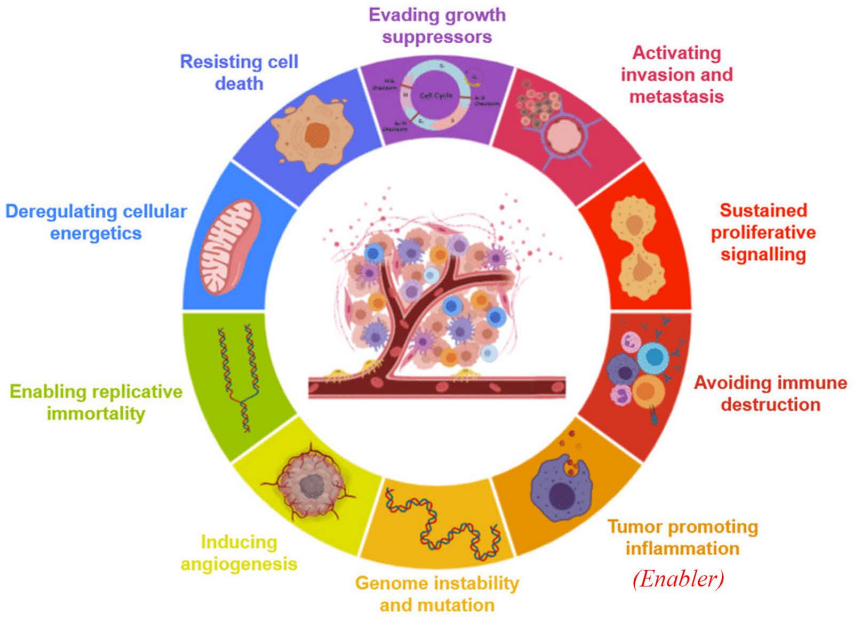




Invasion of cells from the main tumor mass into nearby lymph nodes signals the beginning of the metastasis process; further spread to distant sites often follows

A classic example of tumor progression is seen in colon cancer, where the lining of the colon starts off normal, then develops polyps, the polyps grow, they invade through the colon lining to deeper tissues (at which point they are considered "cancerous"), and finally, metastasize to distant locations in the body. ***For many cancers (but again, not all), the last step in tumor progression is the ability to metastasize, which is what frequently ends up killing the patient.***

OK, so...what, exactly, are these malignant behaviors or phenotypes that make cancer cancer?



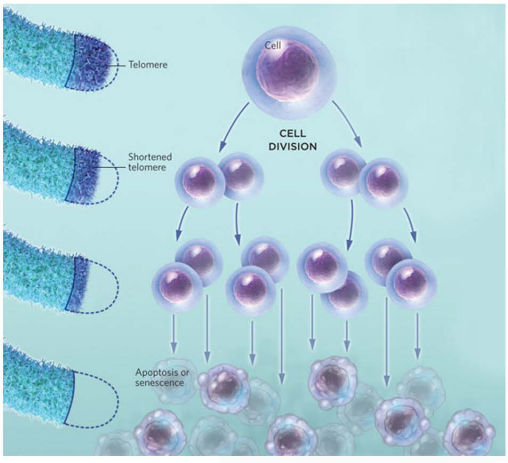
Nanomaterials 2020;*10*:1274.

There are currently ten different malignant phenotypes that have been identified, with some applying to individual tumor cells, and others that only emerge once the tumor has grown in size to a millimeter or two in diameter

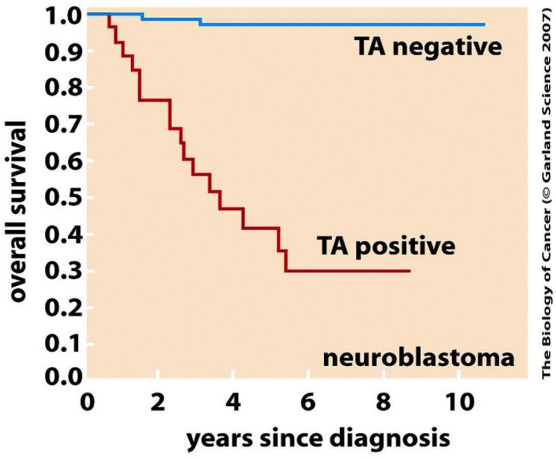
Although these "hallmarks of cancer" are generally true, there are *always* exceptions (e.g., tumors that haven't yet acquired all the hallmarks, yet are still considered cancer; a few normal tissues that also possess some of the hallmarks, but aren't considered cancer, etc.).

Two of the ten malignant phenotypes are sometimes termed "enablers" in that they facilitate the acquisition of the other hallmarks.

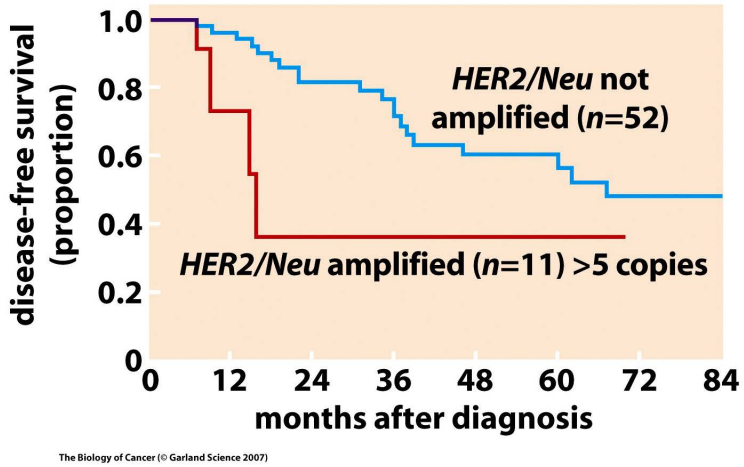
a) **Immortalization** – the ability of tumor cells to divide indefinitely, which is definitely NOT the case for normal cells, which only divide a finite number of times and then undergo *senescence* (which is the main reason why we all have limited lifespans); this can be caused by the inappropriate turning on of the gene for the enzyme ***telomerase***



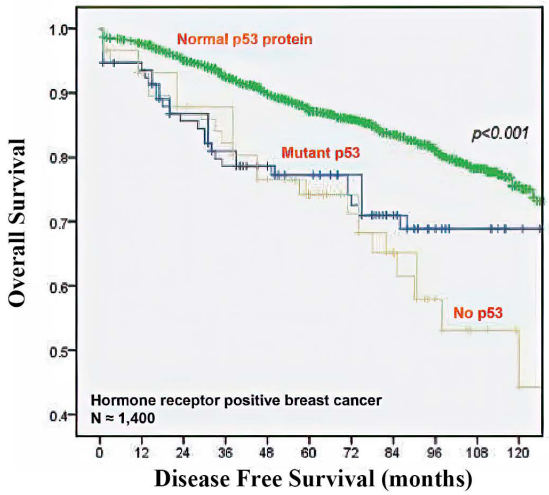
Telomeres cap the ends of chromosomes, and progressively shorten over our lifetimes until the cell stops growing... unless there's telomerase, in which case the cell can continue to grow indefinitely ("immortalized")



b) **Ability to continue proliferating in the absence of "grow" signals** - this is commonly the result of the activation of oncogenes that produce too many and/or defective proteins that get stuck in the "on" position (e.g., the ***HER2/neu*** oncogene in breast cancer)

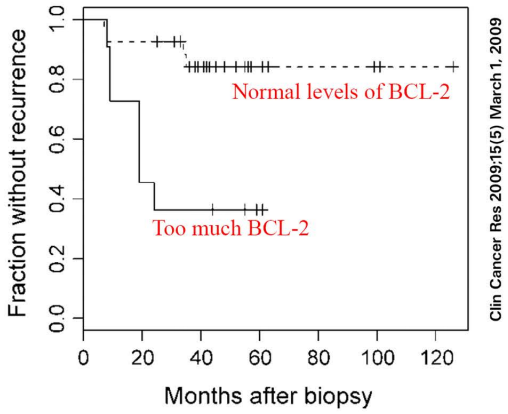


c) **Continued proliferation even in the presence of "stop" signals** - this often happens as a result of the mutation or loss of one or more tumor suppressor genes (e.g., *Rb* or *p53*)

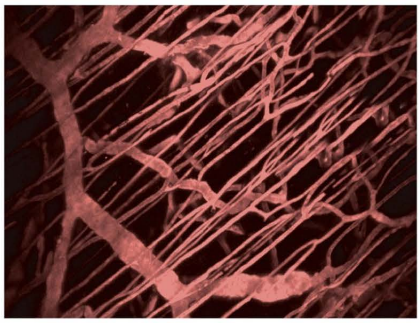


d) **Loss of Cellular "Suicide" or Apoptosis** – many tumor cells have lost the ability to commit suicide in the face of genetic damage that could be detrimental to the host; on the other hand, normal cells with genetic damage *do* undergo apoptosis rather than risk passing on defective genes to their progeny. For example, one genetic defect causes the production of too much of a protein called BCL-2, which makes cells more resistant to dying by apoptosis.

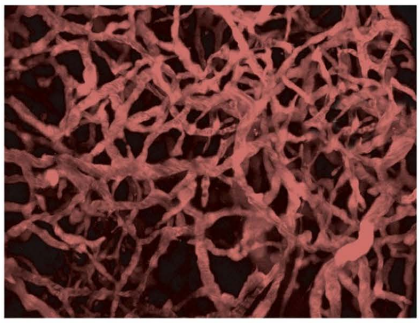
Patients with head and neck cancer have a much higher likelihood of getting a disease recurrence if their tumors overexpress or have mutant forms of the BCL-2 protein, which makes the cells more resistant to dying by apoptosis



e) **Sustained Angiogenesis** – *angiogenesis is the process by which blood vessels are repaired, or new ones formed, after a tissue is injured*, and is part of the normal healing process; tumors however, keep making new blood vessels for themselves even when they are not injured (although the vessels they do make tend to be abnormal in one or more ways); defects in the VEGF ("vascular endothelial growth factor") gene can result in too much/abnormal angiogenesis



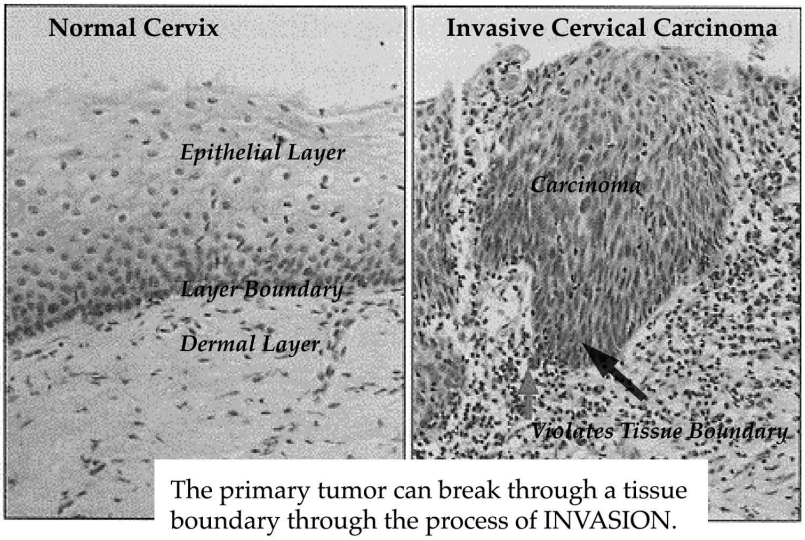
normal tissue



tumor

Hypoxia (Auckl) 5:21-32, 2017
https://doi.org/10.2147/HP.S133231

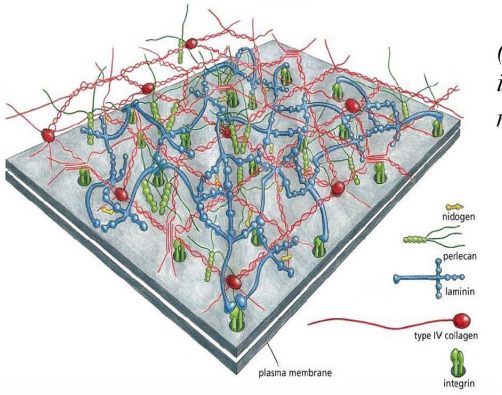
f) **Violation of Tissue Boundaries** – tumor cells have evaded a process known as "contact inhibition", i.e., they grow over and above the minimum number of cells needed to maintain a tissue's structure or function, they "climb over" other cells and ***invade*** **surrounding tissues,** and eventually, some can even leave the primary tumor site to form distant ***metastases***



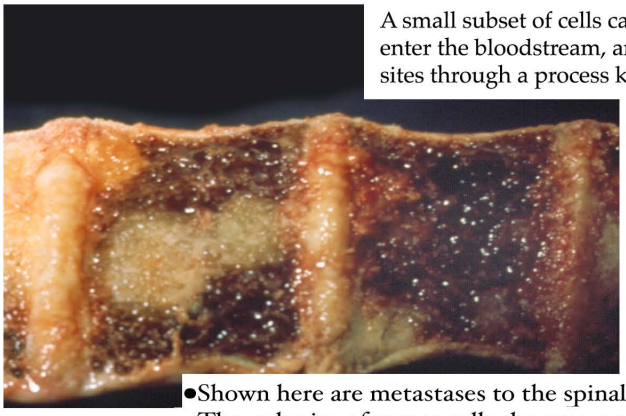
The primary tumor can break through a tissue boundary through the process of INVASION.

(If it doesn't, it can still be cancer, but just not invasive cancer...sometimes referred to as "carcinoma *in situ*".)

The tissue boundary that tumor cells must cross in order to invade and metastasize is called the "**basement membrane**", an acelllular matrix of proteins and fibers that separates tissue layers

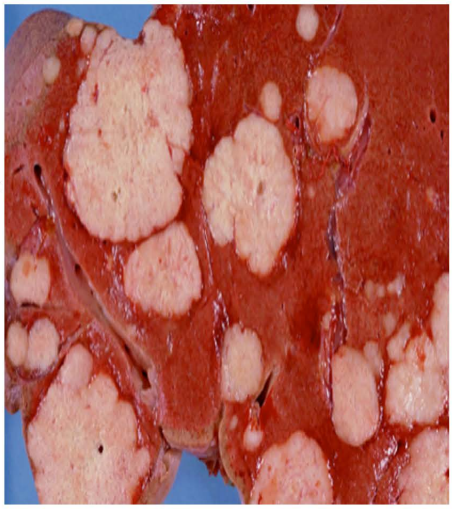


(Technically, it's not a membrane.)



A small subset of cells can detach from the primary tumor, enter the bloodstream, and re-establish themselves at distant sites through a process known as METASTASIS.

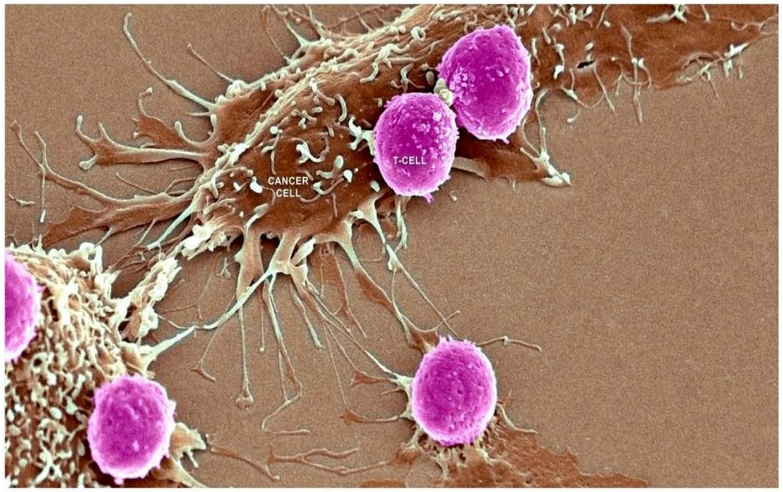
Distant metastases are responsible for approximately 90% of cancer deaths!



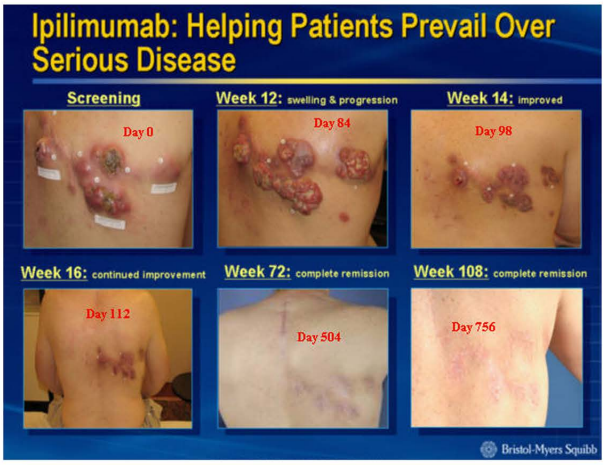
- Shown here are metastases to the spinal cord (left) and liver (right) from a patient with metastatic breast cancer. The colonies of tumor cells show up a pale color against the normal portions of the organs.

- Usually, but not always, tumors become metastatic late in their natural history, which is another reason why early detection of cancer can save lives.

g) **Evasion of the host's immune system** - most tumor cells have the ability to avoid destruction by the host's immune system by "hiding" the fact that they're foreign invaders or by turning off the immune response altogether



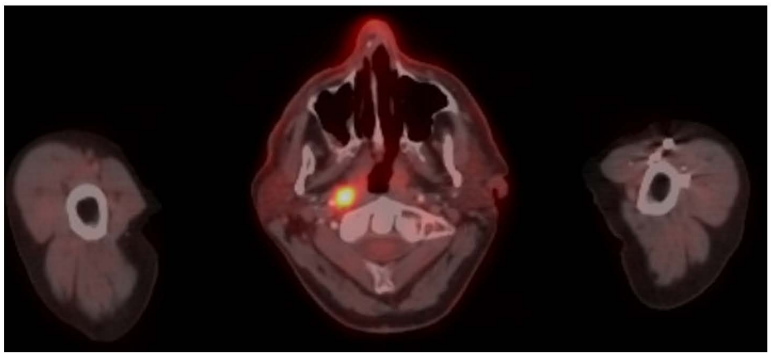
Normally, host lymphocytes would attack cancer cells as foreign invaders and kill them, however both individual tumor cells, and the environment in which the tumor mass resides (the so-called "tumor microenvironment"), act to suppress the immune system

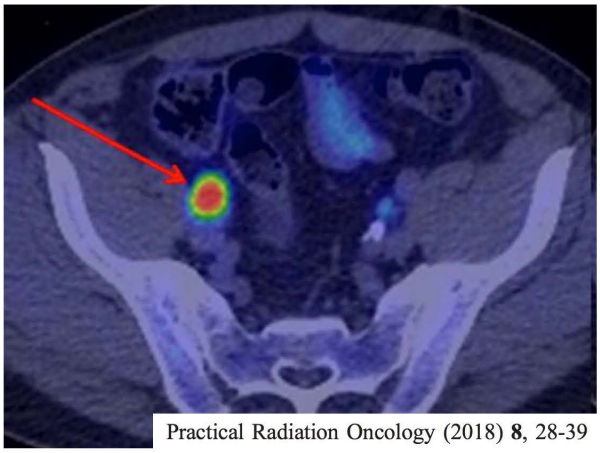


Targeted immunotherapy drugs were developed to combat immunosuppression by tumor cells and their surrounding microenvironment.

This famous example uses a drug called ipilimumab (Yervoy®), which turns the host's immune system back on, even after the tumor has turned it off. **Ipilimumab dramatically reduced deposits of melanoma in a patient with advanced disease that had become resistant to other types of cancer therapy.**

h) **"Reprogramming" of cellular metabolism** - cancer cells alter the biochemical pathways used to break down nutrients and generate energy...typically because they devote most of their time to energy-consuming processes like growth and proliferation





Practical Radiation Oncology (2018) **8**, 28-39

PET scanning detects the revved-up metabolisn of tumors compared to surrounding normal tissues

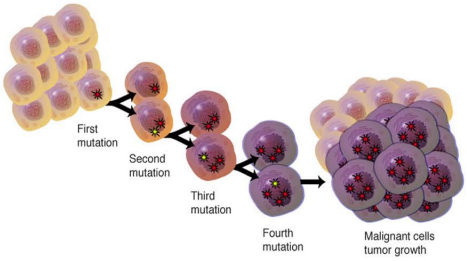
The "Enablers": are there cellular or environmental properties or characteristics that encourage cells to undergo the changes that cause them to acquire the cancer hallmarks?

A) Yes! Two of the cancer hallmarks are considered "enablers"

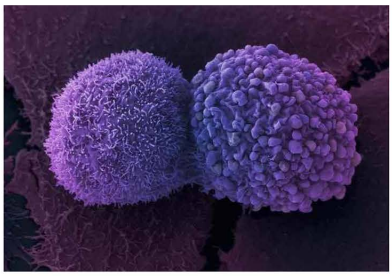
1. ***Genomic Instabilty***: a cellular property in which it becomes much easier for a cell to accumulate more and more mutations at a rate much faster than would occur naturally

a] **Researchers believe that genomic instability is one of the first - if not THE first - link in the chain that leads to cancer**. Genomic instability can explain why oncogenes become active and tumor suppressor gene inactive.

b] genomic instability is also responsible for why many tumors gradually become resistant to chemotherapy drugs as the treatment progresses, and often become more and more aggressive (i.e., more invasion and metastasis) over time



A single cancer cell in the telophase portion of mitosis gives rise to two daughter cells that look quite different thanks to genomic instability; this is how tumors become so heterogeneous

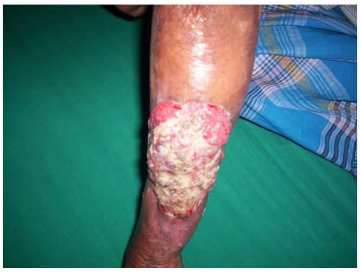


1) this is no small part of the reason why early detection of cancer is so important, before too many of these properties develop in more and more cancer cells as the tumor grows

2) it also explains why ***no two tumors are ever exactly alike, even though they may be the same type and size and appear to be similar or identical clinically-speaking***

2. **Chronic Inflammation/Irritation:** portions of a normal tissue that are chronically irritated or inflamed create a favorable environment for tumor growth; in addition, once a tumor is established, its presence adds to the inflammatory state

a. examples: esophageal cancers arising in patients with chronic acid reflux disease; stomach cancers being associated with a bacterial infection; mesothelioma being associated with asbestos, a lung irritant; skin cancers more frequently arising along clothing seams that rub against the skin or at the site of a previous skin injury (e.g., a "Marjolin's Ulcer" - see below); and finally, it goes without saying that tobacco is a major lung irritant!



Marjolin's Ulcer - a skin cancer that arises at the site of a healing wound (burns in particular), thought to be related to the chronic inflammation caused by the initial injury

When a tumor is first diagnosed and confirmed to be malignant, how does the oncologist know how many of the hallmarks it already possesses, what it's going to do next, how it will respond to treatment, how likely it is that the patient will be cured, etc.?

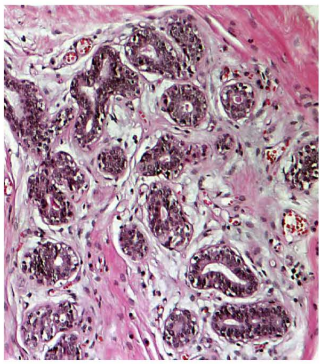
Answer: ***The oncologist never knows with absolute certainty, however there is over 120 years worth of cancer treatment experience for different tumor types that can serve as general guidelines or "educated guesses"***

1. physicians rely on various classification systems to help predict what the tumor will probably do in the future: these are referred to as the tumor's **STAGE and GRADE**, and are usually determined by the pathologist who examines samples of the patient's tumor

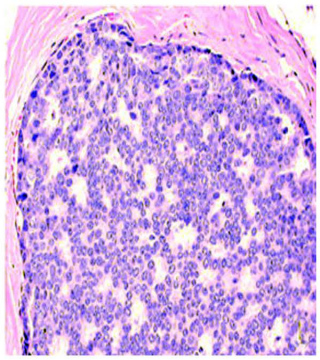
a) **Tumor Grade**: assesses the relative aggressiveness of the cancer based on the appearance and behavior of the tumor cells, e.g., how closely do they resemble their surrounding normal tissue cells, how well or poorly differentiated they've become, do the cells retain some organization, or have they completely run amok, etc.

1) *a low grade tumor is one that still retains at least some characteristics of surrounding normal cells, in terms of differentiation, organization, cellular appearance and tendency to stay put; they are less likely to have already invaded surrounding normal tissues or metatasized to distant locations, and are therefore more likely to respond to treatment and be cured*

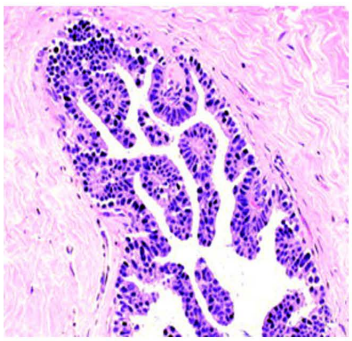
2. *a high grade tumor is characterized by cells that have lost most or all of their tissue-specific differentiation, so wouldn't resemble their normal counterparts at either the cellular or tissue levels; such tumors are more likely to have already invaded surrounding tissues and might even have already metatasized by the time of diagnosis;* these tumors are less likely to respond to treatment and are usually harder to cure



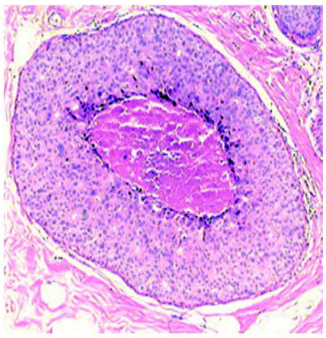
Normal Breast Ducts



Low Grade Ductal Carcinoma *In Situ* (DCIS)

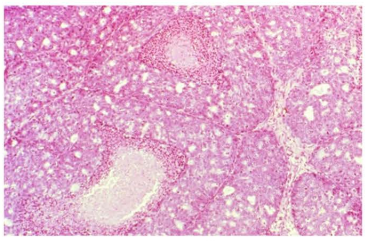


Intermediate Grade DCIS

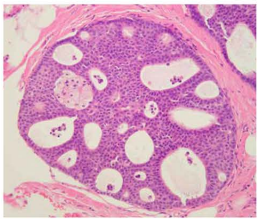


High Grade DCIS

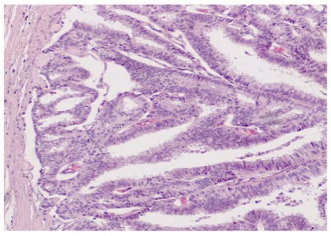
3) *for some tumor types (breast cancer, especially), the tumor's "architecture" also provides clues about its grade*



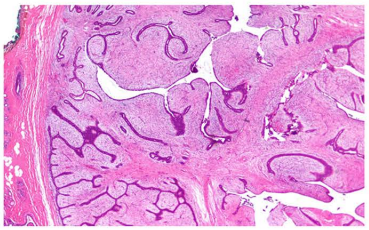
Comedo



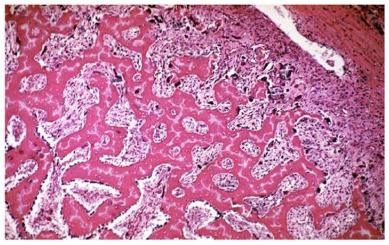
Cribiform



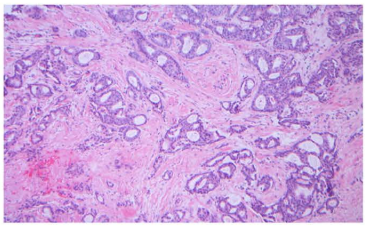
Papillary



Phylloides



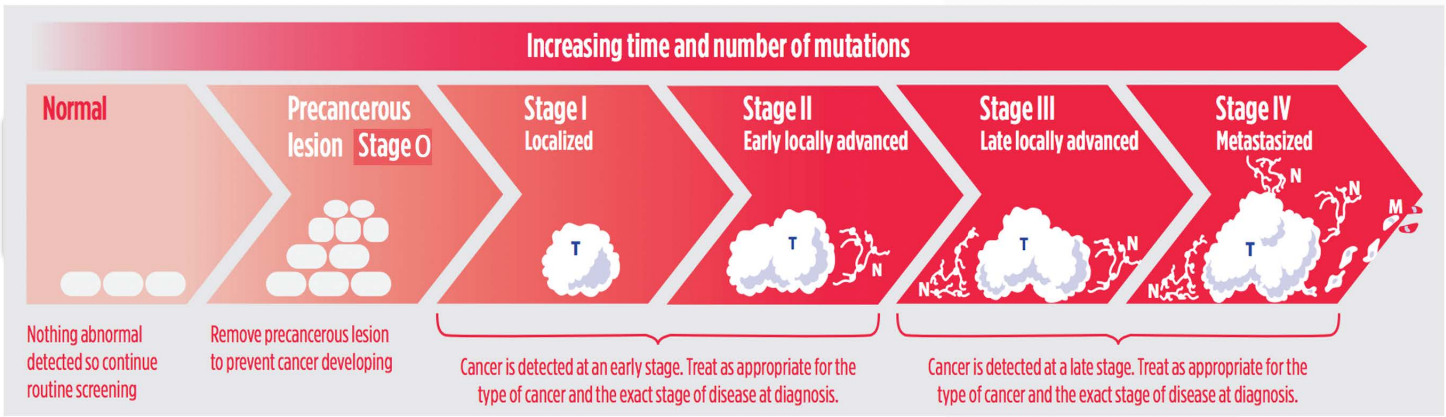
Trabecular



Tubular

b) **Tumor Stage**: refers to the size/extent/spread pattern of the tumor at the time it is first diagnosed, and is derived from both clinical examination of the patient, and pathological appearance of the tumor, and increasingly, genetic characterization of the tumor cells, i.e., which oncogenes are active and which tumor suppressor genes are inactive

1) an early stage tumor is smaller in size and spread, and more likely to be curable, whereas an advanced stage tumor is larger, has spread further, possibly metastasized to distant sites, and is less likely to be curable



2) Staging systems for tumors

a. most tumors are staged using the **TNM system** (as developed by the AJCC, "American Joint Committee on Cancer")...although there are other systems as well (e.g., FIGO system for gynecological cancers)

1] in most cases, the stage is based on four criteria:

Location of the primary (original) tumor
Tumor size and extent
Lymph node involvement
Presence or absence of distant metastasis

TNM Clinical Classification

TNM Classification	Description
PRIMARY TUMOR (T)	
Tx	Primary tumor not assessable
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1, T2, T3, T4	Increasing size and/or local extent of the primary tumor
REGIONAL LYMPH NODES (N)	
Nx	Regional lymph nodes not assessable
N0	No regional lymph node metastasis
N1, N2, N3	Increasing involvement of regional lymph nodes
DISTANT METASTASIS (M)	
Mx	Presence of distant metastasis not assessable
M0	No distant metastasis
M1	Distant metastasis

From American Joint Committee on Cancer· *AJCC cancer staging manual*, ed 6, Chicago, 2002, American Joint Commission on Cancer.

b. then, ***the various TNM values are grouped together into different stages from I - IV, and in some cases, substages indicated with "A", "B" or "C"***; note that the specifics of the staging can vary from tumor type to tumor type (i.e., a Stage II lung cancer might have different specifications than a Stage II breast cancer)

c) in addtion to grade and stage, is there anything else useful for predicting patient response to treatment or treatment outcome?

1) **Karnofsky Performance Status** - allows patients to be classified according to their overall health and ability to function, which is used to compare effectiveness of different therapies and to assess the prognosis in individual patients

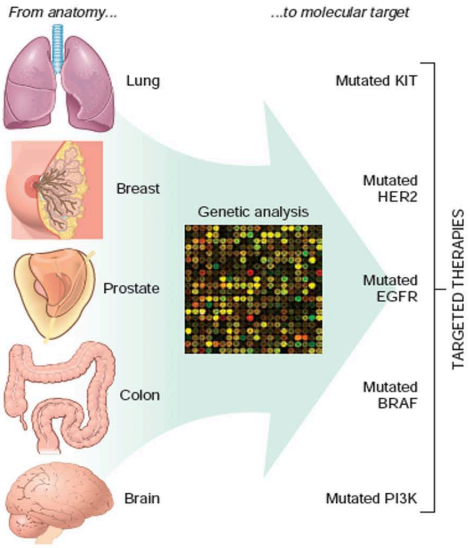
Karnofsky Performance Scale

PERFORMANCE CRITERIA		
Able to carry on normal activity; no special care needed	100	Normal; no complaints; no evidence of disease
	90	Ability to carry on normal activity· minor signs or symptoms of disease
	80	Normal activity with effort; some signs or symptoms of disease
Unable to work; able to live at home and care for most personal needs; a varying amount of assistance needed	70	Self-care; inability to carry on normal activity or do active work
	60	Occasional care for most needs required
	50	Considerable assistance and frequent medical care required
	40	Disabled; special care and assistance required
Unable to care for self; required equivalent of institutional or hospital care; disease may be progressing rapidly	30	Severely disabled; hospitalization indicated, although death not imminent
	20	Extremely sick; hospitalization necessary; active support treatment necessary
	10	Moribund; fatal processes progressing rapidly
	0	Dead

Modified from Carter S, et al: *Principles of cancer treatment*, New York, 1982, McGraw-Hill.

Everything else being equal, the lower the Karnofsky score, the worse the patient's cancer outcome

2) **Molecular Profiling** - increasingly, the genetics and molecular biology of cancer cells from individual patients' tumors are being used both to supplement grading and staging systems, as well as to help "individualize" patient treatment



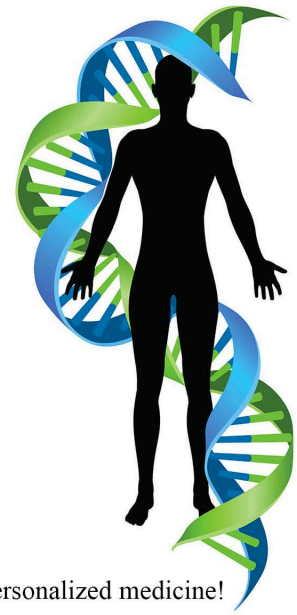
A paradigm shift: classification of cancer according to therapeutic targets rather than cell of origin and morphology. (Courtesy Dr. Levi Garraway, Dana Farber Cancer Institute.)

Genetic analysis of tumors can reveal specific mutations associated with the acquisition of the cancer hallmarks, which in turn can inform what types of drugs should be used (often, in combination with radiation).

The most progress in this regard has been in breast cancer, where at least four different molecular subtypes of the disease have been identified, each of which is treated differently.

Recently, the FDA approved the first molecularly-targeted drug whose use is based solely on the presence of specific genetic defects in a patient's tumor... NOT on its grade, stage or even its type!

This has been termed a "tumor agnostic" approach.



Personalized medicine!

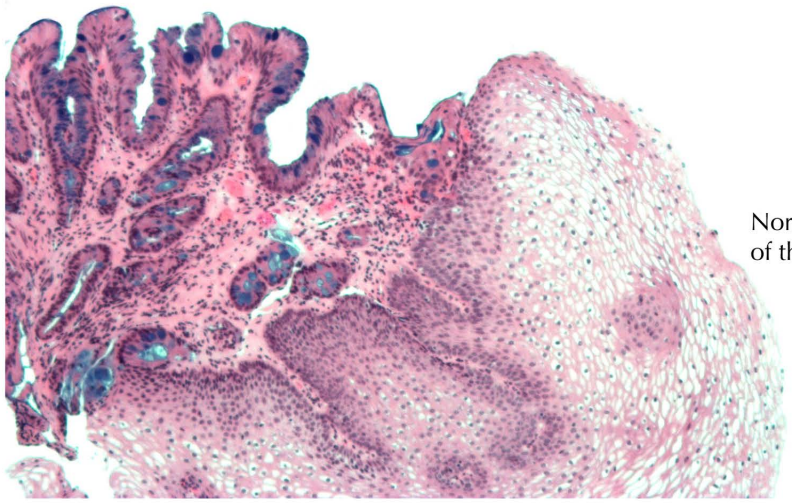
Know Your '-plasias'

Neoplasia = "*new growth*", which could be benign or malignant; malignant neoplasms contain cells that have already acquired most or all of the "hallmarks of cancer", whereas benign neoplasms might have, at most, a couple

Metaplasia = "*changed growth*", is the reversible replacement of one differentiated cell type with another differentiated cell type. The change from one type of cell to another is generally caused by some sort of abnormal stimulus. If the stimulus that caused metaplasia is removed or ceases, tissues return to their normal pattern of differentiation.

Metaplasia is sometimes associated with the subsequent development of cancer (possibly because it is also associated with inflammation and irritation), but is not cancerous itself, and doesn't directly become cancerous

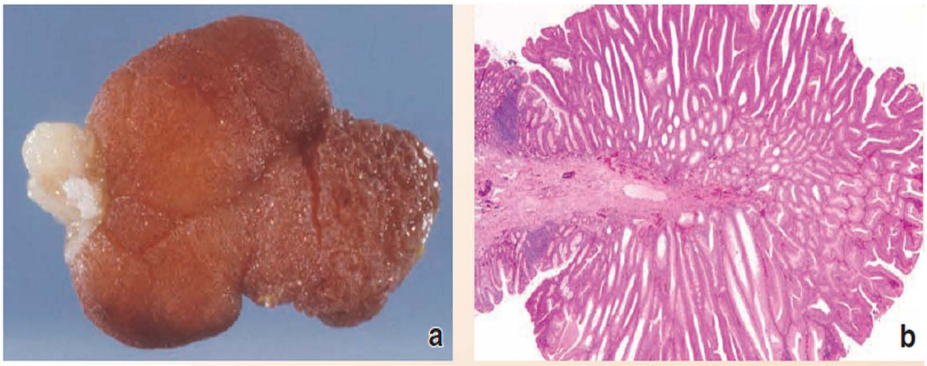
Region of metaplasia to a more glandular epithelium as a result of chronic acid reflux



Normal squamous epithelium of the esophagus

Hyperplasia = "*over growth*", refers to the proliferation of cells within an organ or tissue beyond that which is ordinarily seen. Hyperplasia may result in the gross enlargement of an organ, the formation of a benign tumor, or may be visible only under a microscope.

Hyperplasia is thought to be an early step in the cancer process, but is not yet considered cancer *per se*; while this condition is not reversible (unlike metaplasia), hyperplastic cells do not necessarily progress further to become cancerous...but might



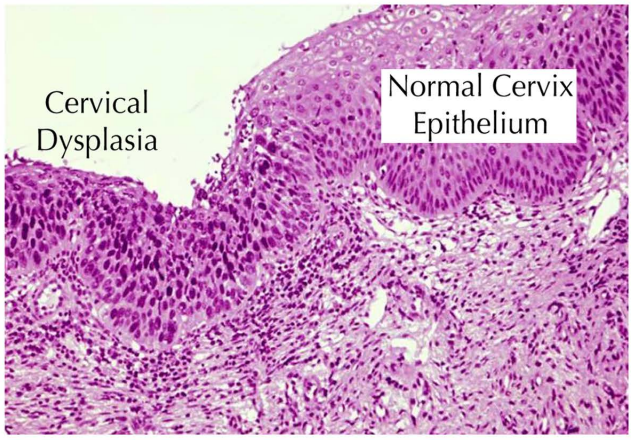
Adenomatous polyp of the large intestine. a. This image shows a macroscopic view of the polyp (about 2 cm in diameter) that was surgically removed from the large intestine during endoscopic colonoscopy. It has a characteristic bosselated surface (with rounded swellings) and a stalk by which it attaches to the wall of the colon. **b.** This photomicrograph was obtained from the center of the polyp.

A colon polyp – a benign adenoma – which is obviously overgrown compared to the normal lining of the colon. These are routinely removed during a screening colonoscopy...just in case.

Dysplasia = *"disorganized or 'bad' growth"*, is a term used to describe an abnormality in the maturation of cells within a tissue. This generally consists of an expansion of immature cells, with a corresponding decrease in the number and location of mature cells. Dysplasia is an early – to – intermediate step in the cancer process, and usually progresses further. Dysplastic cells may already have acquired several of the "hallmarks".

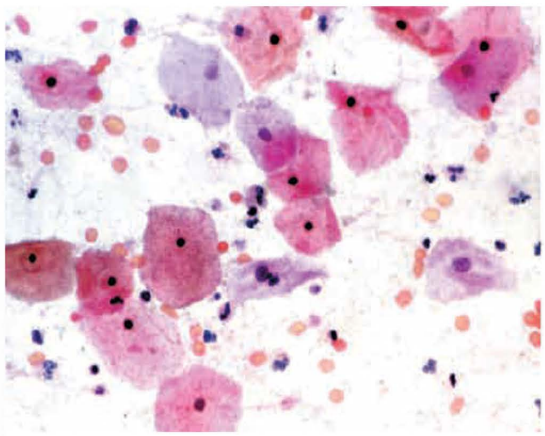
Dysplasia is characterised by four pathological changes:

1. Anisocytosis (cells of unequal size)
2. Poikilocytosis (abnormally shaped cells)
3. Hyperchromatism (dark staining nuclei)
4. Too many cells in mitosis



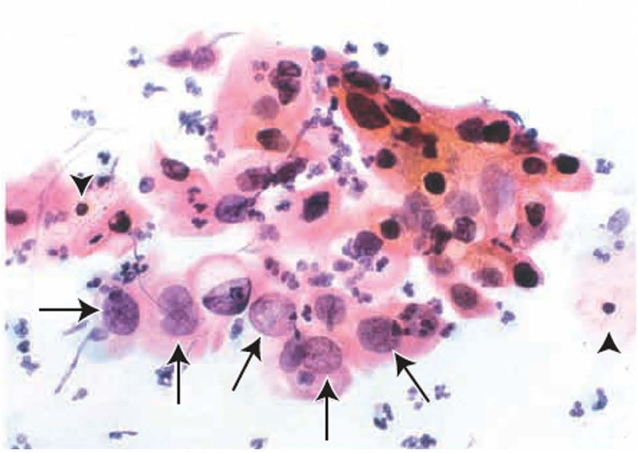
Anaplasia = *"backwards growth"* refers to a reversal in cellular differentiation, and is considered a full malignancy that already possesses most or all of the hallmarks of cancer. The nuclei of anaplastic cells are characteristically extremely hyperchromatic (darkly stained), large, and variable in size and shape. The nuclear-cytoplasmic ratio may approach 1:1 instead of the normal 1:4 or 1:6. Giant cells that are considerably larger than their neighbors may be formed and possess either one enormous nucleus or several small nuclei (*"syncytia"*).

Anaplastic cells display marked ***pleomorphism*** (*"many forms"*).



Normal cervical cells

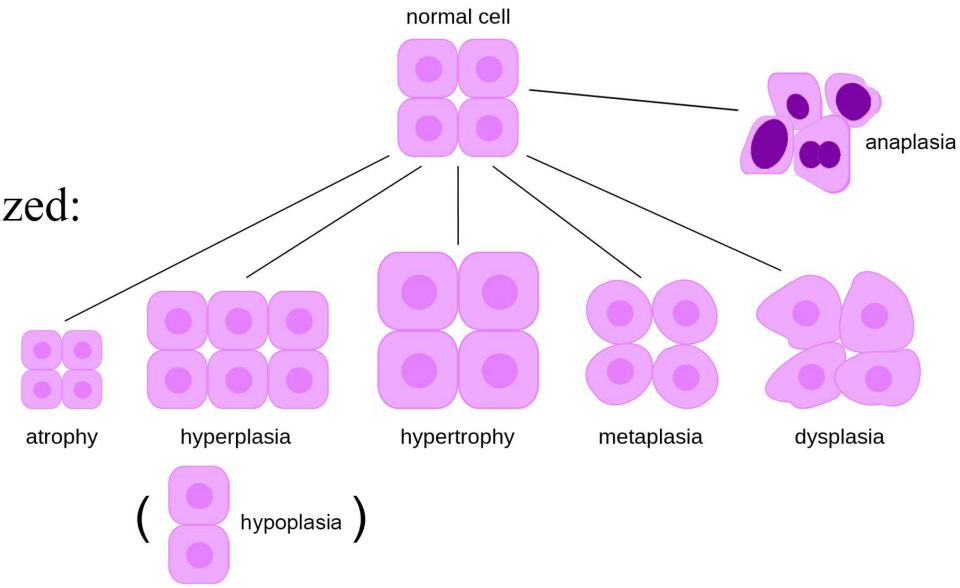
Mature cells of the squamous epithelium are regular in size and shape with small, distinct nuclei



Anaplastic cervical carcinoma

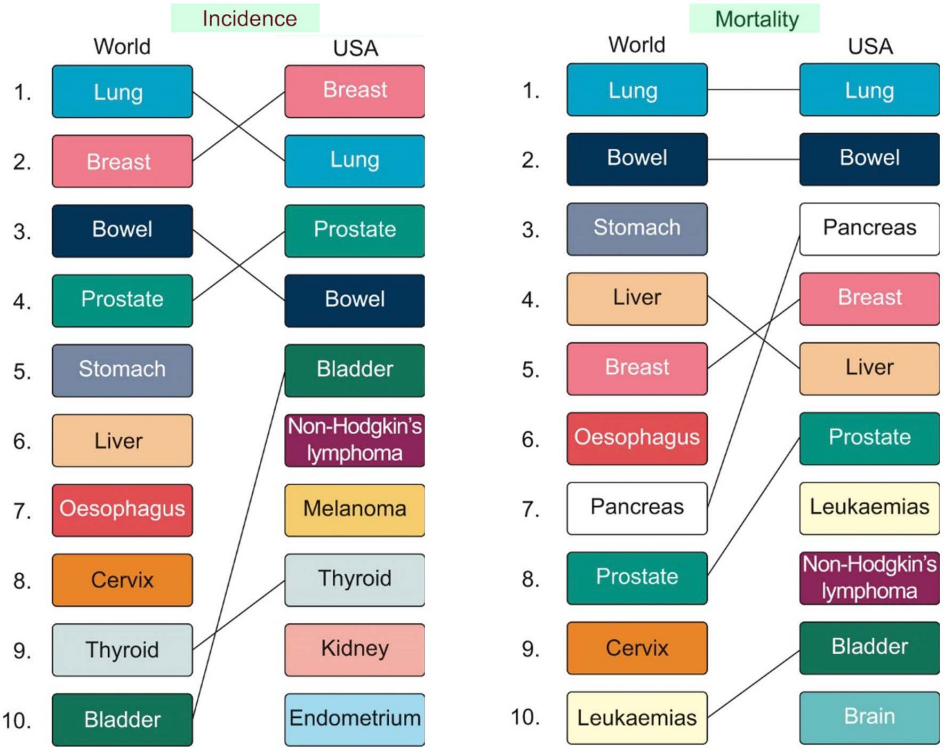
The transformed epithelium is darker, more dense and cohesive. Nuclei are crowded, abnormal and in disarray

The “plasias” summarized:



Cancer: A Global Perspective

The most prevalent and deadly cancers in the US are not always the same as in the rest of the world (but often, they’re close)



World cancer factoids:

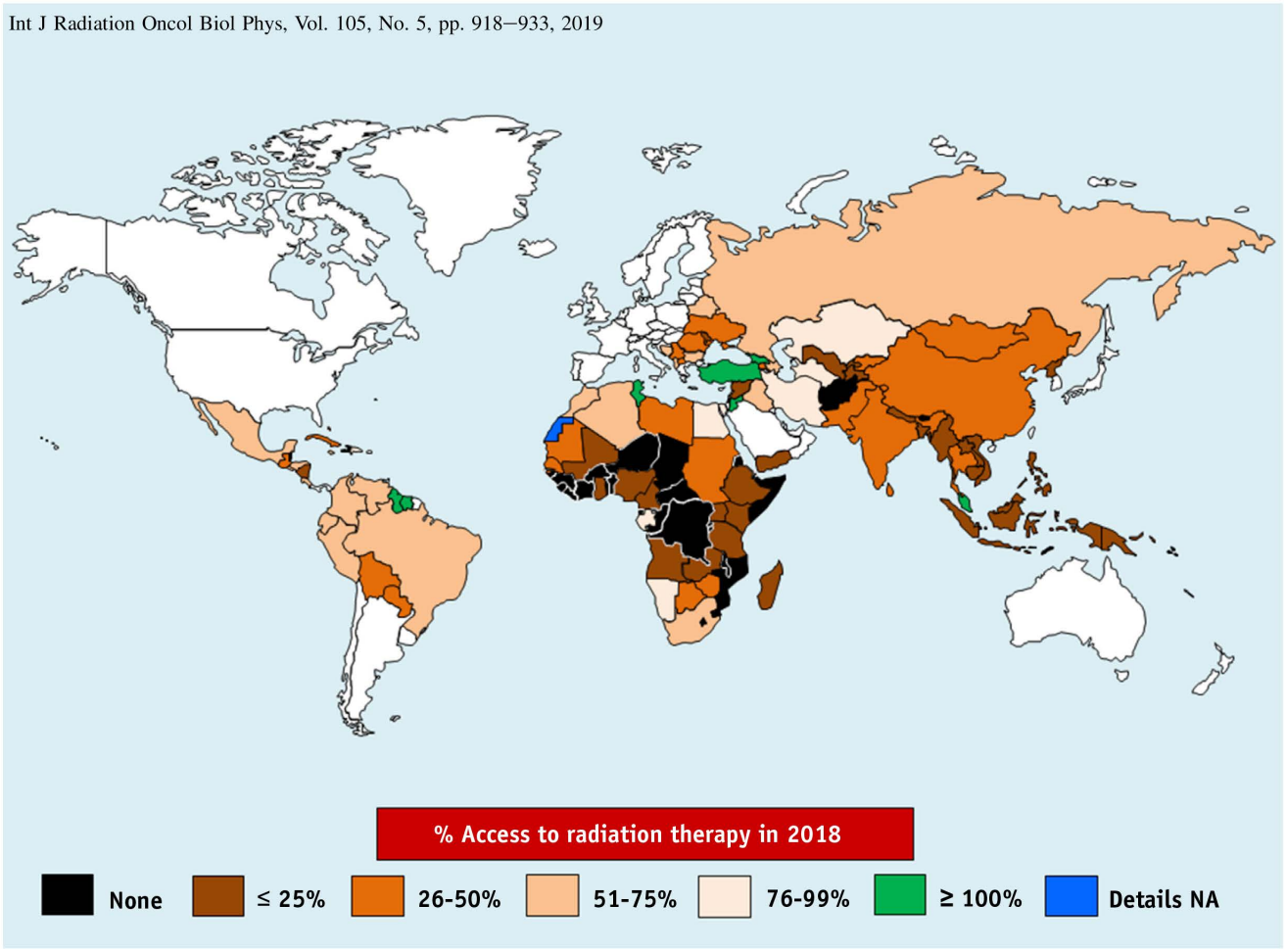
• 70% of all cancer deaths occur in low and middle income countries (LMICs)

• in LMICs, 25% of all cancers due to carcinogenic infectious diseases

• 35% of all cancer deaths due to modifiable risk factors:

obesity
low fruit and vegetable intake
lack of exercise/sedentary lifestyle
smoking (22% of all cancer deaths)

In many parts of the world, radiation therapy services are quite limited, and in some regions, practically nonexistent



Percentage access to radiation therapy by patients in 2018 in low- and middle-income country (LMIC) groups. No teletherapy facilities exist in 51 of the 137 LMICs.