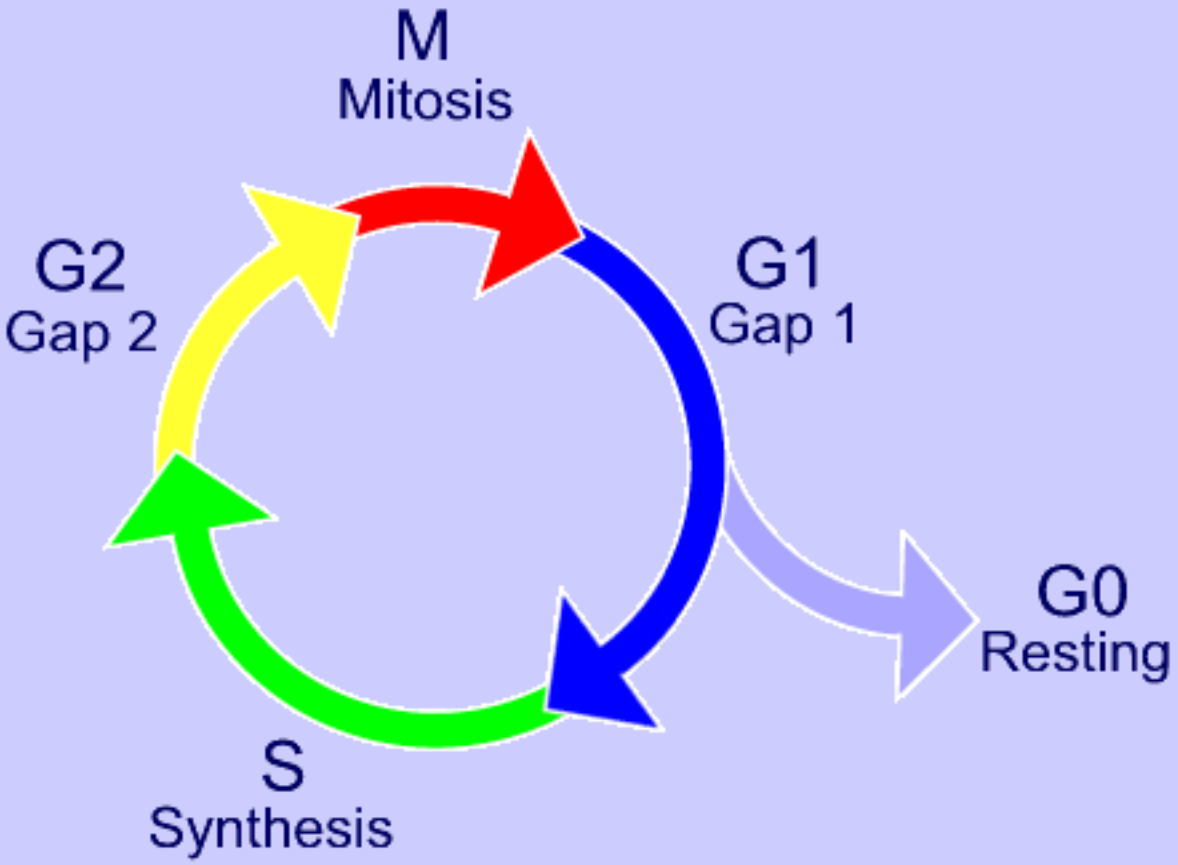
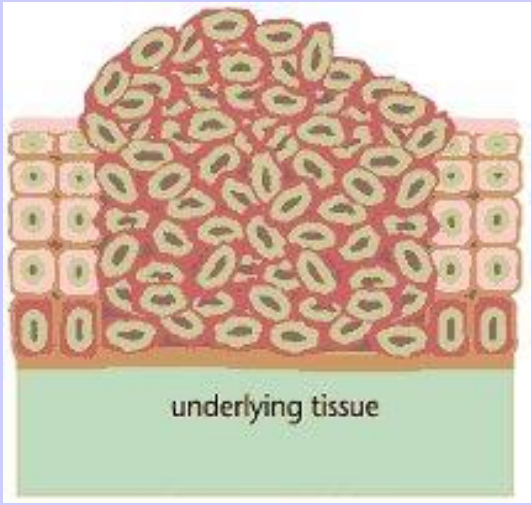
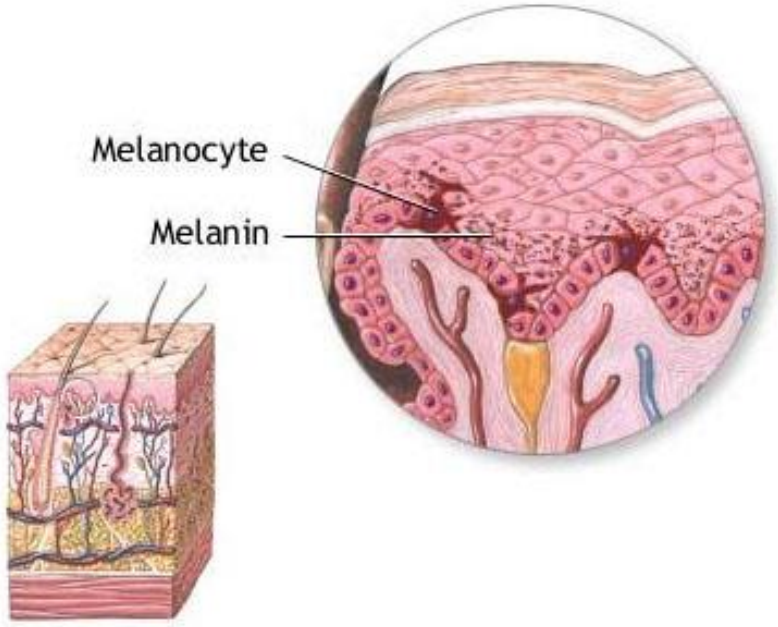
CH 12 NOTES, part 2:
Regulation of the Cell Cycle (12.3)

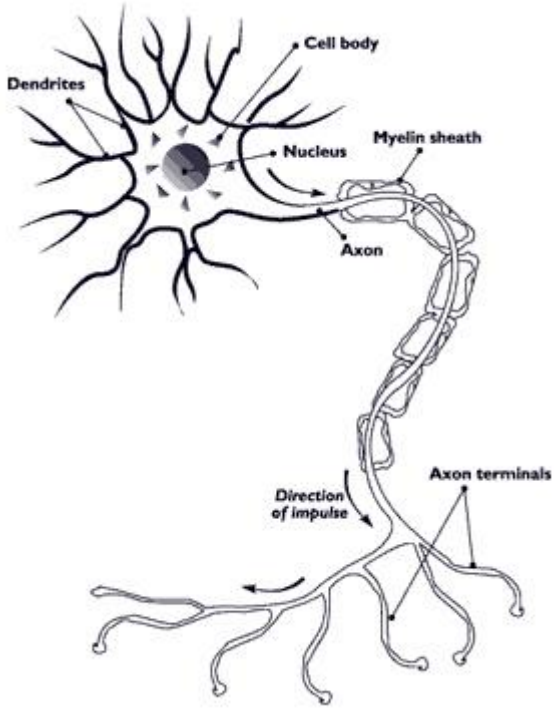




12.3 - The eukaryotic cell cycle is regulated by a molecular control system

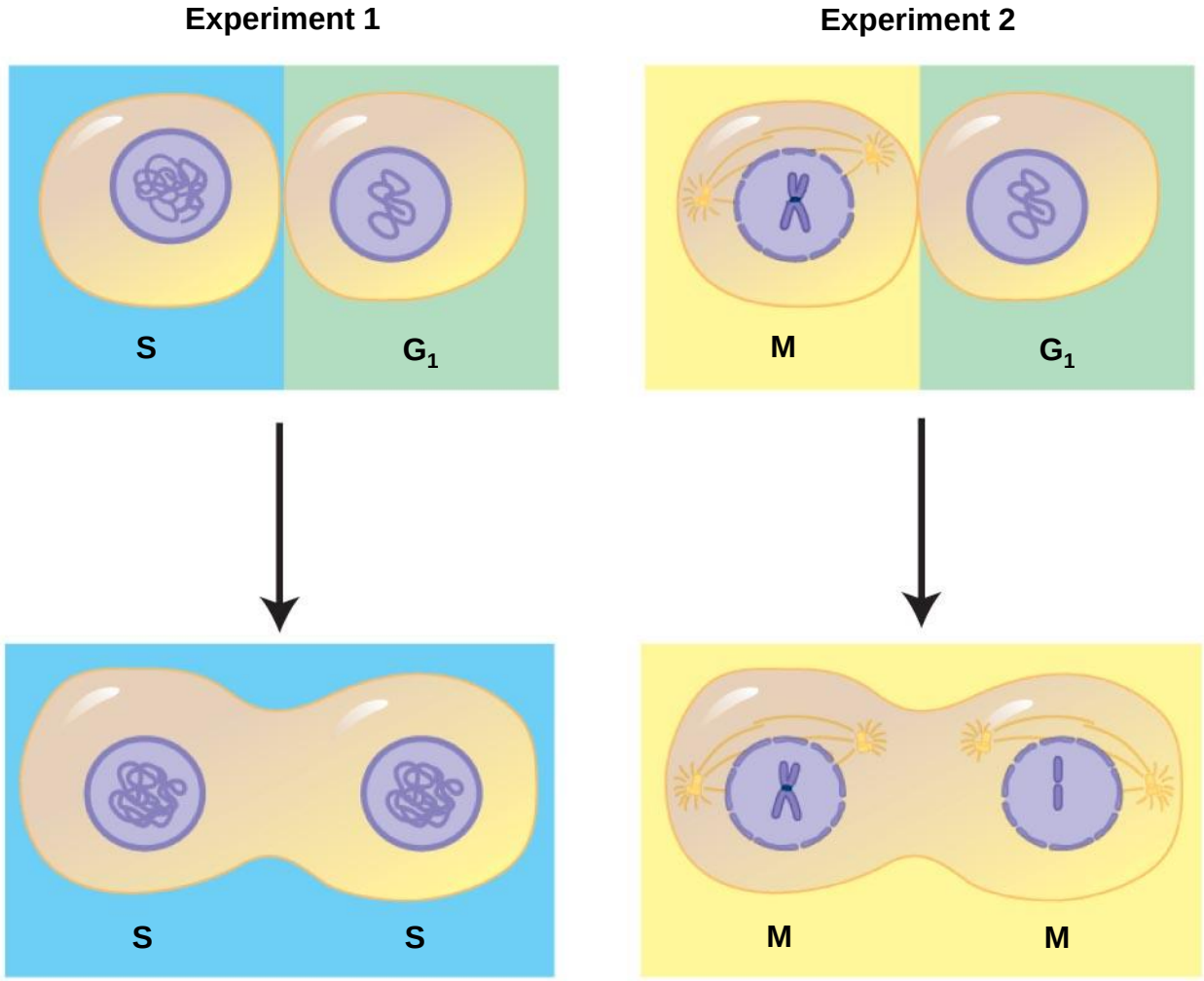
- The frequency of cell division varies with the type of cell:
  - ➔ **human skin cell: every 24-28 hrs**
  - ➔ **human nerve cell: never after maturity**
  - ➔ **frog embryo cell: every hour**
- These cell cycle differences result from regulation at the molecular level


Melanocyte
Melanin


Cell body
Dendrites
Nucleus
Myelin sheath
Axon
Axon terminals
Direction of impulse

Evidence for Cytoplasmic Signals

- The cell cycle appears to be driven by specific chemical signals present in the cytoplasm
- Some evidence for this hypothesis comes from experiments in which cultured mammalian cells at different phases of the cell cycle were fused to form a single cell with two nuclei

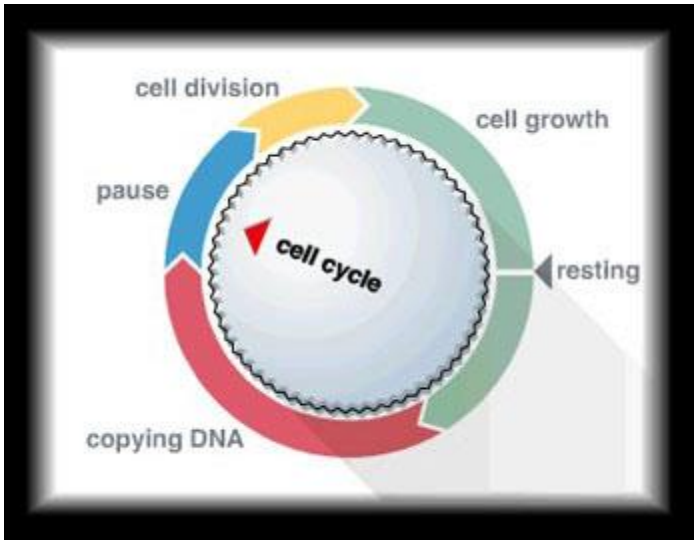


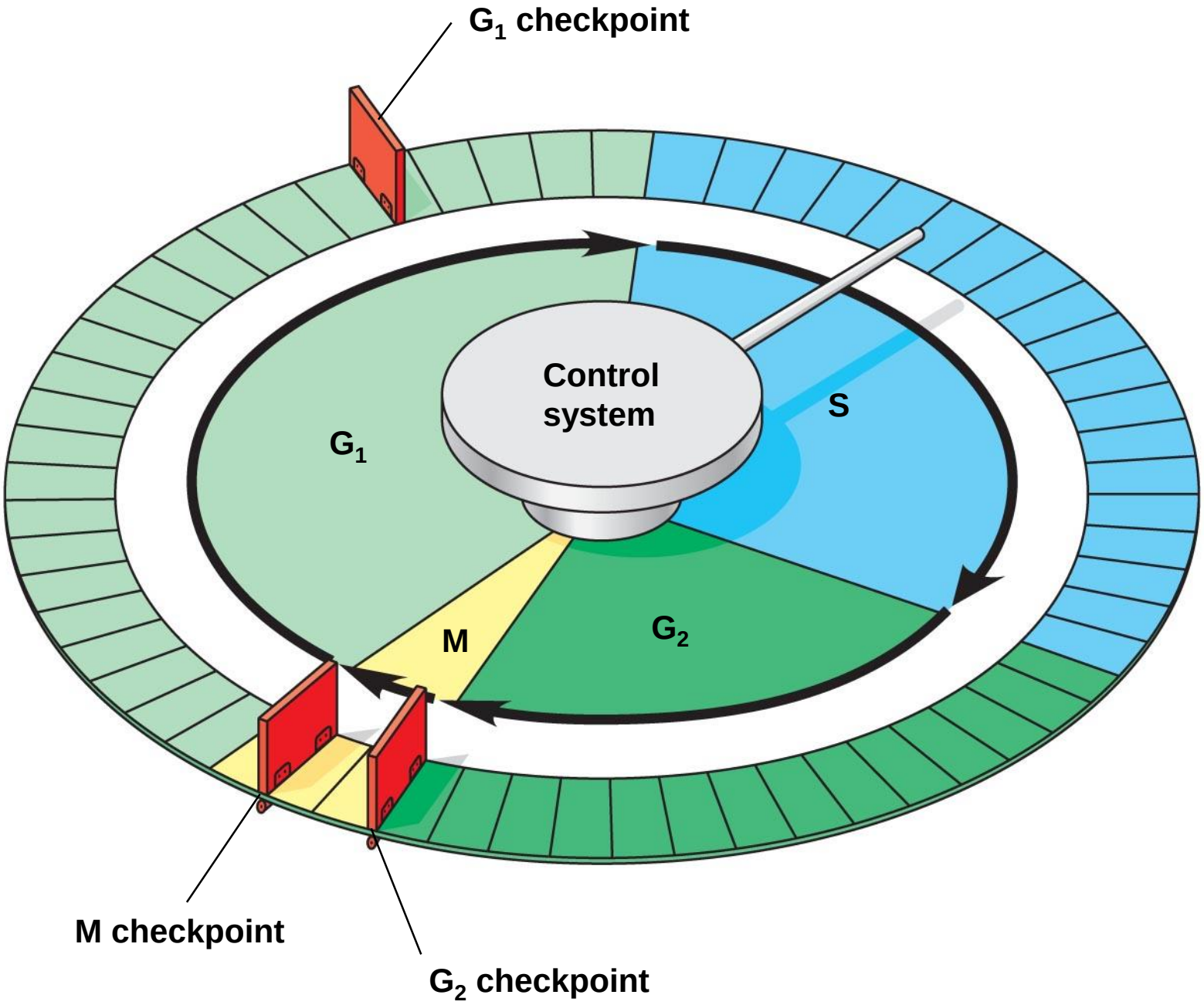
When a cell in the S phase was fused with a cell in G_1, the G_1 cell immediately entered the S phase—DNA was synthesized.

When a cell in the M phase was fused with a cell in G_1, the G_1 cell immediately began mitosis—a spindle formed and chromatin condensed, even though the chromosome had not been duplicated.

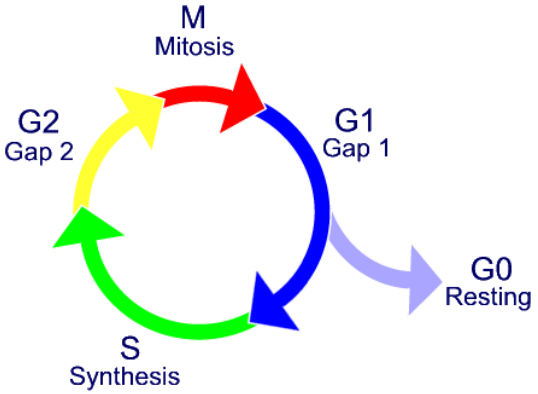
The Cell Cycle Control System

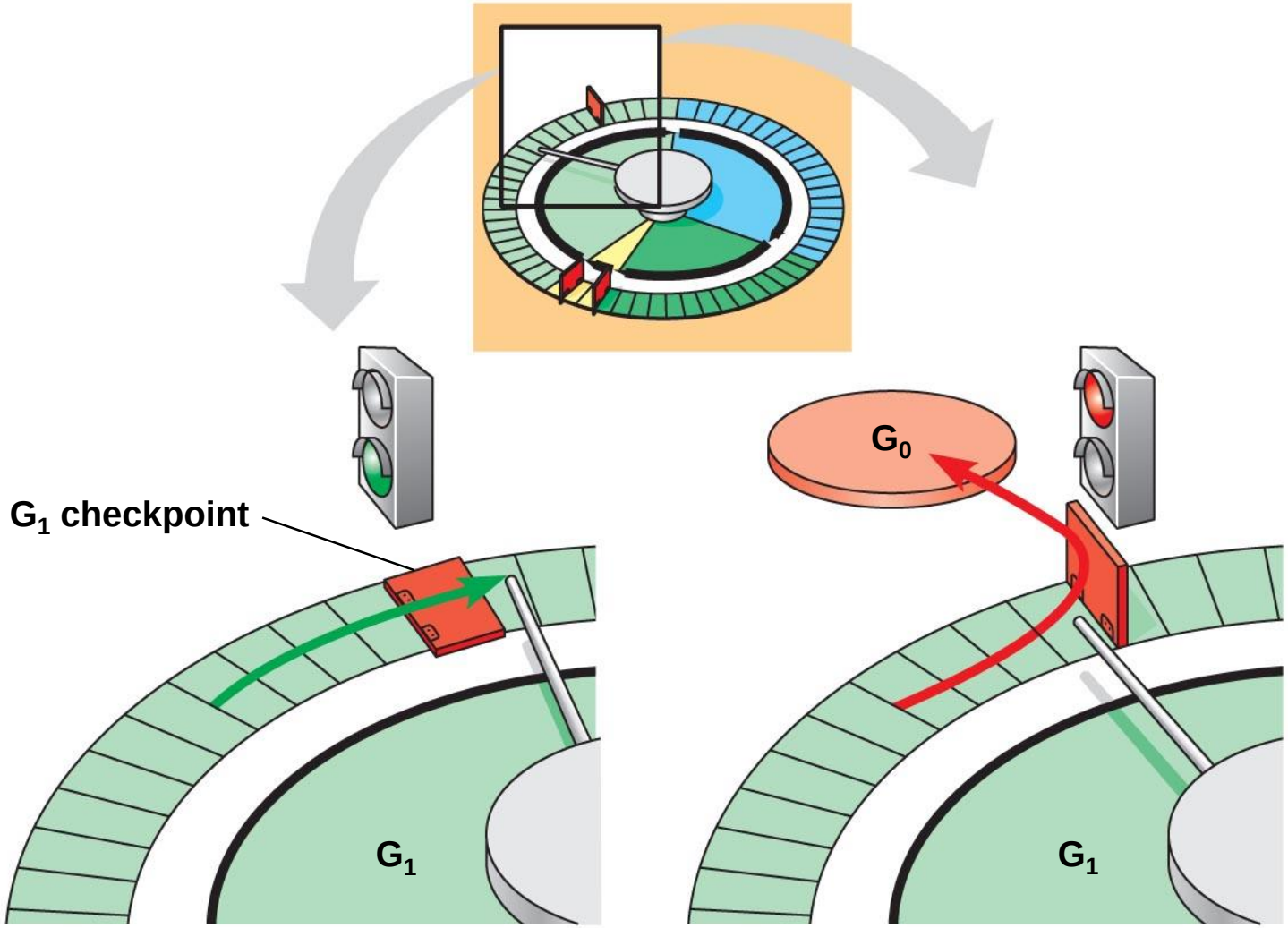
- The sequential events of the cell cycle are directed by a distinct cell cycle control system, which is similar to a built-in clock
- The clock has specific **checkpoints** where the cell cycle stops until a go-ahead signal is received





- For many cells, the **G_1 checkpoint** seems to be the most important one
- If a cell receives a go-ahead signal at the G_1 checkpoint, it will usually complete the S, G_2, and M phases and divide
- If the cell does not receive the go-ahead signal, it will exit the cycle, switching into a nondividing state called the G_0 phase





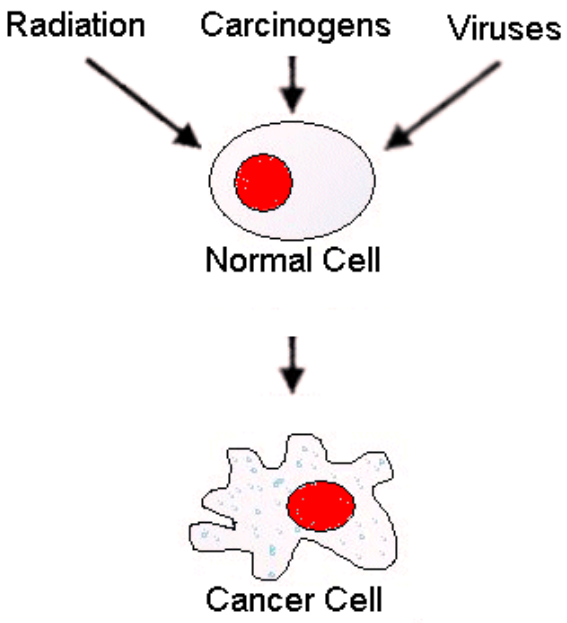
(a) If a cell receives a go-ahead signal at the G_1 checkpoint, the cell continues on in the cell cycle.

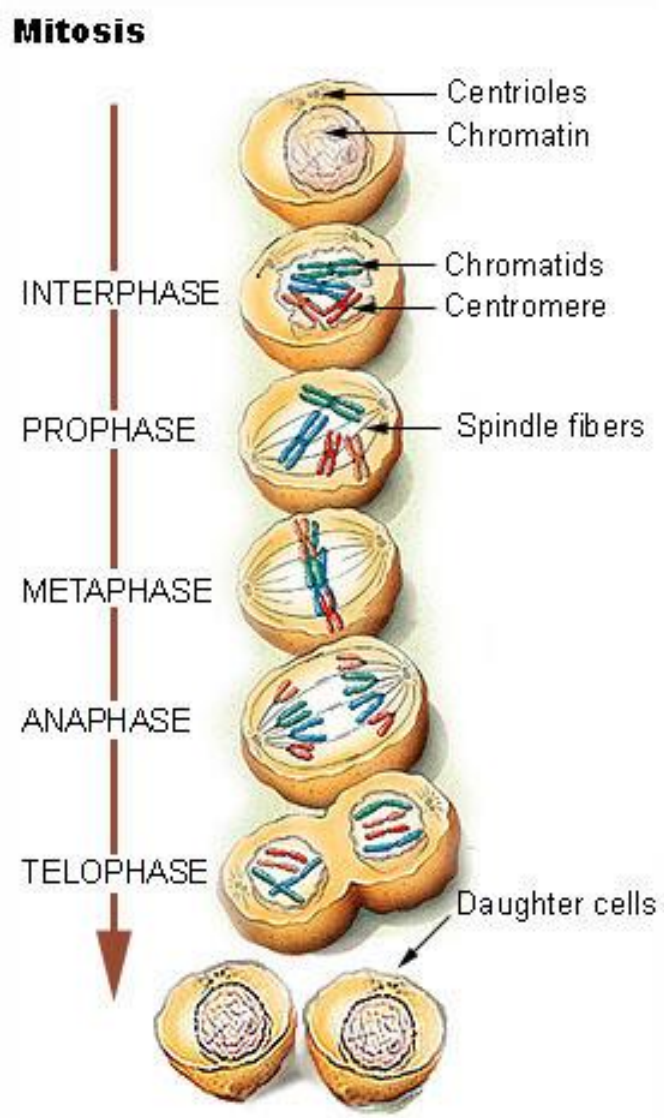
(b) If a cell does not receive a go-ahead signal at the G_1 checkpoint, the cell exits the cell cycle and goes into G_0, a nondividing state.

Researchers have identified several factors that can influence cell division:

1) Chemical factors

2) Physical Factors





External CHEMICAL FACTORS – Nutrients & Growth Factors:

- if essential **NUTRIENTS** are left out of the culture medium, cells will not divide.

- **GROWTH FACTORS** = specific regulatory proteins released by certain body cells that stimulate other cells to divide

  ➔ **PDGF (platelet derived growth factor)** binds to cell membrane receptors and stimulates cell division in fibroblasts (i.e. as a response to heal wounds)

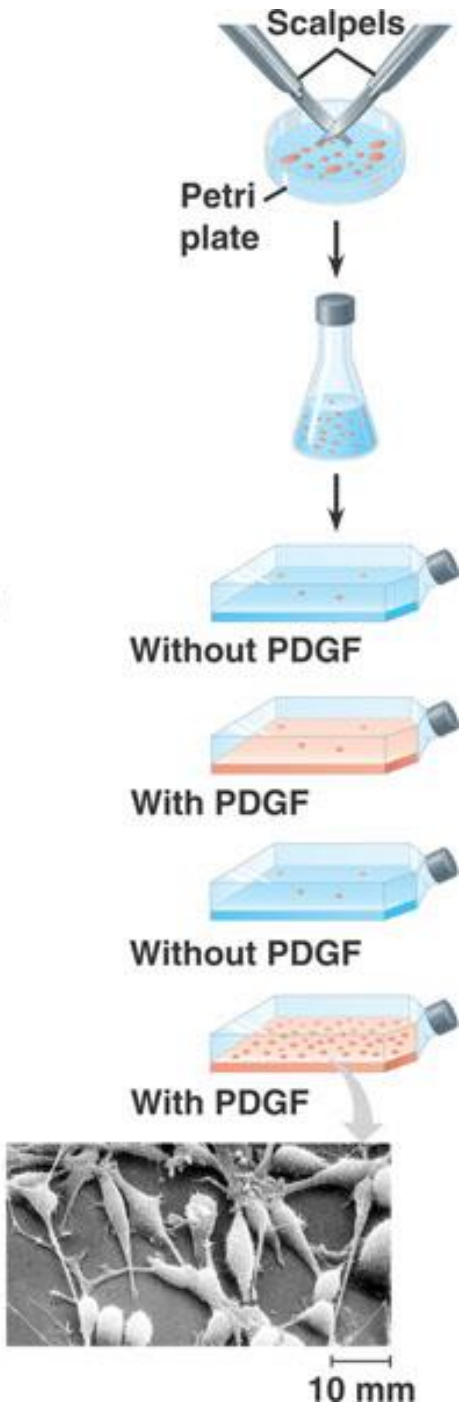
1 A sample of connective tissue was cut up into small pieces.

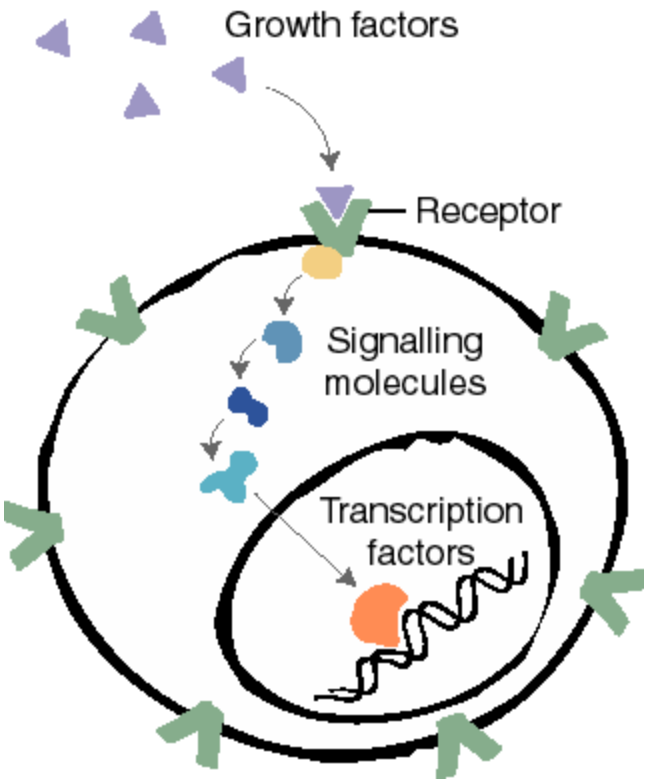
2 Enzymes were used to digest the extracellular matrix, resulting in a suspension of free fibroblast cells.

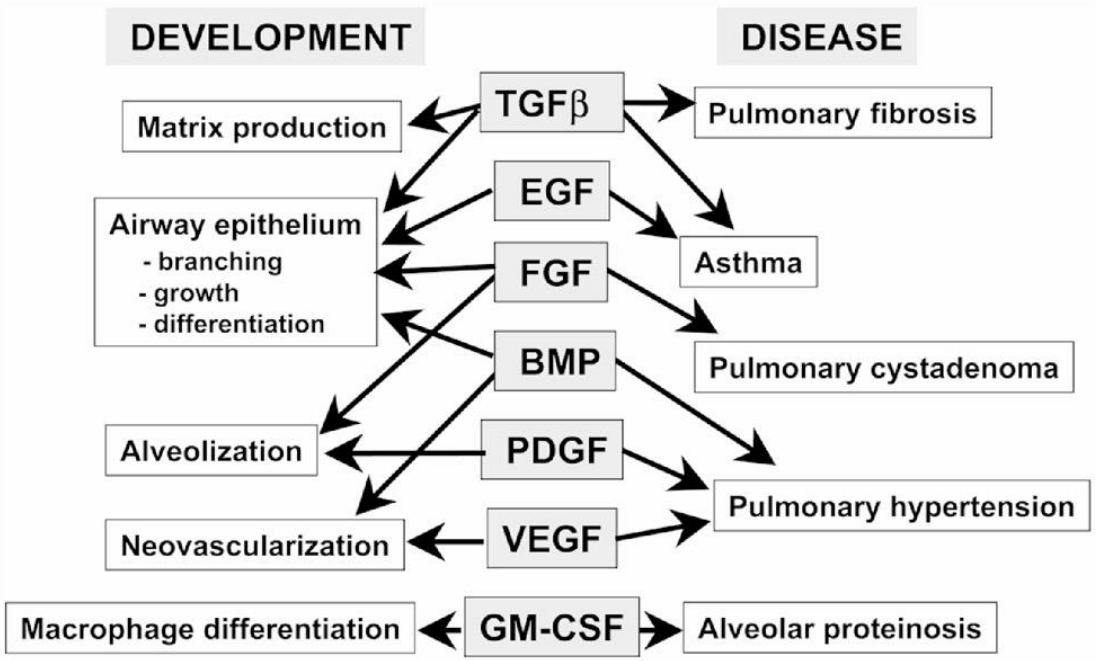
3 Cells were transferred to sterile culture vessels containing a basic growth medium consisting of glucose, amino acids, salts, and antibiotics (as a precaution against bacterial growth). PDGF was added to half the vessels. The culture vessels were incubated at 37°C.

(a) In a basic growth medium without PDGF (the control), cells failed to divide.

(b) In a basic growth medium plus PDGF, cells proliferated. The SEM shows cultured fibroblasts.





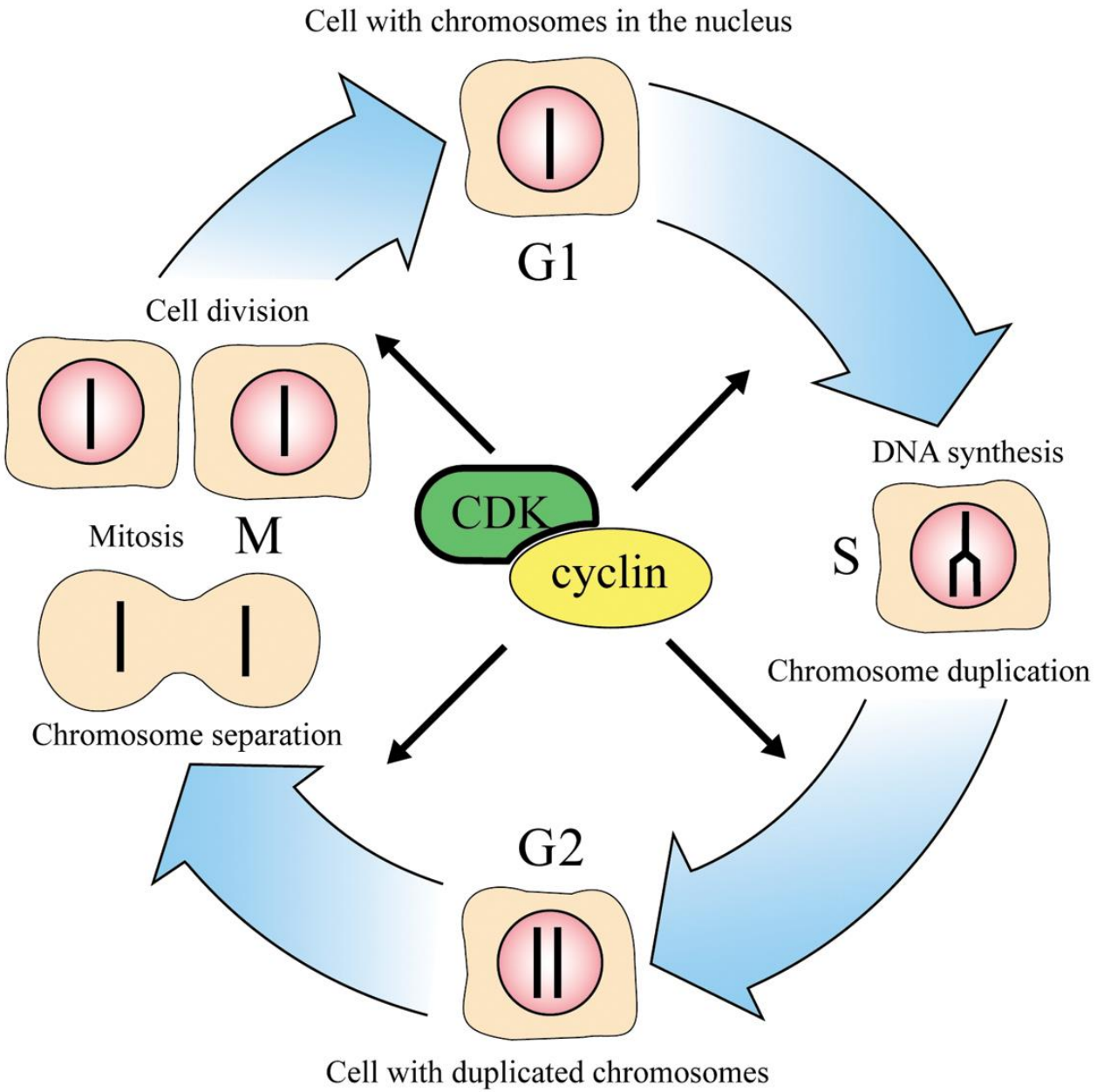


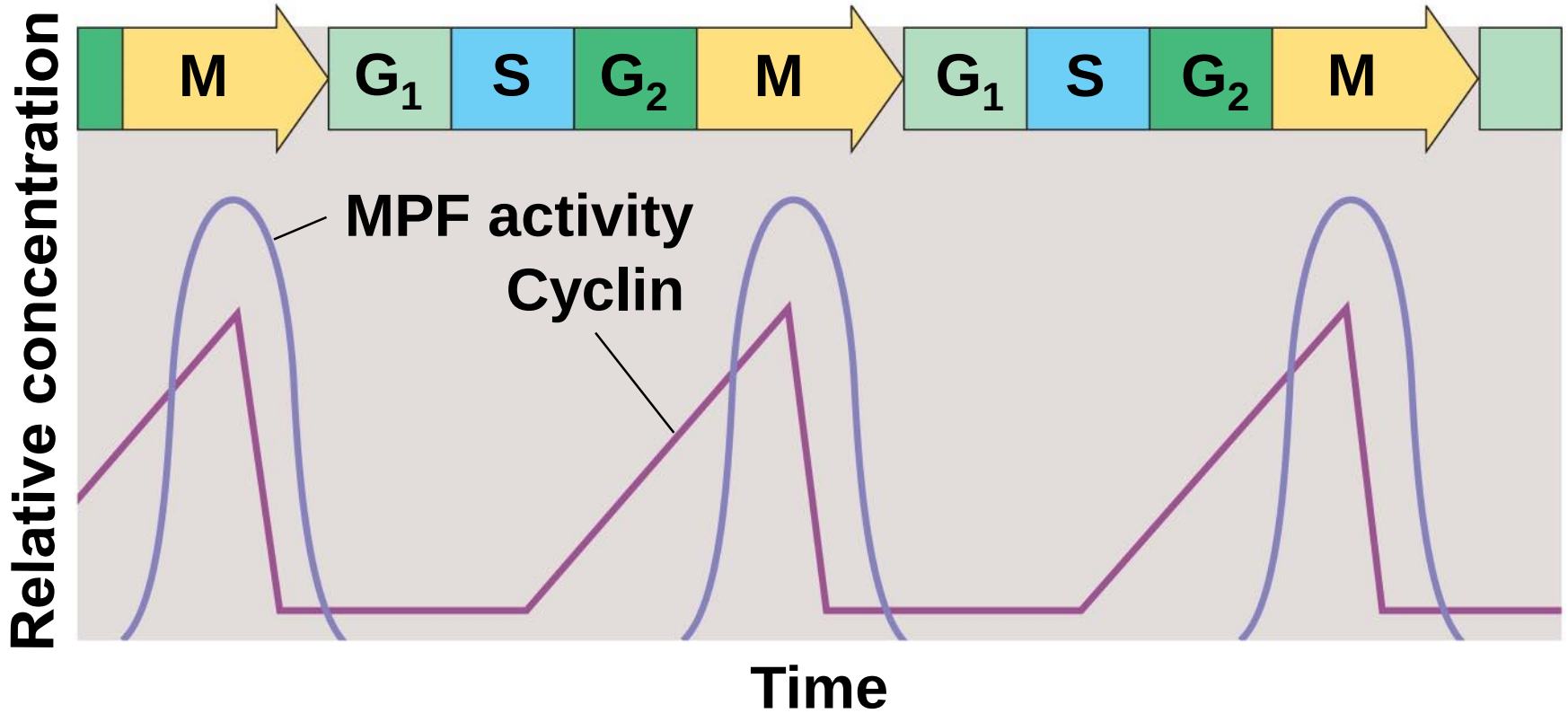
Respiratory Research

Internal CHEMICAL FACTORS - Cyclins & Cdks

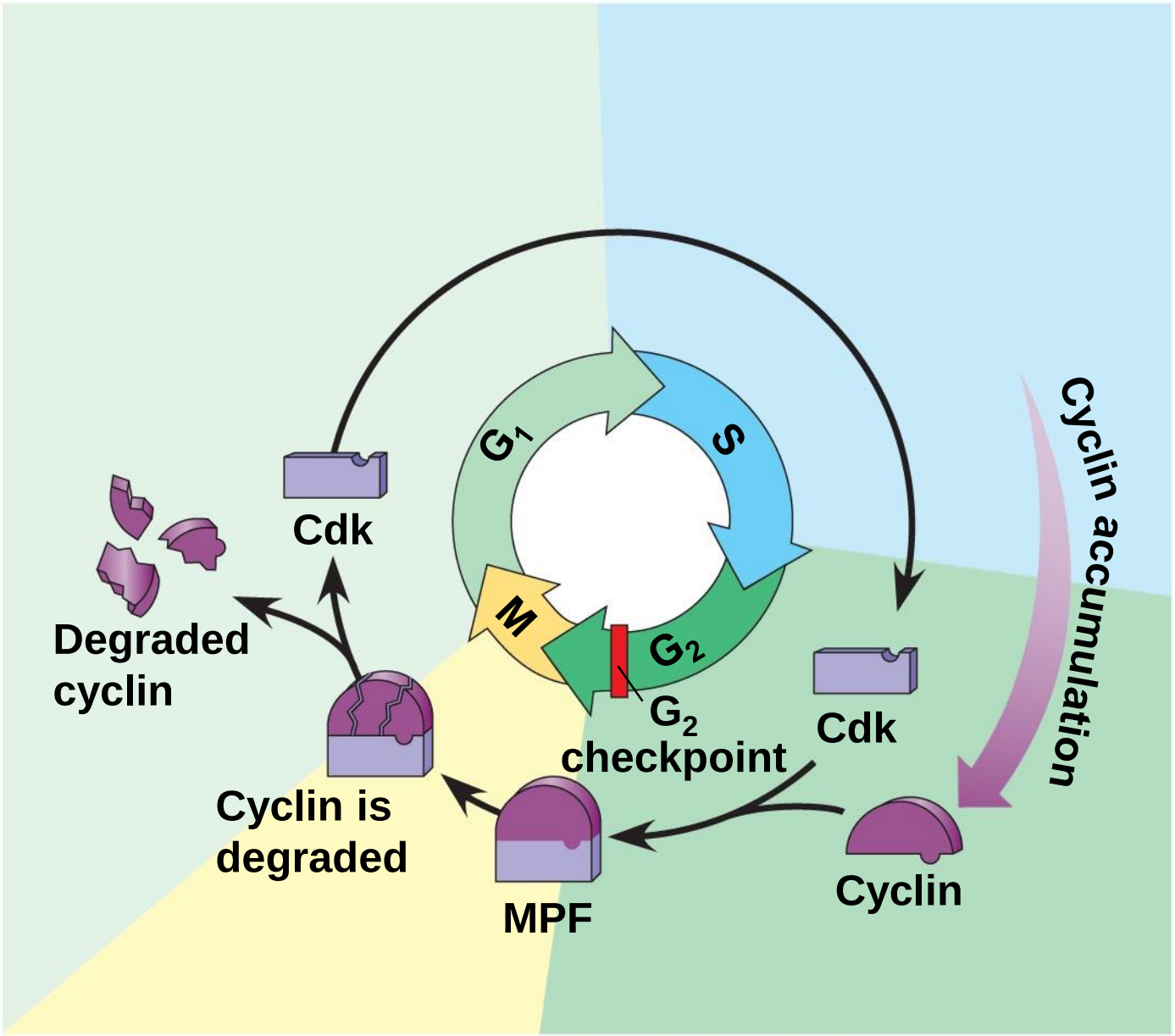
- Two types of regulatory proteins are involved in cell cycle control: **CYCLINS** and **CYCLIN-DEPENDENT KINASES** (**Cdks**)
- The activity of cyclins and Cdks fluctuates during the cell cycle

The Cell Cycle





(a) Fluctuation of MPF activity and cyclin concentration during the cell cycle

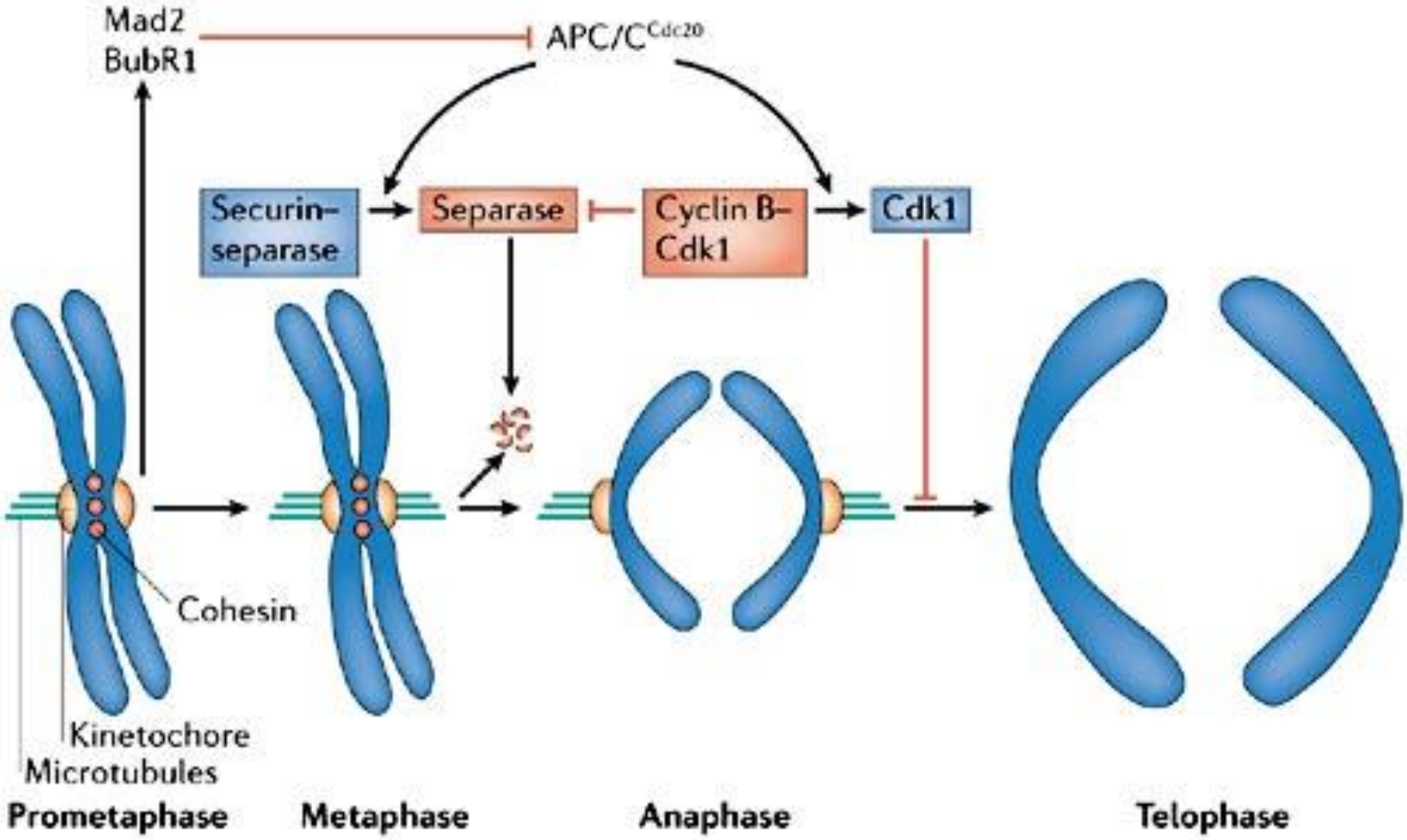


(b) Molecular mechanisms that help regulate the cell cycle

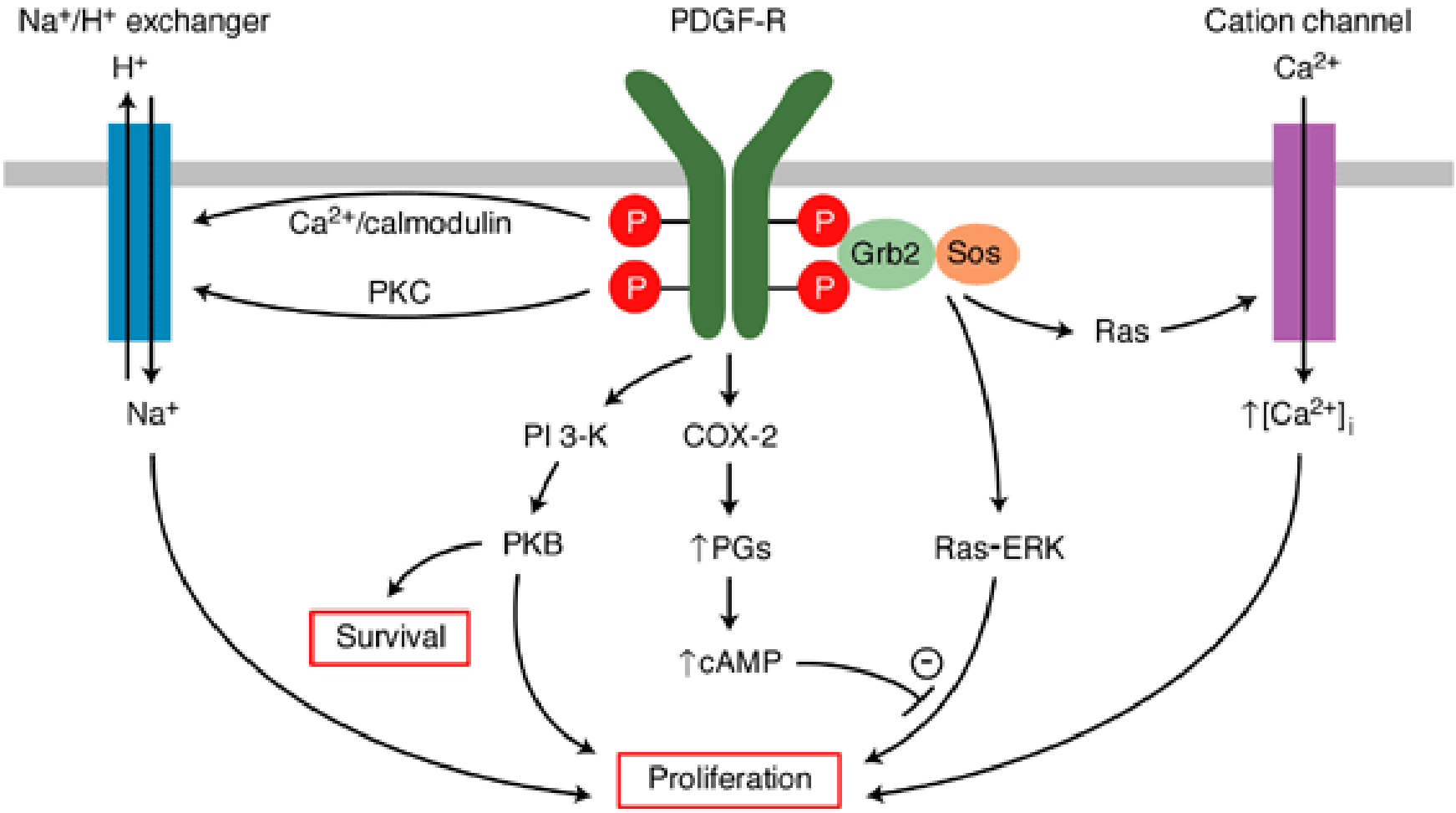
Stop and Go Signs: Internal and External Signals at the Checkpoints

- **EX. of internal signal:** kinetochores not attached to spindle microtubules send a molecular signal that delays anaphase

  (by keeping an anaphase-promoting complex (APC) in an inactive state)
- **EX. of external signal:** PDGF released by damaged/injured body cells stimulates fibroblast growth to heal injury



Nature Reviews | Molecular Cell Biology



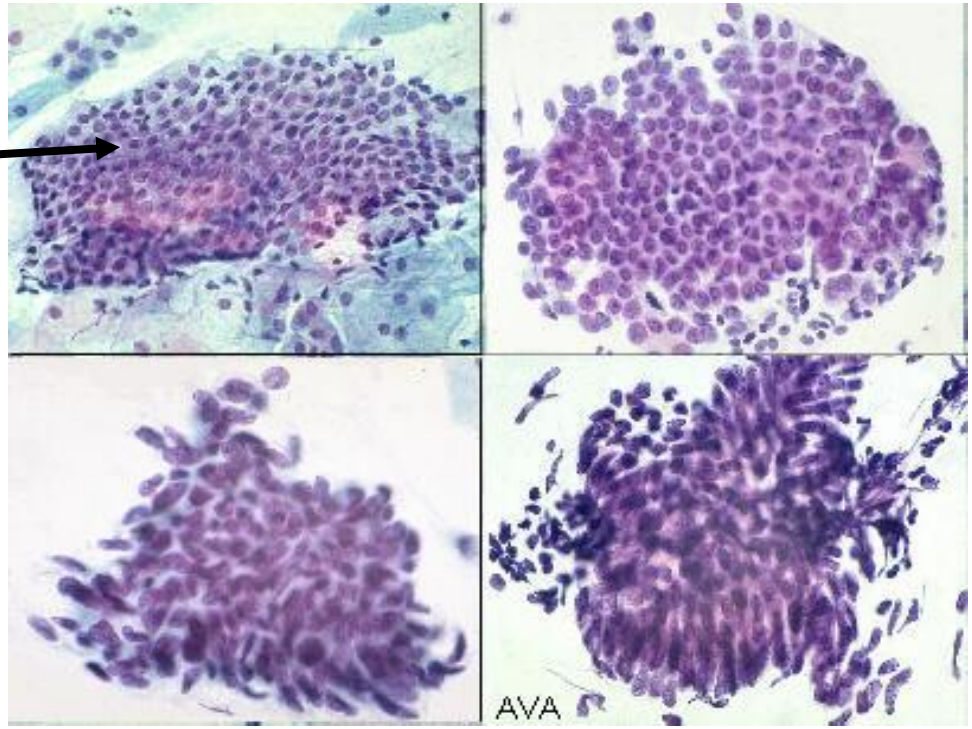
The platelet-derived growth factor (PDGF) mitogenic signalling pathway in hepatic stellate cells

Published in Expert Reviews in Molecular Medicine by Cambridge University Press 2003

PHYSICAL FACTORS:

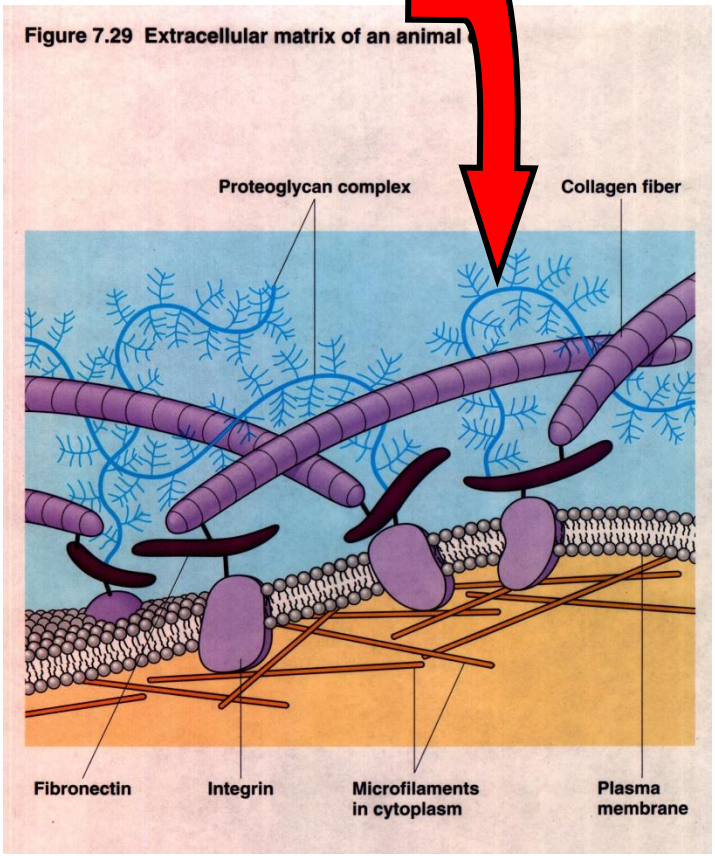
- crowding inhibits cell division in what is called **DENSITY-DEPENDENT INHIBITION.**

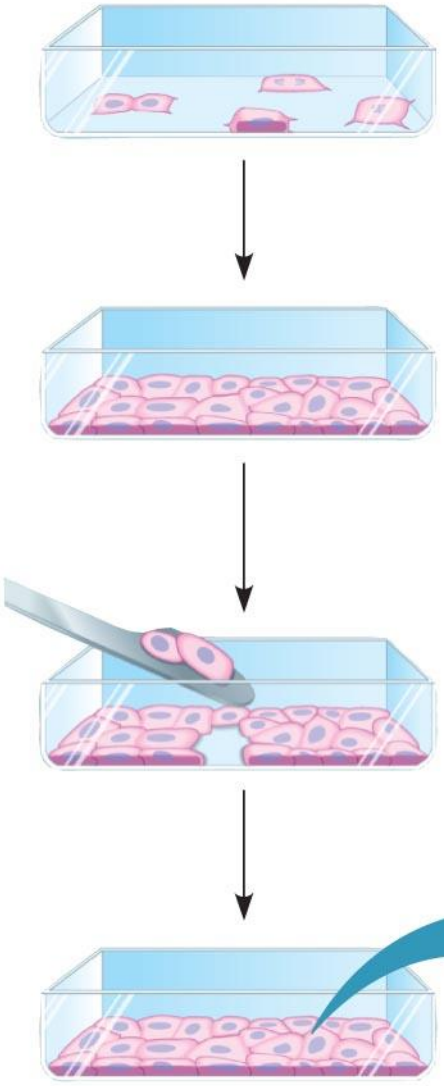
Normal sheet (upper, left) and "cell crowding" in three grades of expression



- many animal cells exhibit **ANCHORAGE DEPENDENCE** (cells must adhere to a substratum, such as the surface of a culture dish or the extracellular matrix of a tissue)

***Cancer cells are abnormal and do not exhibit density-dependent inhibition or anchorage-dependent inhibition.**

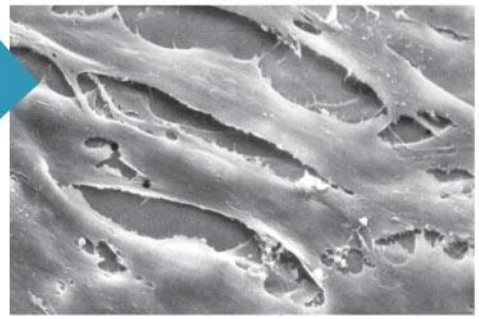




Cells anchor to dish surface and divide (anchorage dependence).

When cells have formed a complete single layer, they stop dividing (density-dependent inhibition).

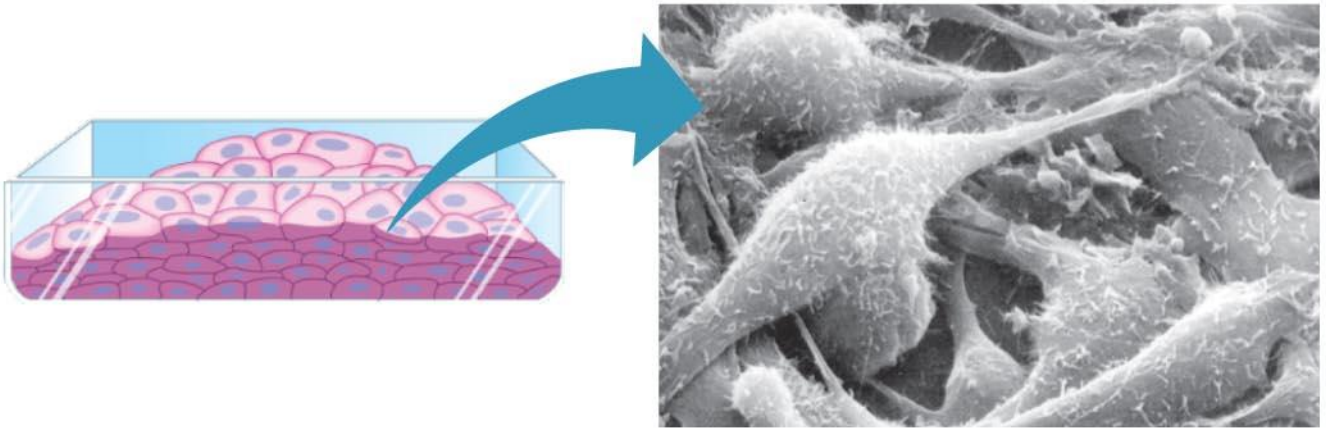
If some cells are scraped away, the remaining cells divide to fill the gap and then stop (density-dependent inhibition).



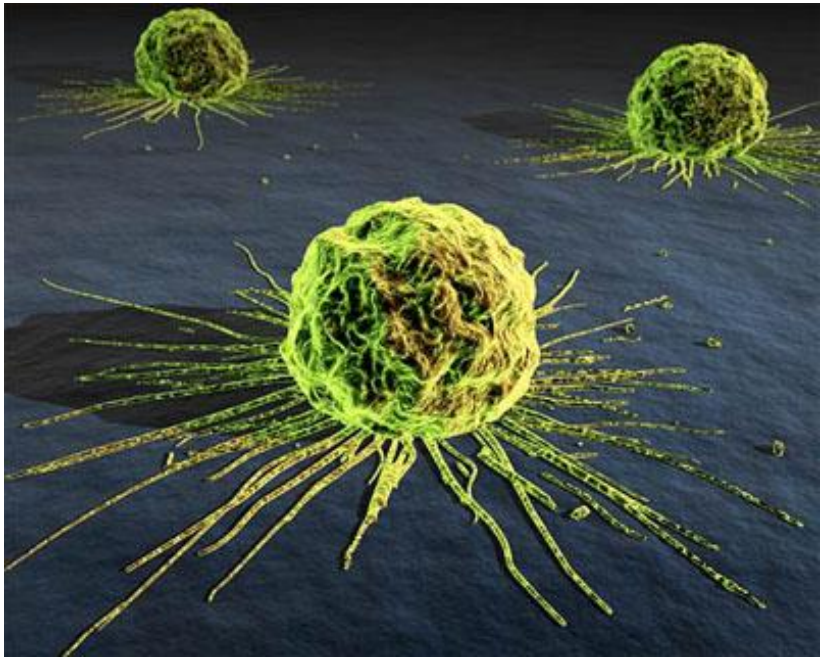
25 µm

(a) Normal mammalian cells

Cancer cells do not exhibit anchorage dependence or density-dependent inhibition.

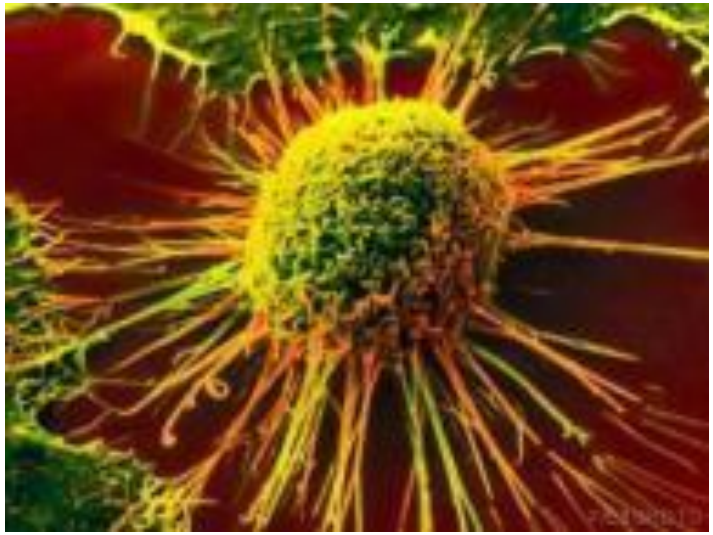


(b) Cancer cells



CANCER:

- cancer cells do not respond to body's control mechanisms



- cancer cells divide excessively, invade other tissues, and can kill the organism if left unchecked

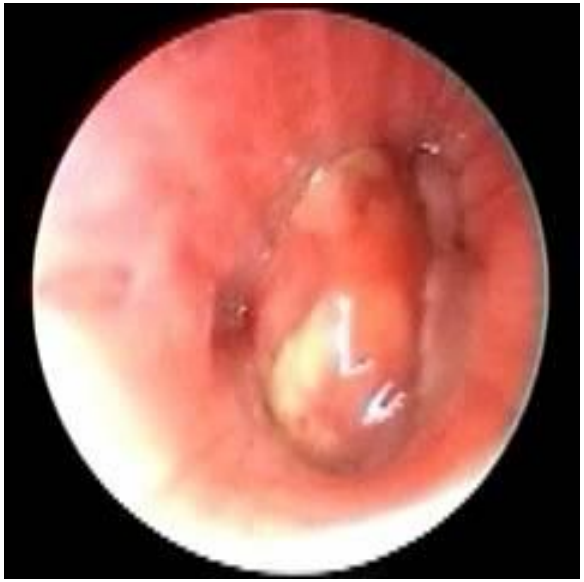
HOW do they do this?

- some cancer cells may make their own growth factors;

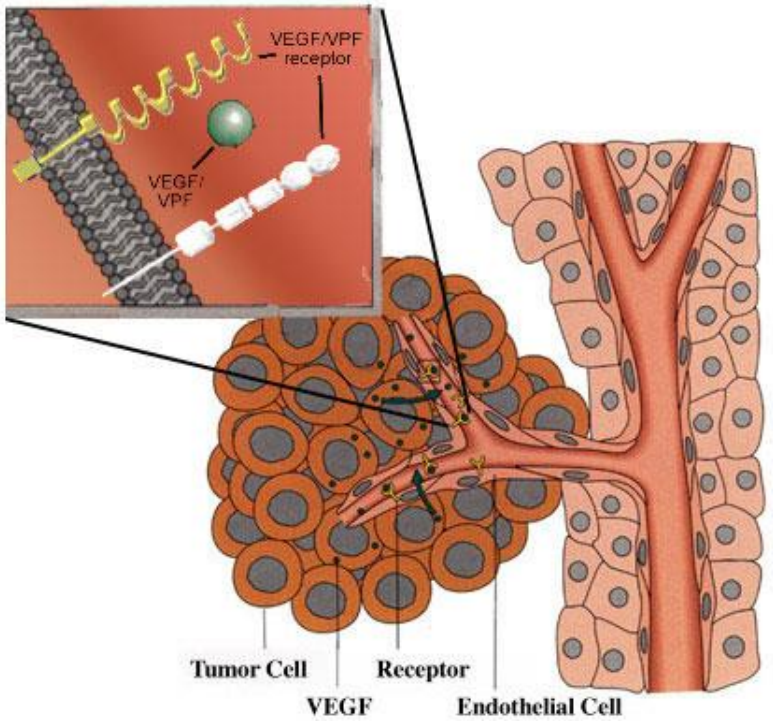
- cancer cells may have an abnormal growth factor signaling system;

- cancer cells divide indefinitely (as opposed to normal cells, which typically divide about 20-50 times before they stop).

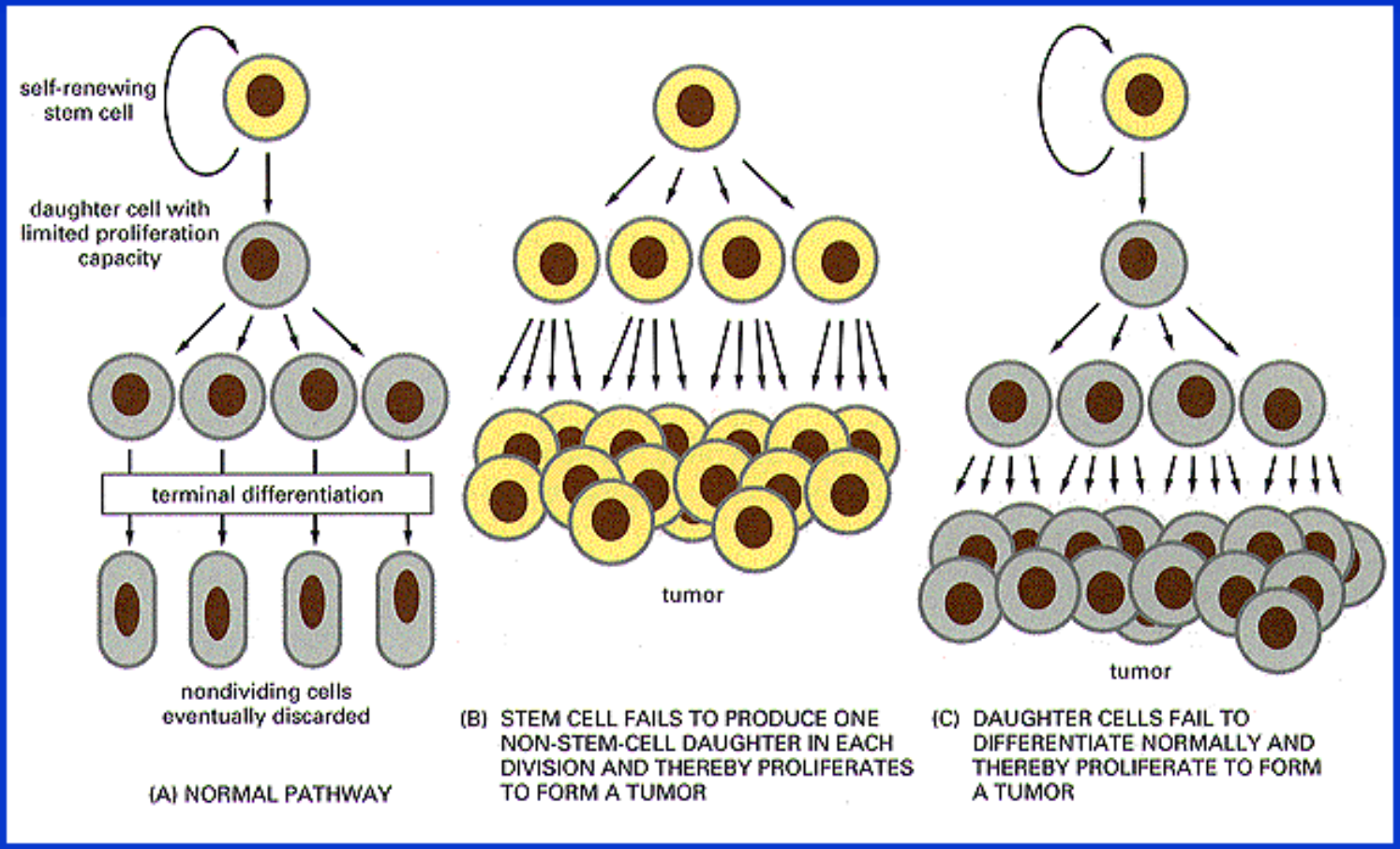
- Normally, the immune system recognizes and destroys transformed or mutated cells which are growing abnormally
- if abnormal cells evade the immune system, they may form a **TUMOR**.



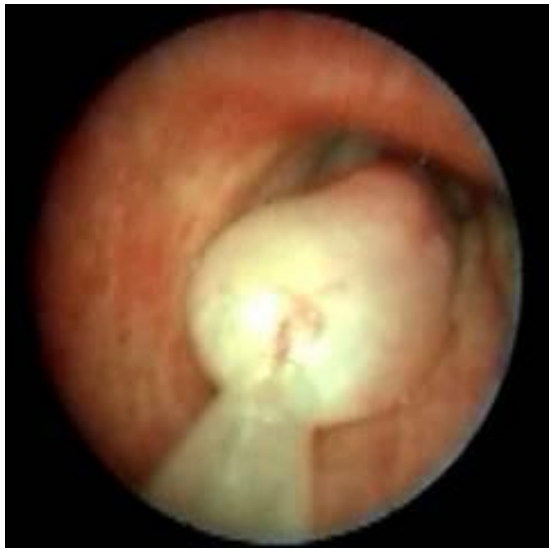
Bronchus tumor



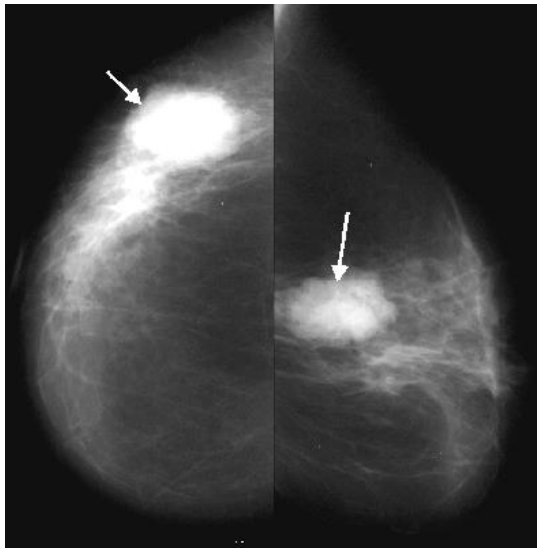
Cancer - a problem of cell proliferation and differentiation



- if the cells remain at the original site, the mass is called a **BENIGN TUMOR** and can be completely removed by surgery.



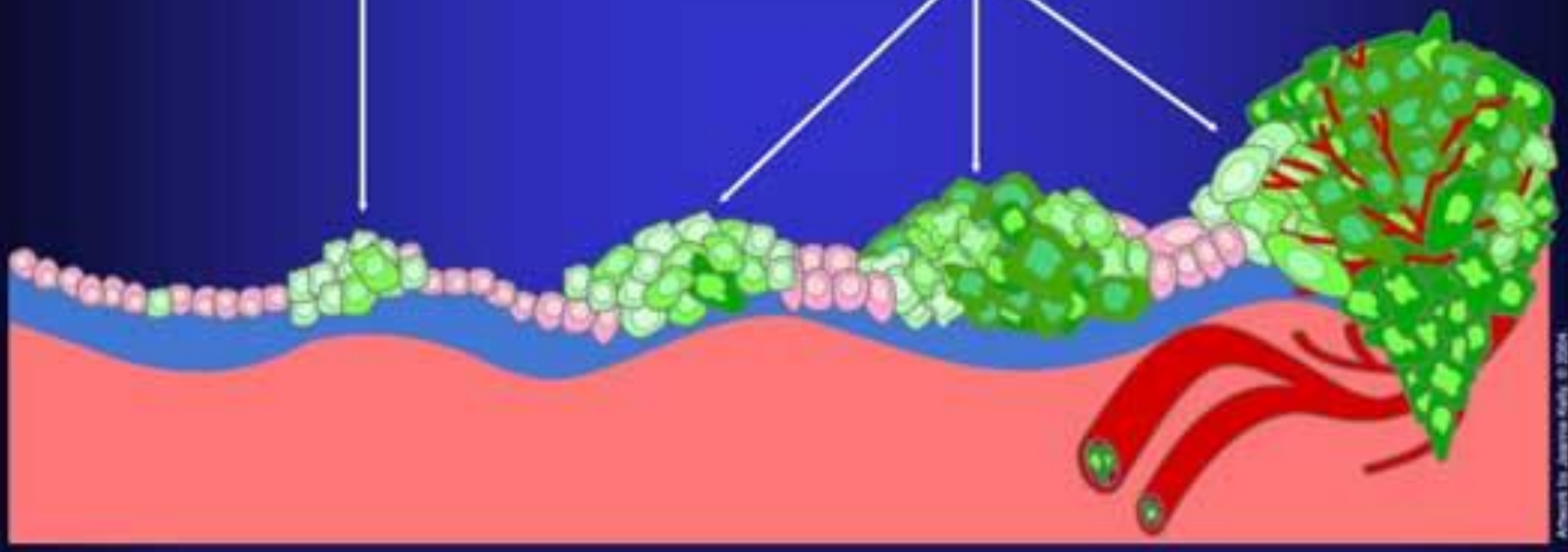
- if the tumor cells have invaded other tissues / organs, it is a **MALIGNANT TUMOR**.



Malignant versus Benign Tumors

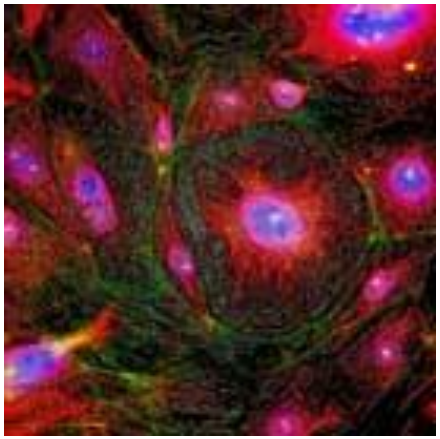
Benign (not cancer) tumor cells grow only locally and cannot spread by invasion or metastasis

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



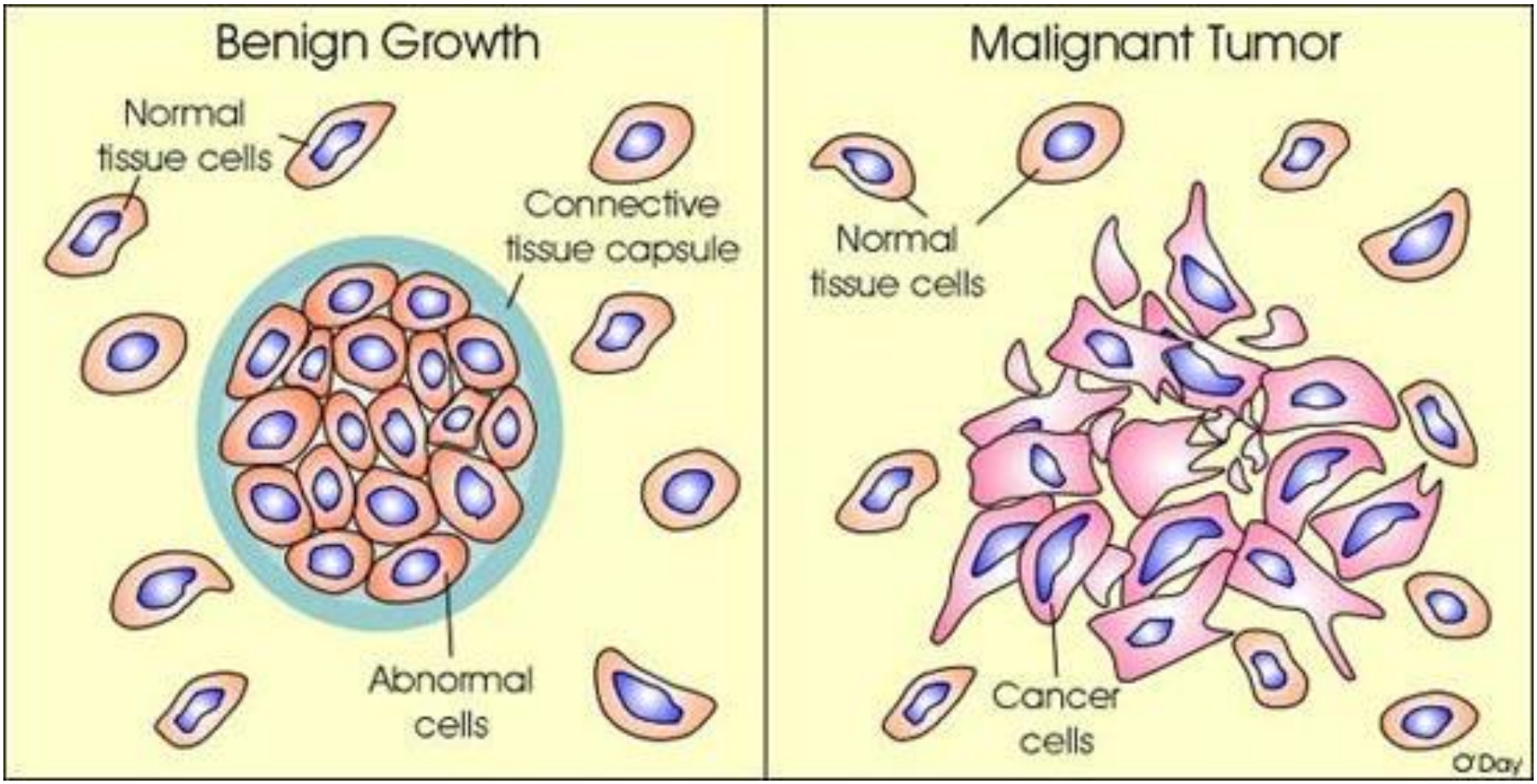
Time

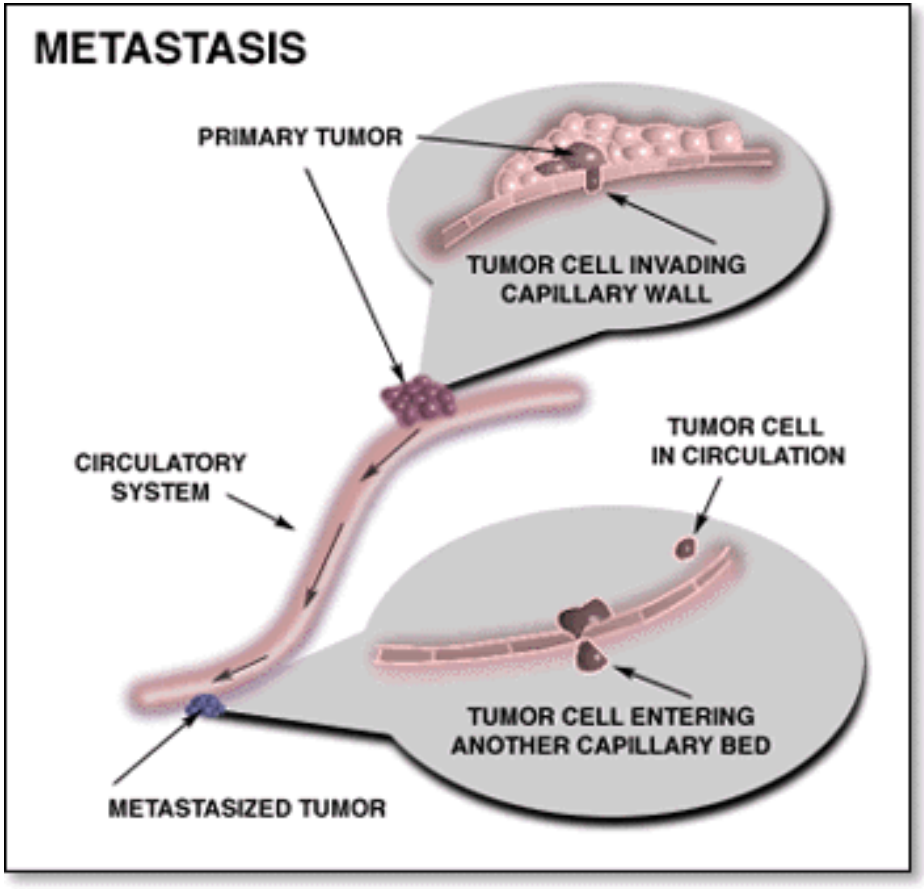
Properties of malignant tumors:



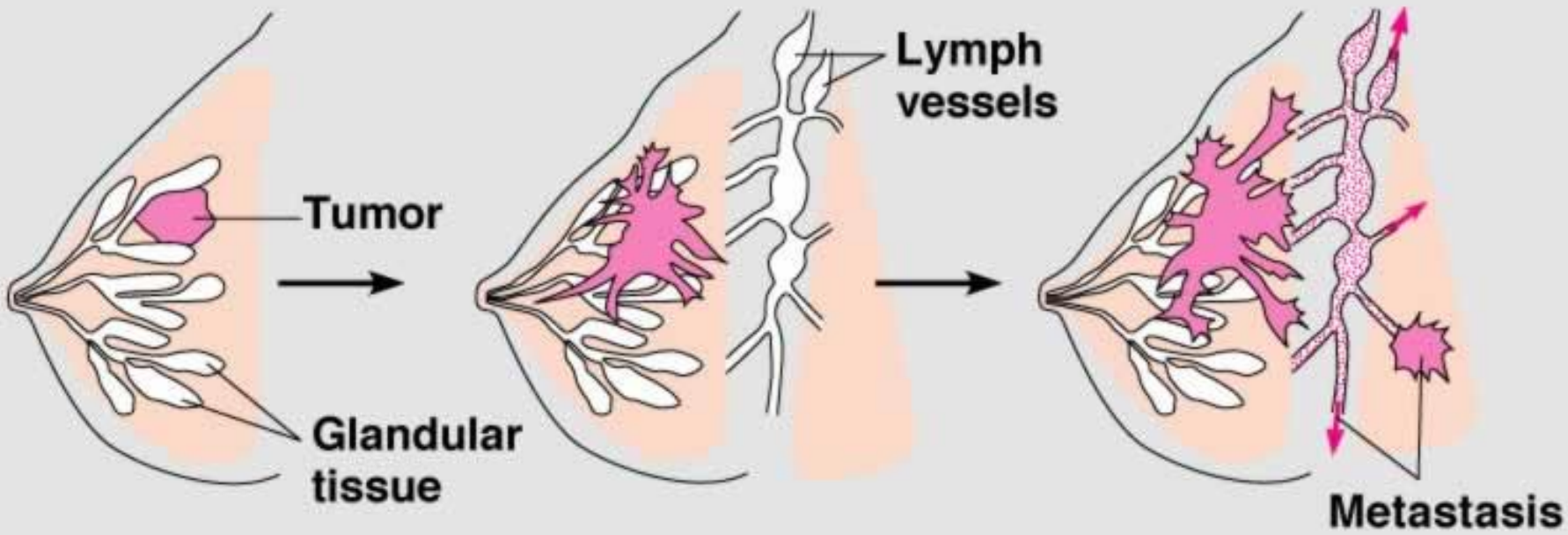
- excessive cell proliferation
- may have unusual numbers of chromosomes
- may have abnormal metabolism
- abnormal cell surface changes

  (i.e. lost attachments to neighboring cells)
- they cease to function in any constructive way


Benign Growth
Normal tissue cells
Connective tissue capsule
Abnormal cells
Malignant Tumor
Normal tissue cells
Cancer cells
O'Day



- if cancer cells separate from the original tumor and spread into other tissues, entering the blood and lymph vessels, they may invade other parts of the body and develop into new tumors…this is called… **METASTASIS**.

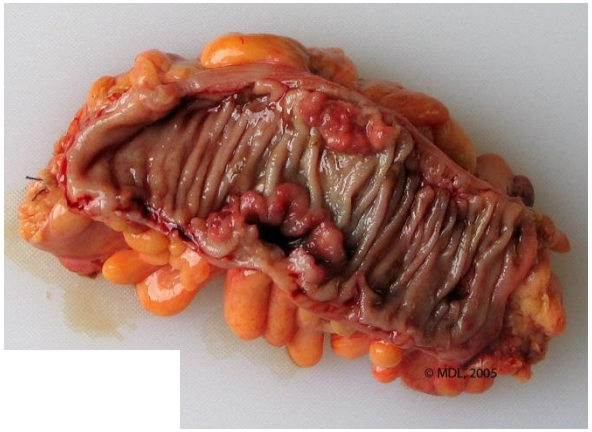


A tumor grows from a single cancer cell.

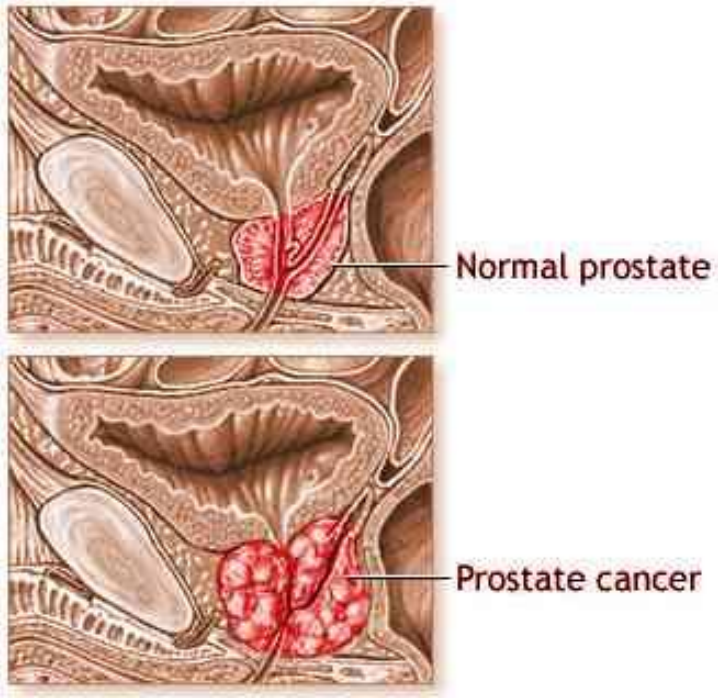
Cancer cells invade neighboring tissue.

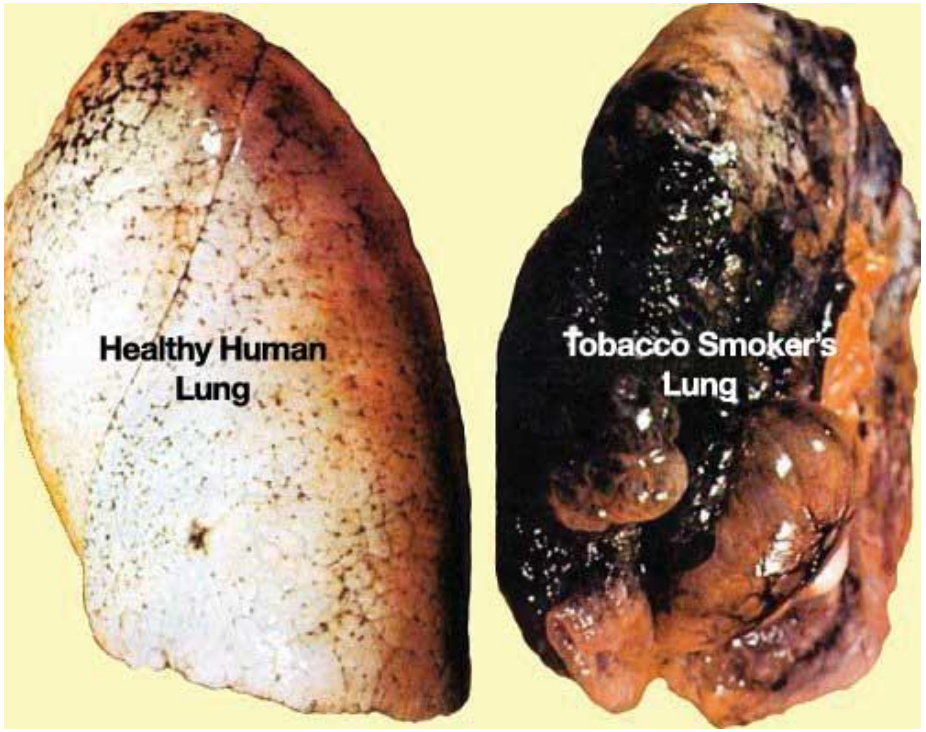
Cancer cells spread through lymph and blood vessels to other parts of the body.

Cancer is the 2nd leading cause of death in the U.S.



- It can affect any tissue, but the most commonly affected are:
  - ➔ lung
  - ➔ colon
  - ➔ breast
  - ➔ prostate





TOLUENE
Industrial solvent

CARBON MONOXIDE
Car exhaust

CADMIUM
Batteries

ARSENIC
Rat poison

AMMONIA
Toilet cleaner

RADON
Radioactive gas

HEXAMINE
Barbecue lighter

METHANE
Sewer gas

TAR
Road surfaces

ACETONE
Nail varnish remover

NICOTINE
Pesticide

POLONIUM-210
Radioactive element

METHANOL
Rocket fuel

HYDROGEN CYANIDE
Poison

BUTANE
Lighter fuel

There are 60 known cancer-causing substances in tobacco.

THESE HARMFUL CHEMICALS INCLUDE:

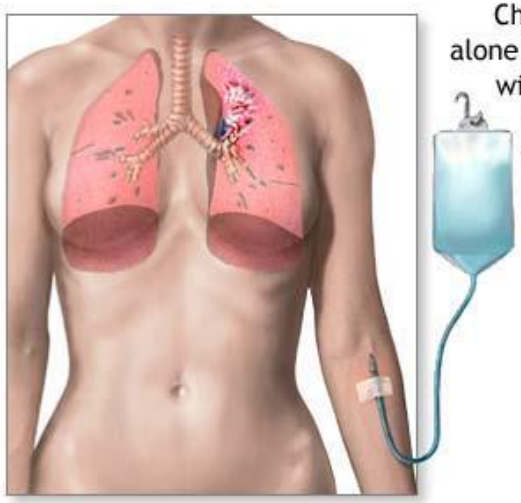
Nicotine – a powerful, fast-acting and addictive drug which reaches your brain in seven seconds. It increases heart rate and raises blood pressure.

Carbon monoxide – a colourless poisonous gas found in high concentrations in tobacco smoke. When you inhale it enters your bloodstream and interferes with the working of your heart and blood vessels.

Tar – a sticky brown substance that forms when tobacco cools and thickens. It collects in your lungs and can cause cancer.

Treatments

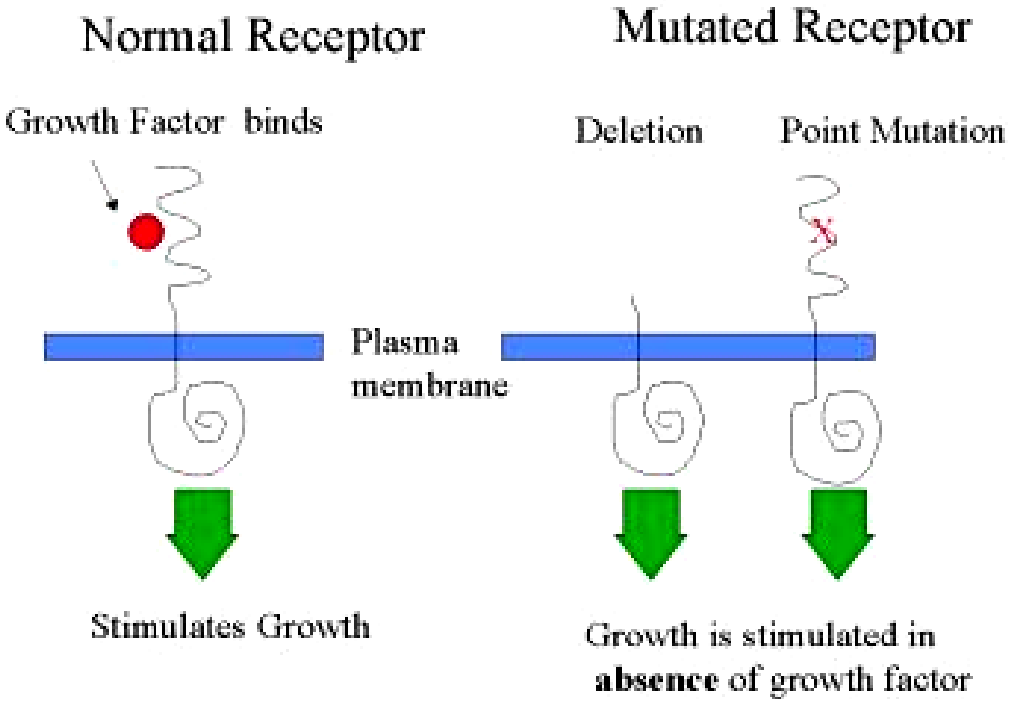
- surgery (for benign tumors)
- radiation
- chemotherapy



Chemotherapy, alone or combined with radiation, may be used before, after or instead of surgery in treating lung cancer

A.D.A.M.

Although we do not fully understand how a normal cell is transformed into a cancerous cell, it seems clear that there is an ***alteration of genes* that somehow influence the cell-cycle control system.

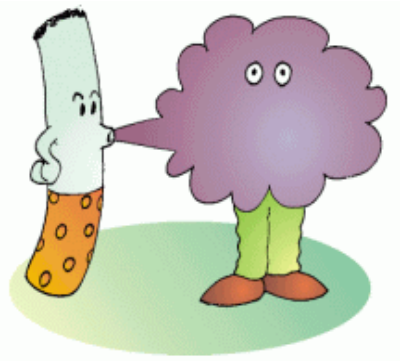


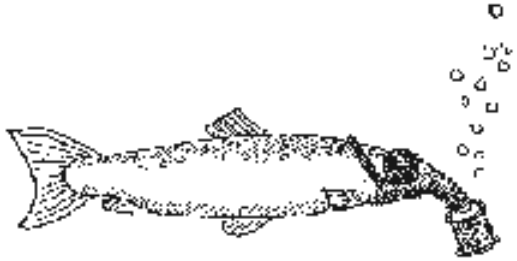
Factors which can cause an “alteration of genes” *(a.k.a. **MUTAGENS**)*** include:

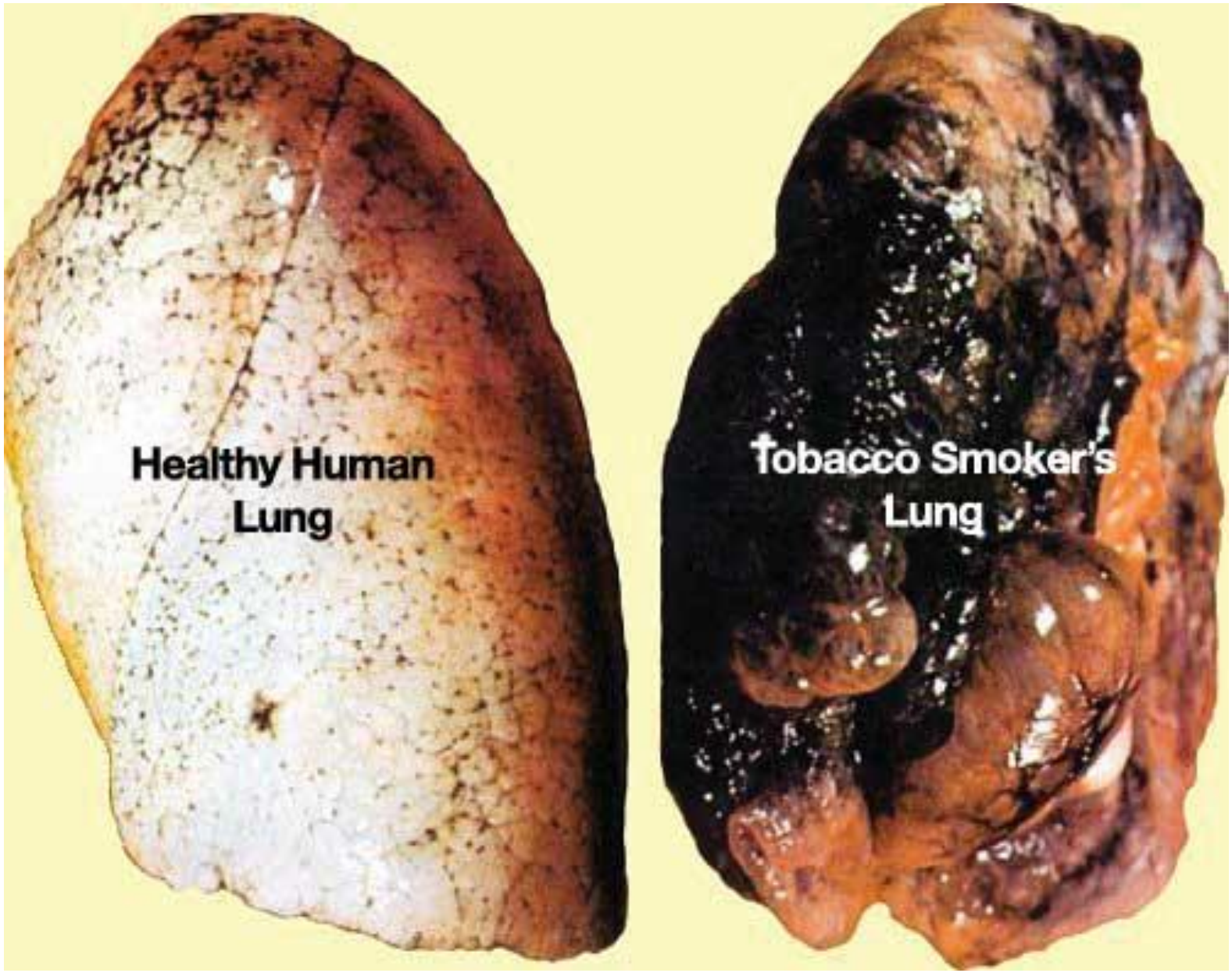
1) Chemicals

2) Radiation

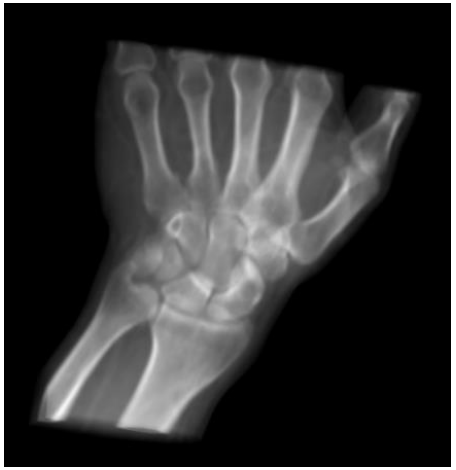
- Examples of Chemical Mutagens:
  - **cigarette smoke**
  - **DDT**
  - **chewing tobacco**
  - **pollution**
  - **chromium-6**

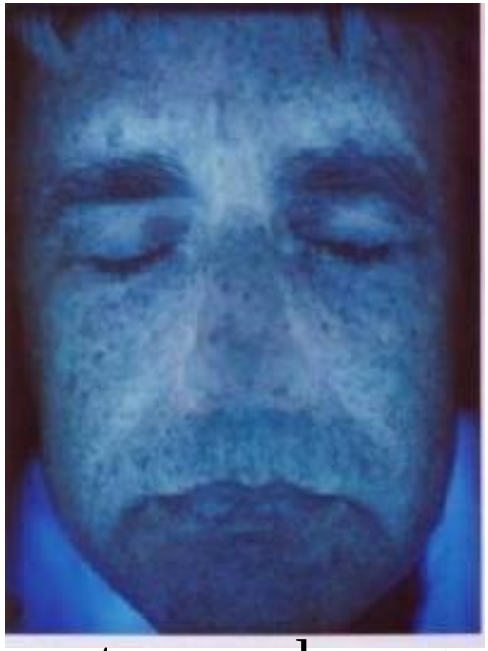




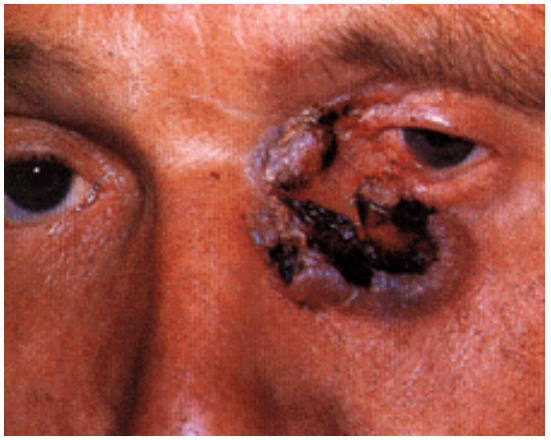

Healthy Human Lung
Tobacco Smoker's Lung

- Examples of Radiation Mutagens:
  - **sun (UV rays)**
  - **nuclear waste**
  - **x-rays**

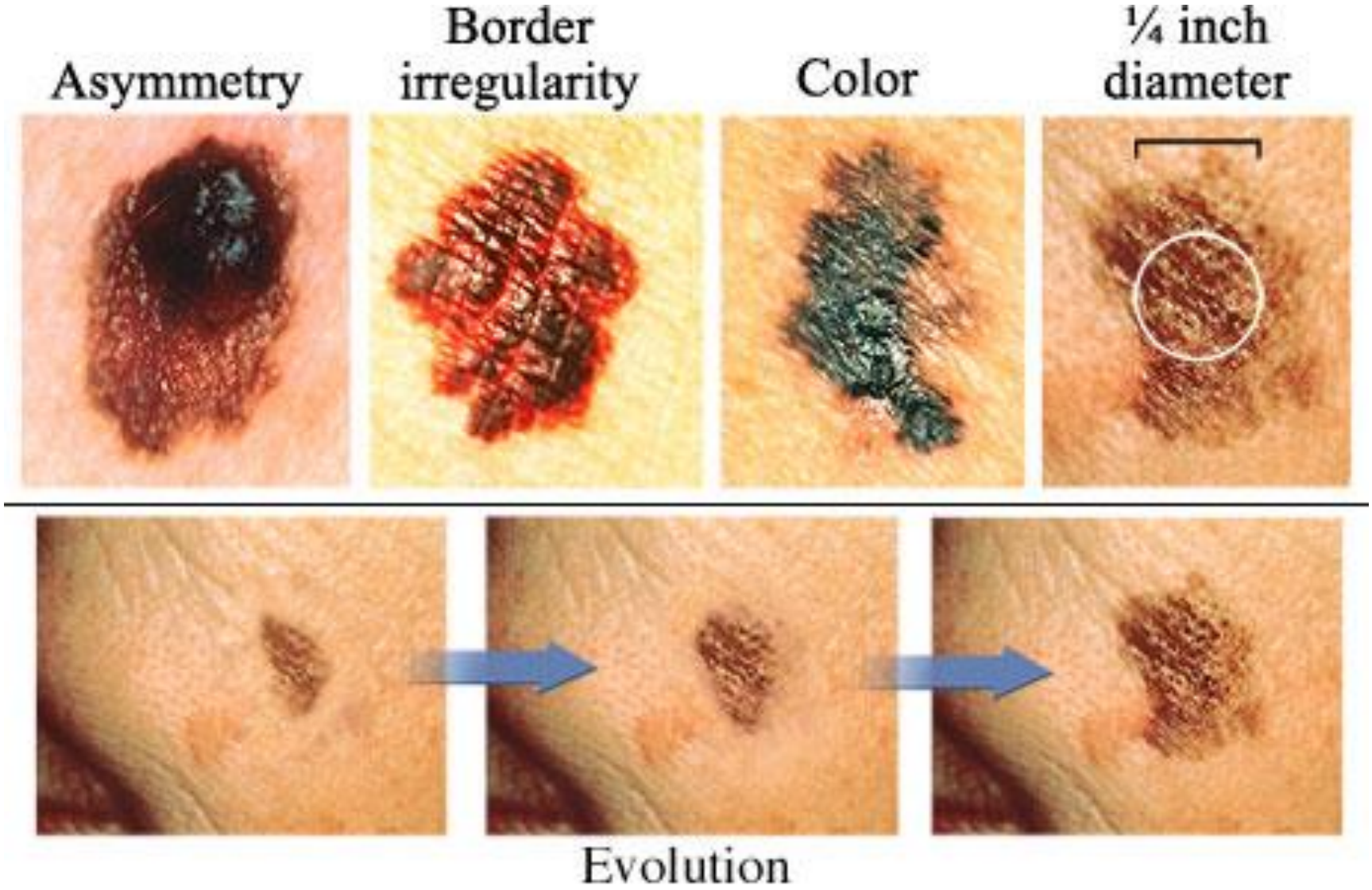




spots: sun damage



skin cancer caused by too much sun


Asymmetry
Border irregularity
Color
¼ inch diameter
Evolution

HHMI Website: Biointeractive.org

- CELL CYCLE “Click & Learn”