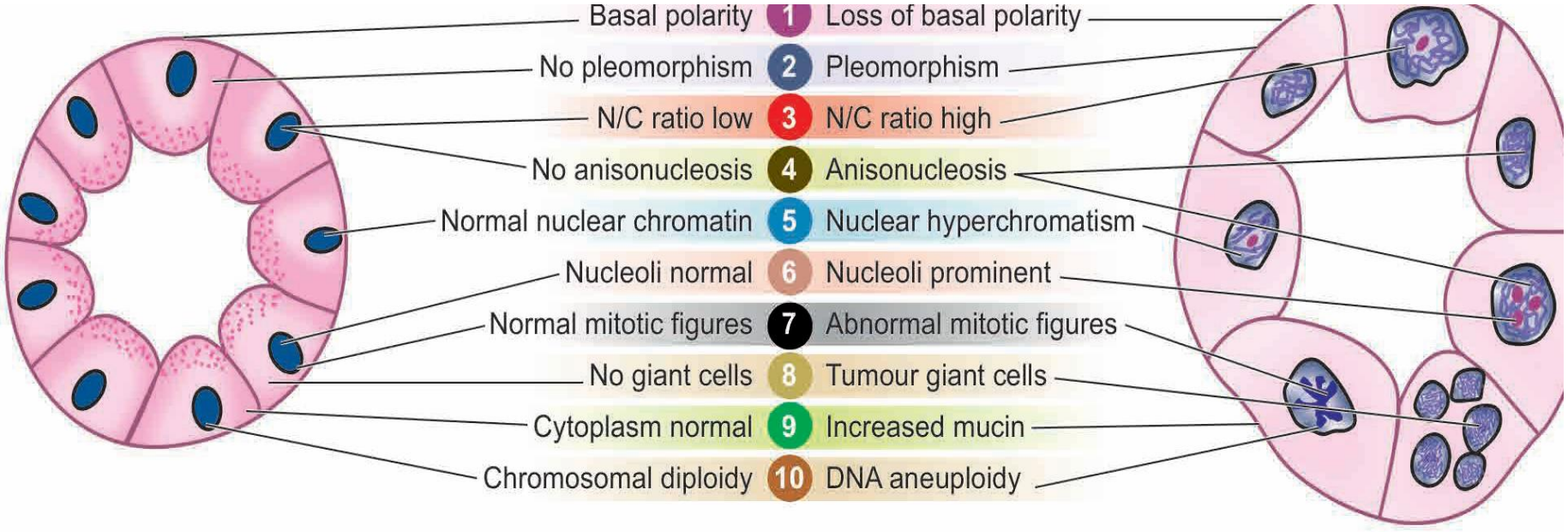
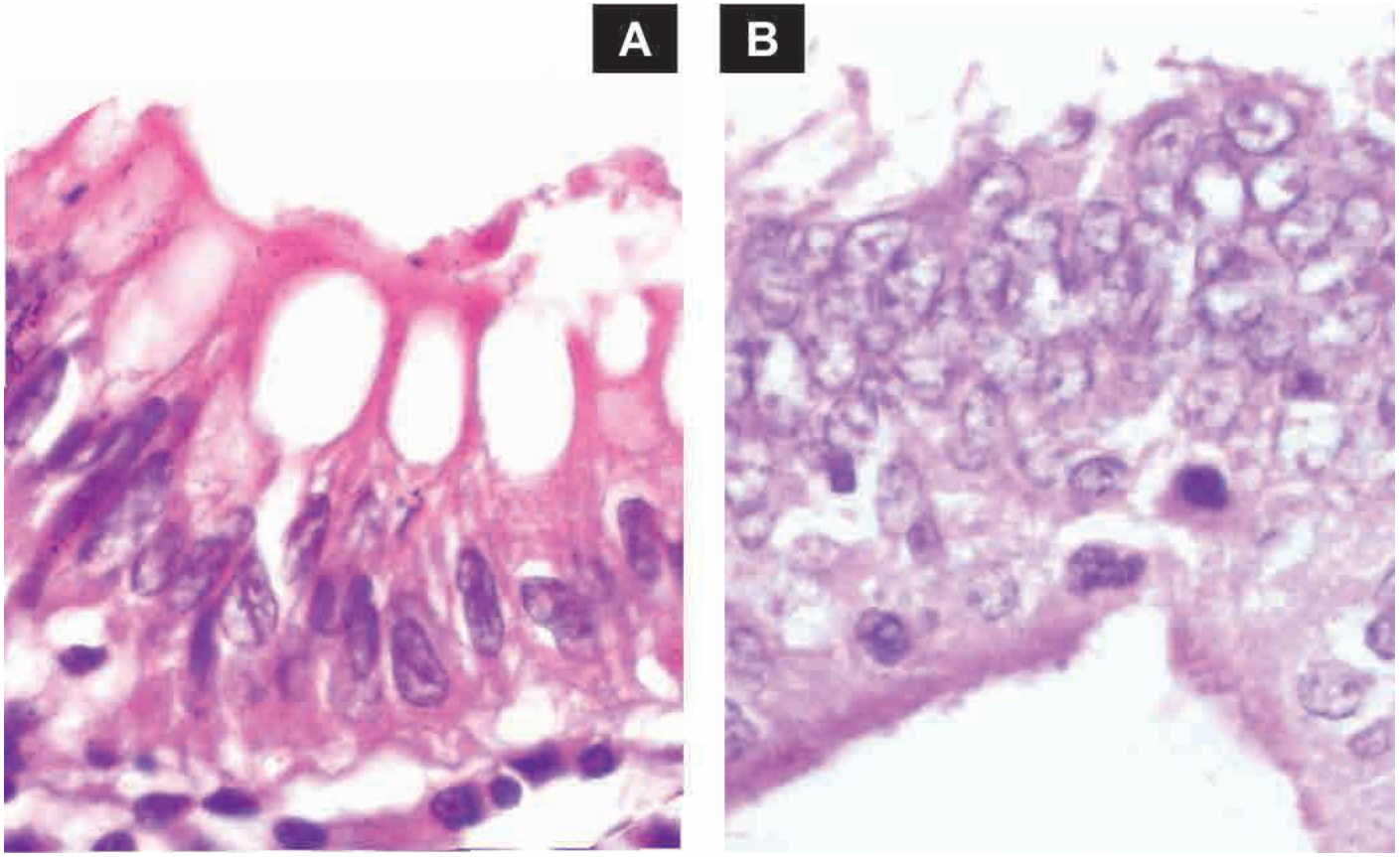
Routes Of Metastasis
and
CARCINOGENESIS:
THE MOLECULAR BASIS OF CANCER

Prof. dr. khalid javed

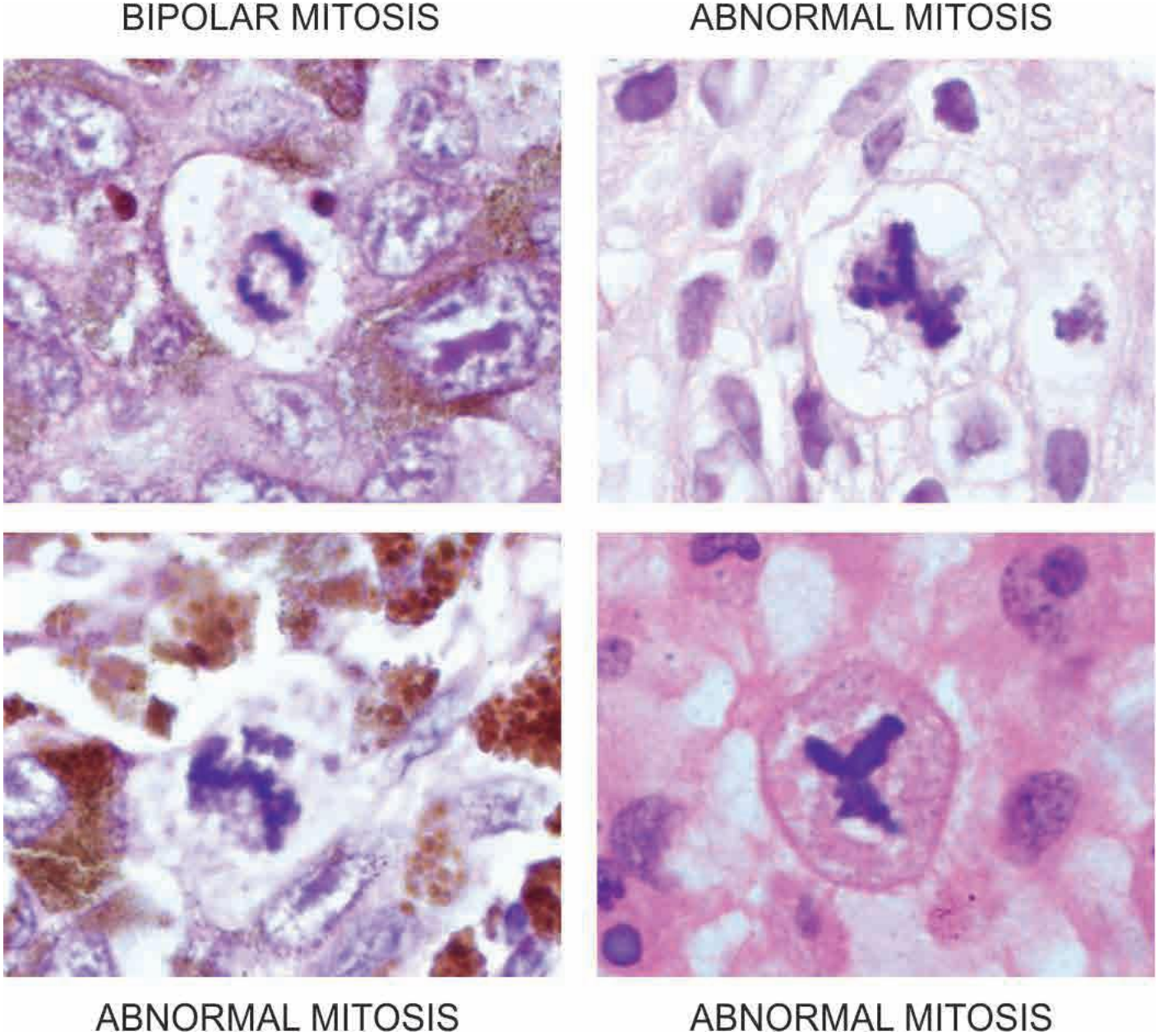
Diagrammatic representation of cytomorphologic features of neoplastic cells. Characteristics of cancer (B) are contrasted with the normal appearance of an acinus (A).

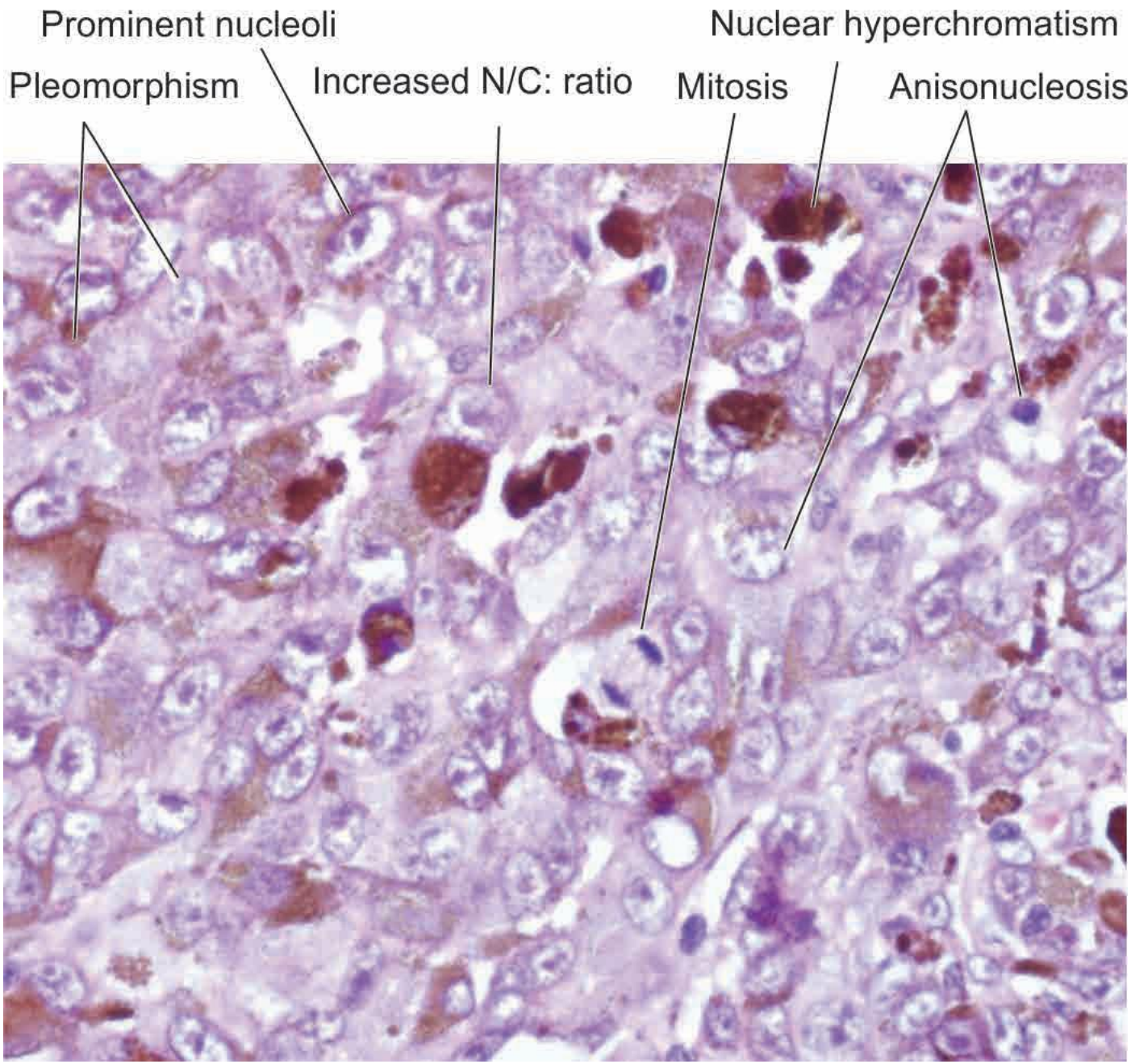


Microscopic appearance of loss of nuclear polarity (B) contrasted with normal basal polarity in columnar epithelium (A). The basement membrane is intact in both

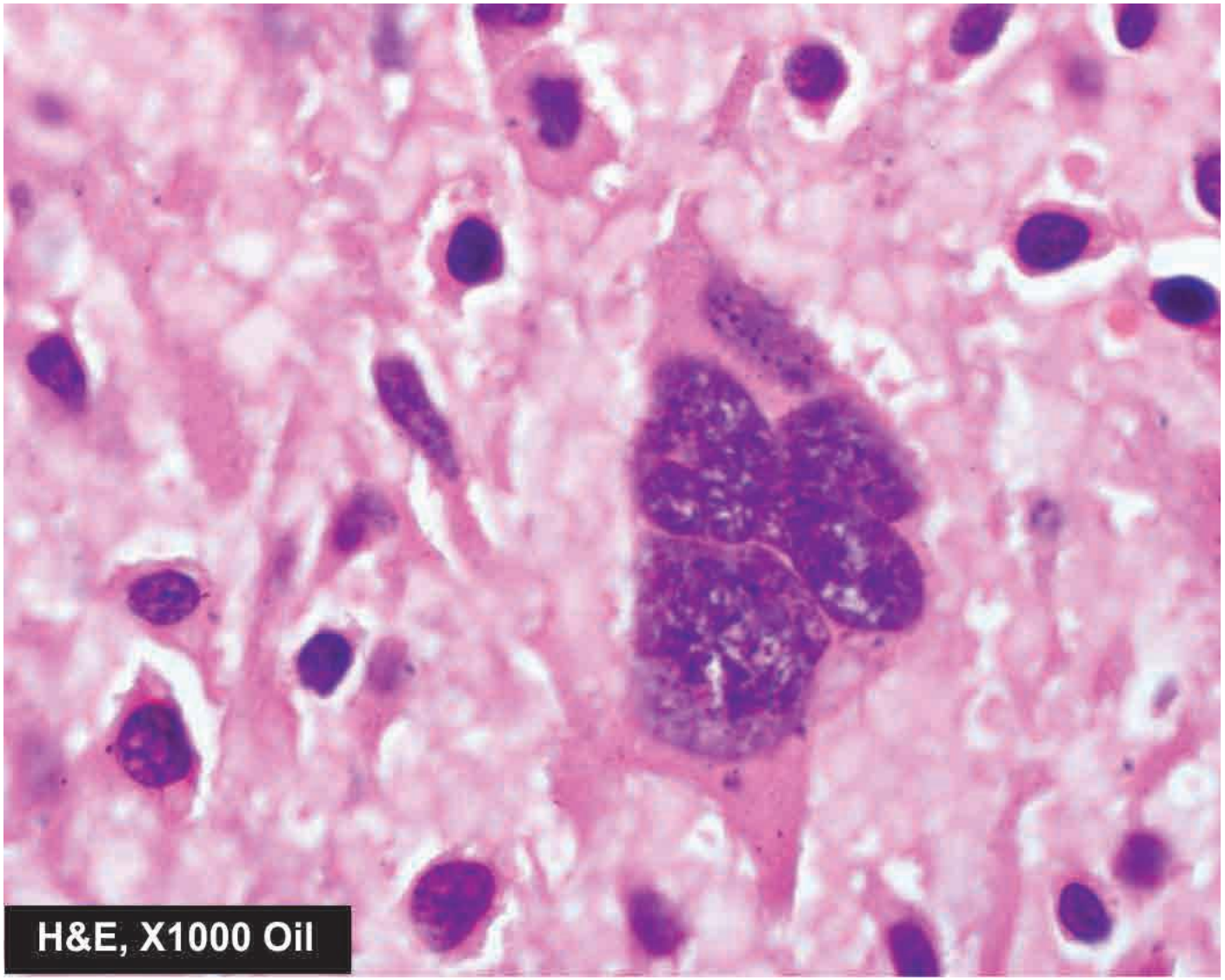


Normal and abnormal (atypical) mitotic figures.




Prominent nucleoli
Nuclear hyperchromatism
Pleomorphism
Increased N/C: ratio
Mitosis
Anisonucleosis

A multinucleate tumour giant cell in osteosarcoma.



Invasion (Infiltration)
Routes Of Metastasis

Invasion (Infiltration)

- Benign neoplasms do not invade adjacent tissue
- Expand centrifugally,
- Forming a capsule of compressed normal tissue and collagen.

- Malignant neoplasms encroach on normal tissue planes
- Form tongues of neoplastic cells extending on all sides.
- Usually do not form a capsule

Carcinomas and Sarcomas demonstrate similar patterns of invasion despite their different tissues of origin

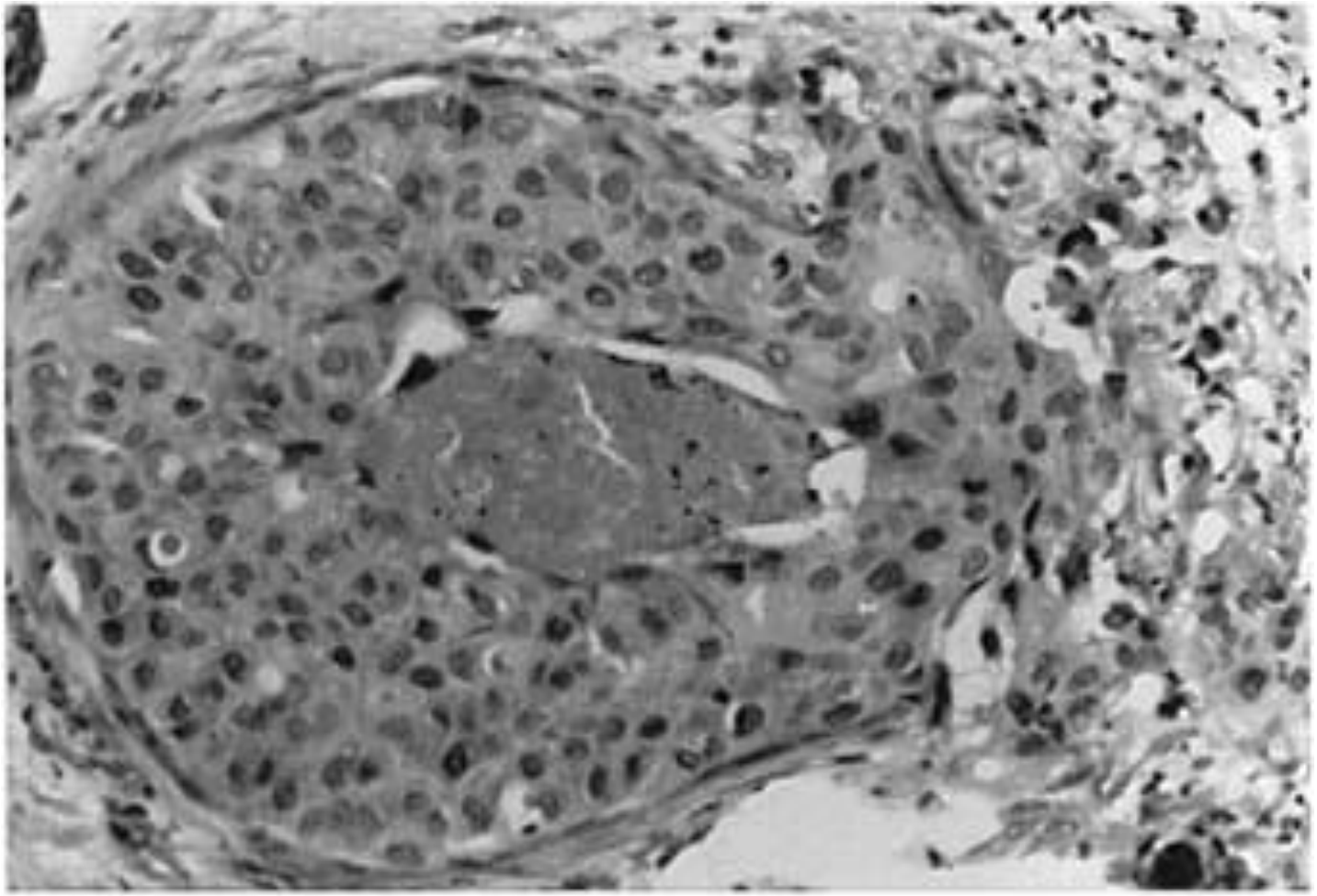
- Invasion of the basement membrane by carcinoma distinguishes invasive cancer and in situ cancer.

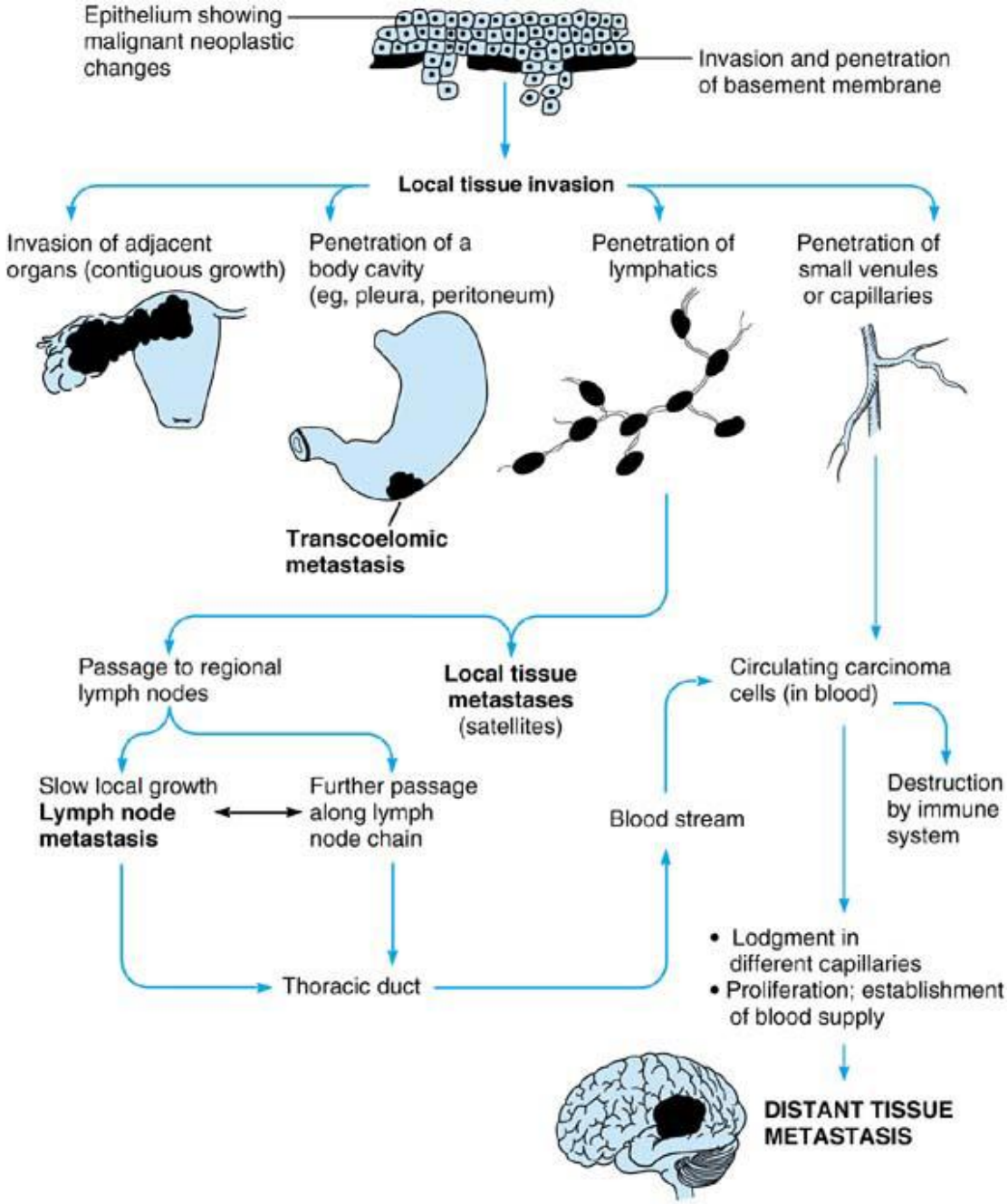
- Having penetrated the basement membrane, malignant cells gain access to the lymphatics and blood vessels, the first step toward general dissemination

- Infiltrating neoplastic cells tend to follow fascial planes along the pathway of least resistance; => destruction of tissue

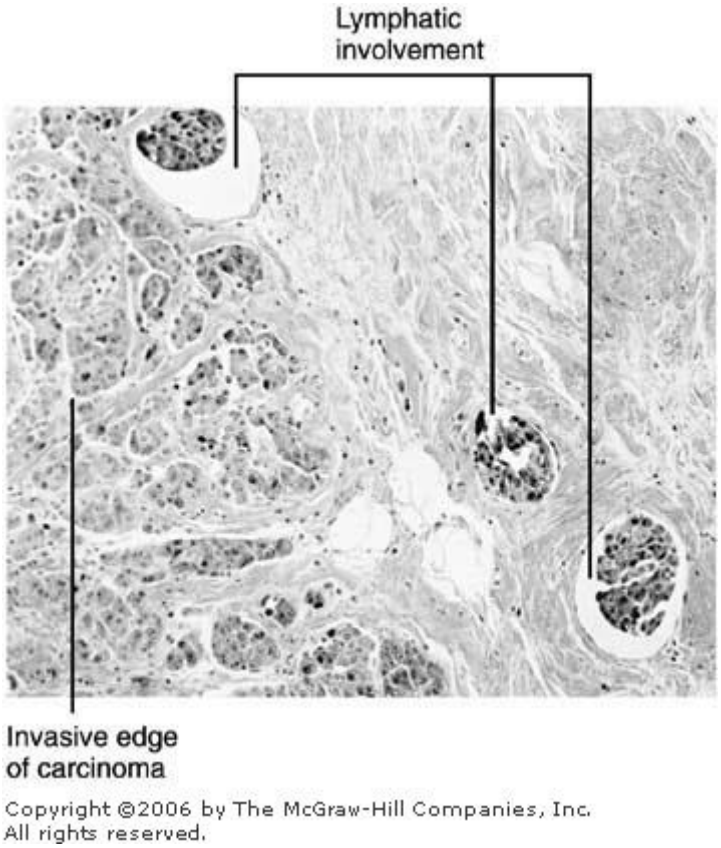
- Protease production,
- Loss of contact inhibition of neoplastic cells,
- Decreased cell adhesiveness

Carcinoma of the breast that is predominantly confined within the duct except at the right side, where it has infiltrated through the ductal basement membrane into the surrounding stroma





Infiltrating carcinoma, showing invasion of lymphatics by the tumor cells



Assessment of the extent of invasion by gross examination at the time of surgery is often difficult

- Because neoplastic cells can frequently remain undetected away from the apparent borders of the neoplasm.

- Wide margin of excision of apparently normal tissue surrounding the tumor.

Metastasis

- Establishment of a second neoplastic mass
- Through transfer of neoplastic cells
- From the first neoplasm to a secondary location separate from the original tumor.
- Occurs only in malignant neoplasms and explains why they are life-threatening and difficult to eradicate

Lymphatogenous Metastasis

- Metastasis via the lymphatics occurs early in carcinomas and melanomas

- Unusual occurrence in most sarcomas, which tend to spread mainly via the bloodstream.

- Malignant cells are carried by the lymphatics to the regional lymph nodes .

Rationale for radical surgery

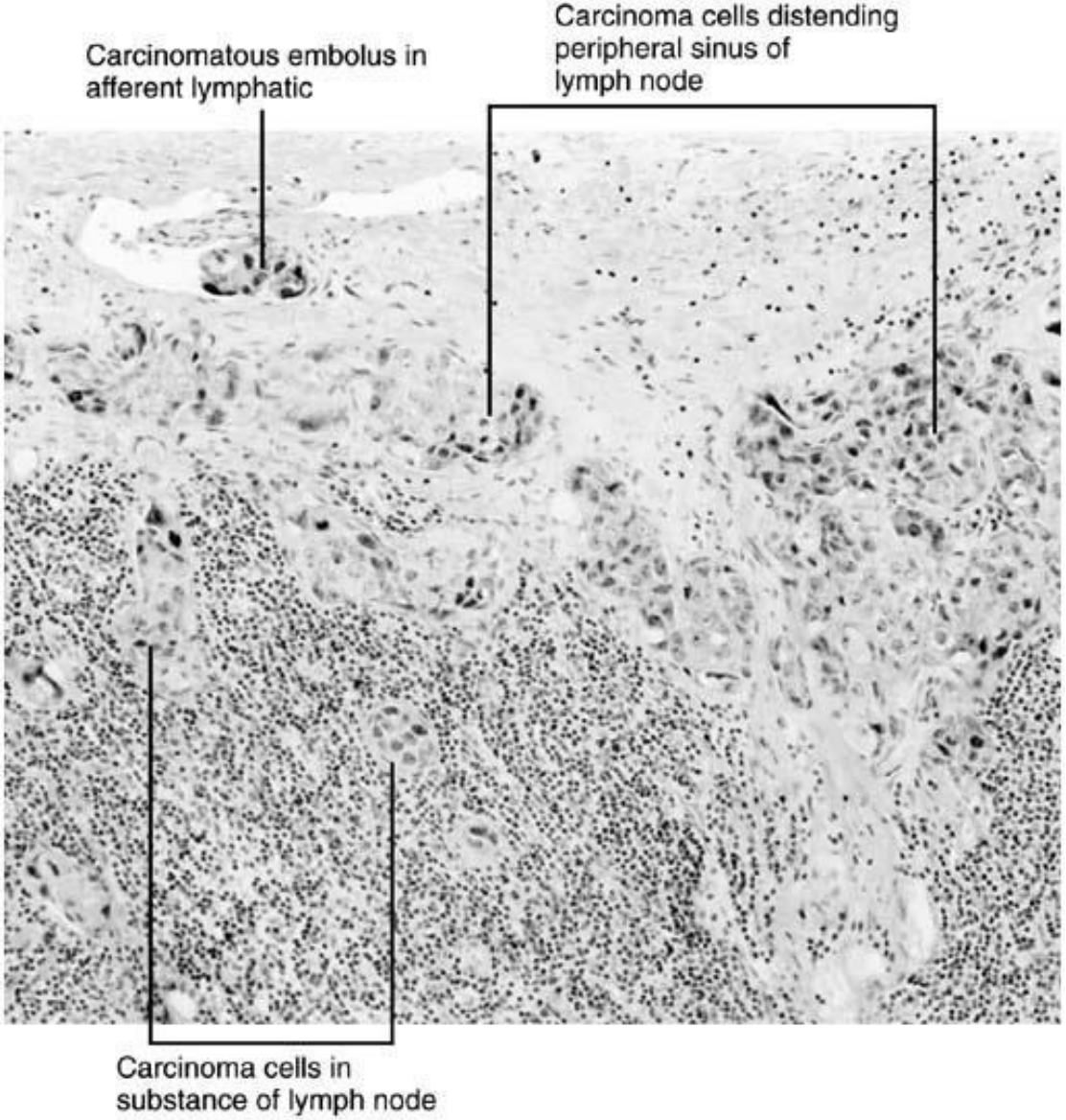
- The belief that cancerous cells spread first to the regional lymph nodes—
- Where their advance may be temporarily arrested by the immune response—

- Removes both the primary neoplasm and the regional lymph nodes to thereby eliminate the most likely sites of early metastases.

- Removal of lymph nodes is performed only for those neoplasms in which lymphatic metastasis is common, eg, carcinoma and melanoma.

- Knowledge of the lymphatic drainage of various tissues enables the clinician to predict the most likely sites of lymph node involvement

Metastatic carcinoma in a lymph node

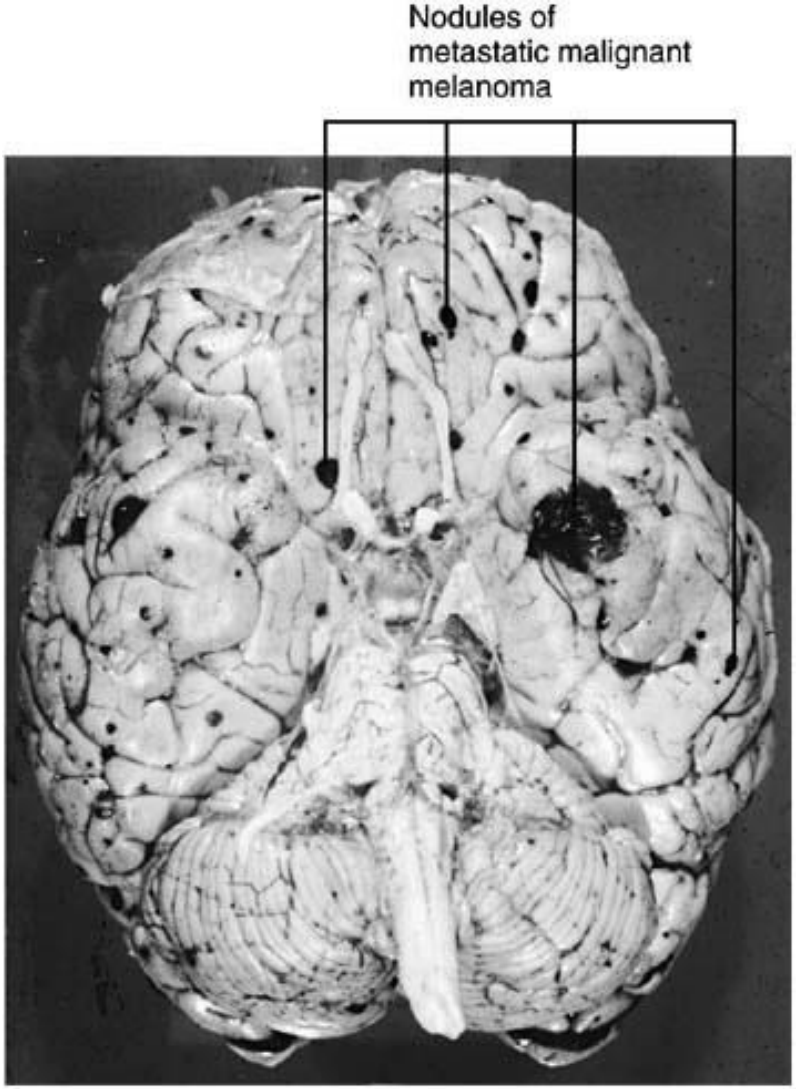


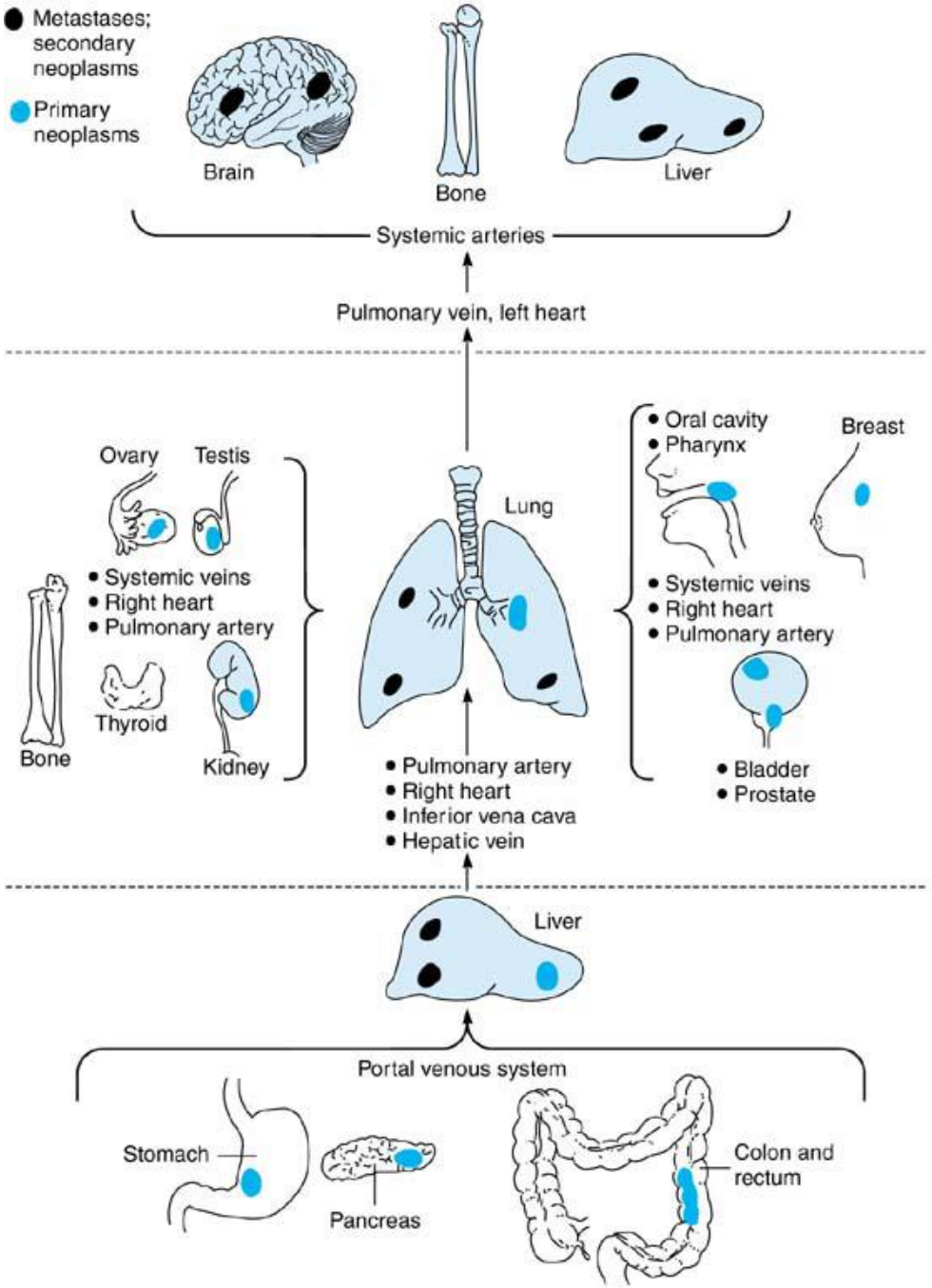
Hematogenous Metastasis

- Entry of cancerous cells into the bloodstream
- Most of these malignant cells are thought to be destroyed by the immune system, but some become coated with fibrin and entrapped in capillaries.
- Metastasis can occur only if enough cancerous cells survive in the tissues to become established and proliferate at a second site

- Production of **tumor angiogenesis factor** (TAF) by the cancerous cells
- Stimulates growth of new capillaries in the vicinity of tumor cells and
- Encourages vascularization of the growing metastasis

Hematogenous metastasis to the brain by a malignant melanoma, showing multiple pigmented tumor deposits





Seed And Soil Theory

Some types of cancer apparently favor particular metastatic sites

- Skeletal metastases are common in cancer of the prostate, thyroid, lung, breast, and kidney.
- Adrenal metastases are common in lung cancer.
- Experiments using repeated animal passage have enabled researchers to select clones of human cancer cells that selectively metastasize to specific sites

Metastasis in Body Cavities (Seeding)

- Entry of malignant cells into body cavities
- May be followed by dissemination of the cells anywhere within these cavities
- Ovary are common locations for peritoneal metastasis in patients with gastric cancer.

Dormancy of Metastases

- Cancerous cells that spread to distant sites may remain dormant there sometimes for many years.

- The presence of such dormant cancerous cells (or slowly growing subclinical metastases) has led to attempts to eradicate them by means of systemic chemotherapy after treatment of the primary tumor.

- While results have been encouraging in some types (malignant lymphoma, choriocarcinoma, and testicular germ cell tumors),

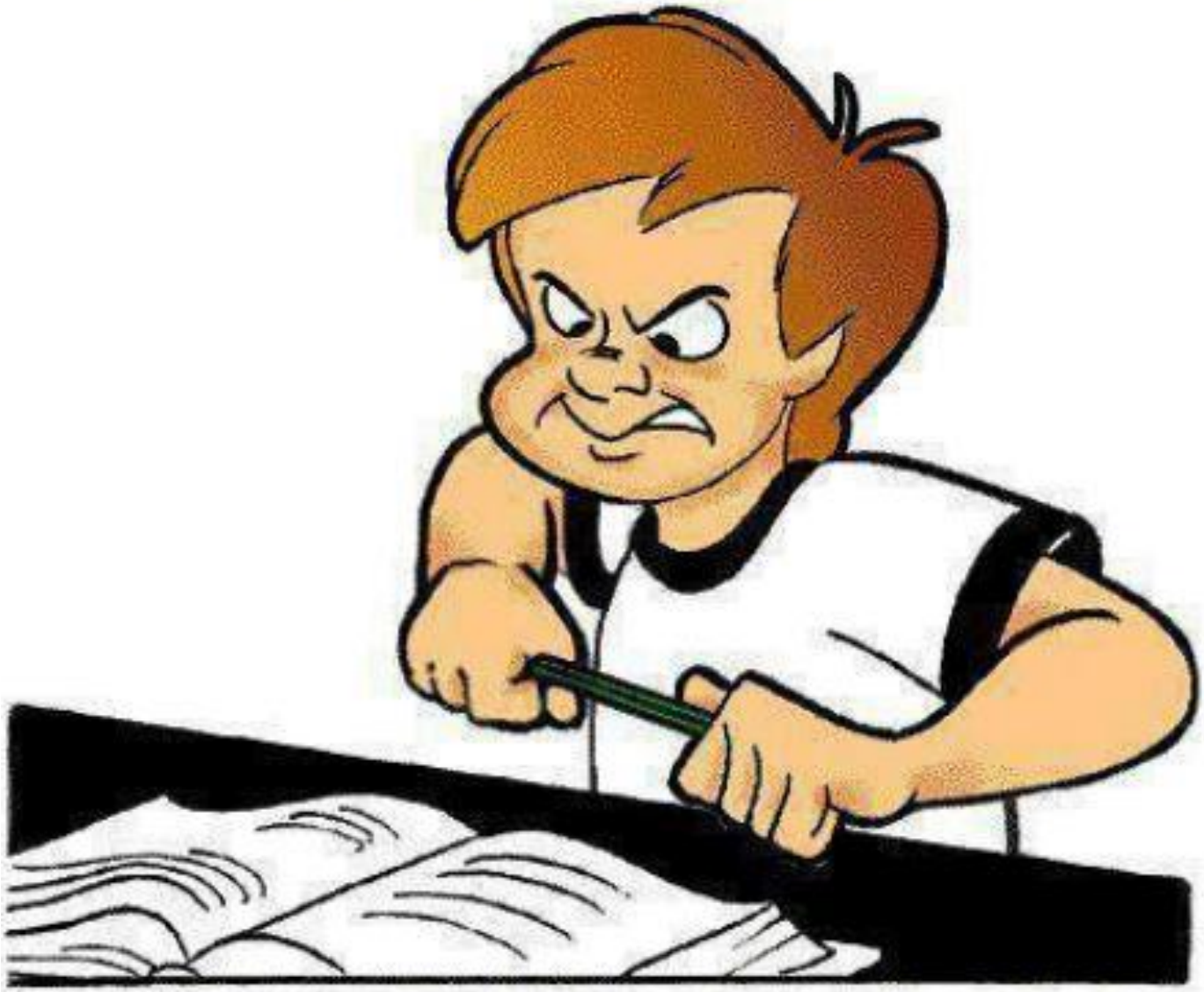
- The overall cure rate is so low morbidity of chemotherapy so high

Development of delayed metastases makes it difficult to pronounce a patient cured with any confidence.

- Survival for 5 years after treatment is considered a sign of cure for most cancers.

- However, 10- and 20-year survival rates are almost always lower than the 5-year survival rates, which suggests that many patients experience late metastases

TWO DAYS BEFORE EXAMS



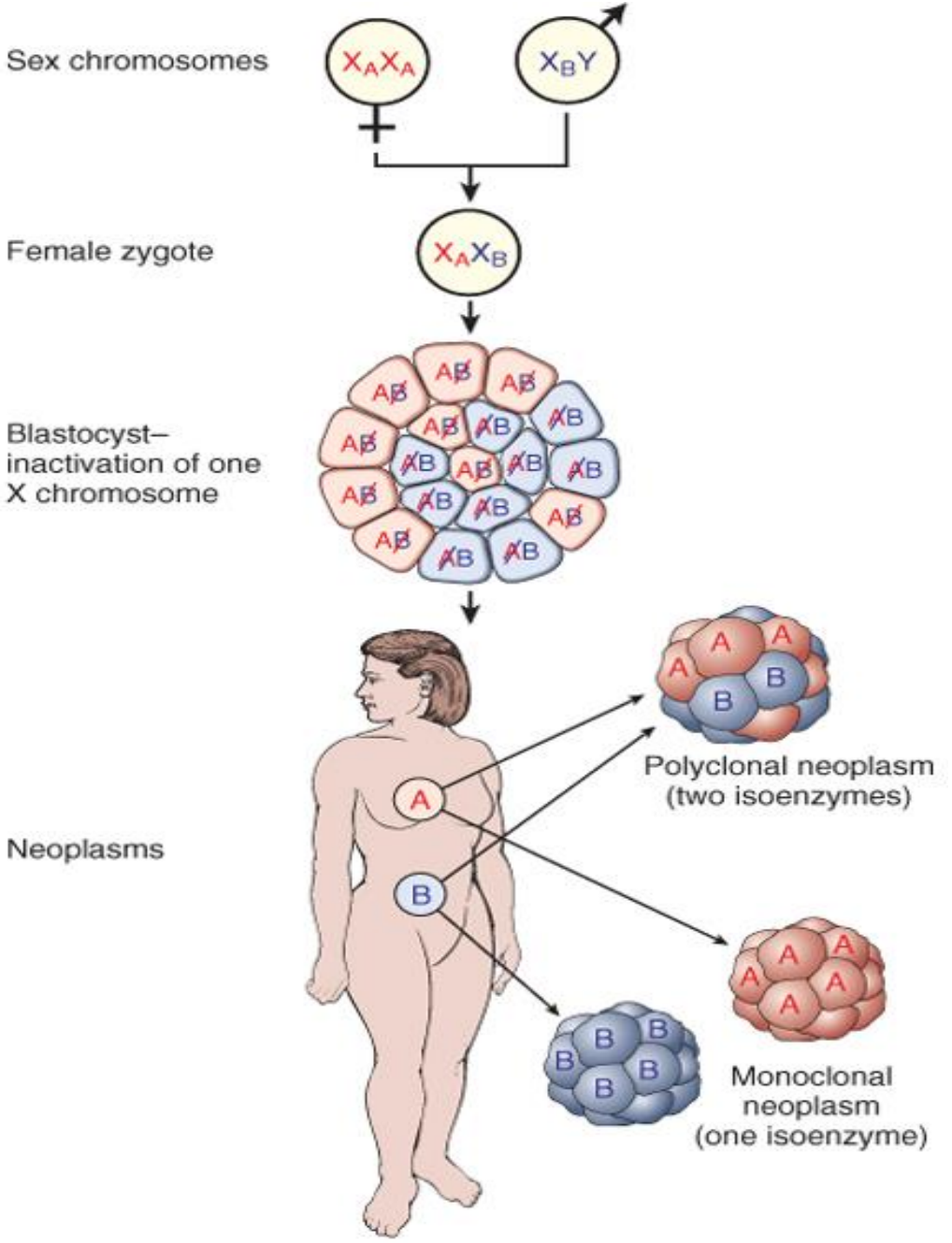
1 WEEK AUR MIL JATA TO KASAM SE TABAHI PHER DETA..

Fundamental principles

- ***Nonlethal genetic damage lies at the heart of carcinogenesis***
- Acquired or it may be inherited in the germ line.
- Mutations, may be spontaneous.

- *A tumor is formed by the clonal expansion of a single precursor cell that has incurred the genetic damage* (*i.e.*, *tumors are monoclonal*).

- Clonality of tumors can be assessed in women who are heterozygous for polymorphic X-linked markers, such as the enzymes (G6PD)



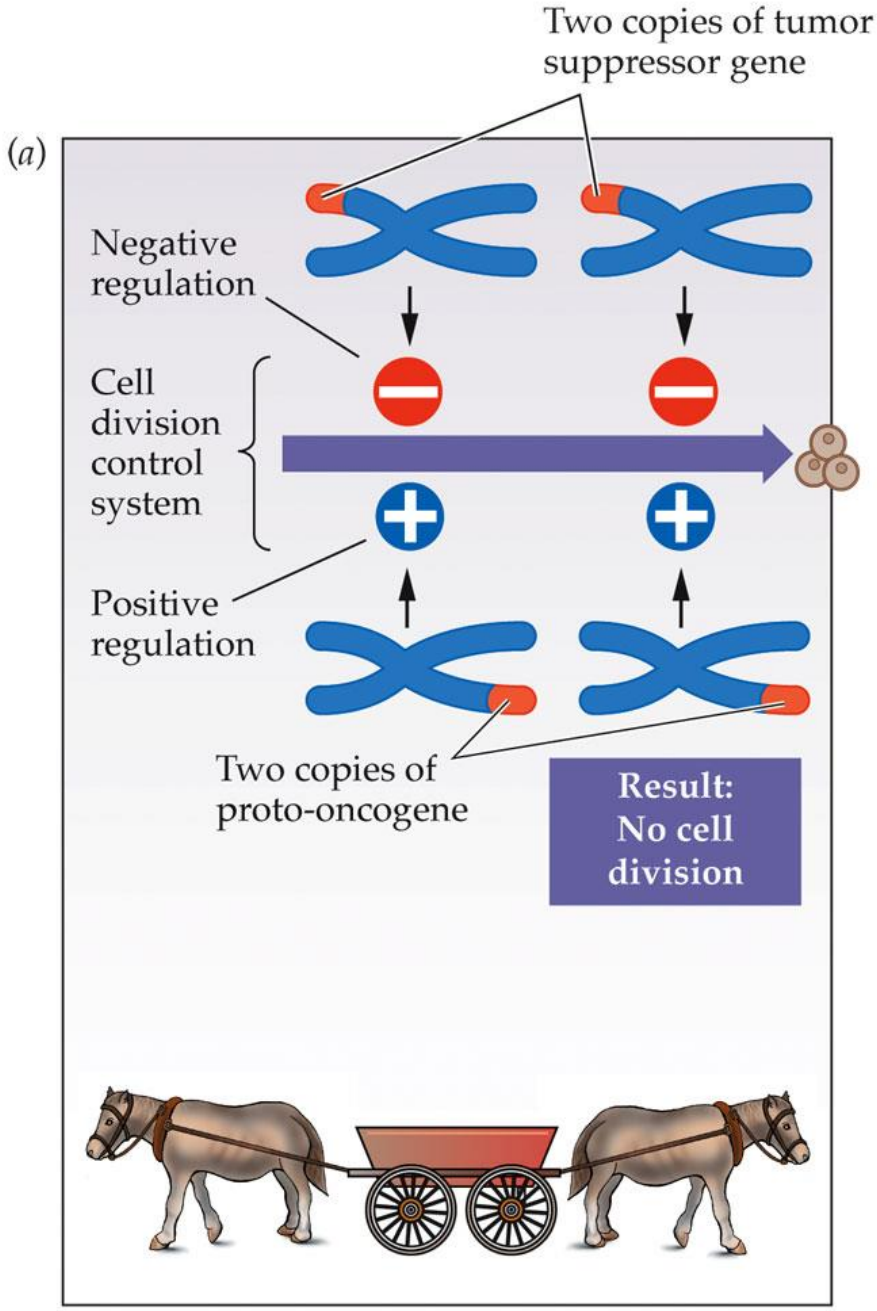
Four classes of normal regulatory genes

1. *The growth-promoting protooncogenes,*

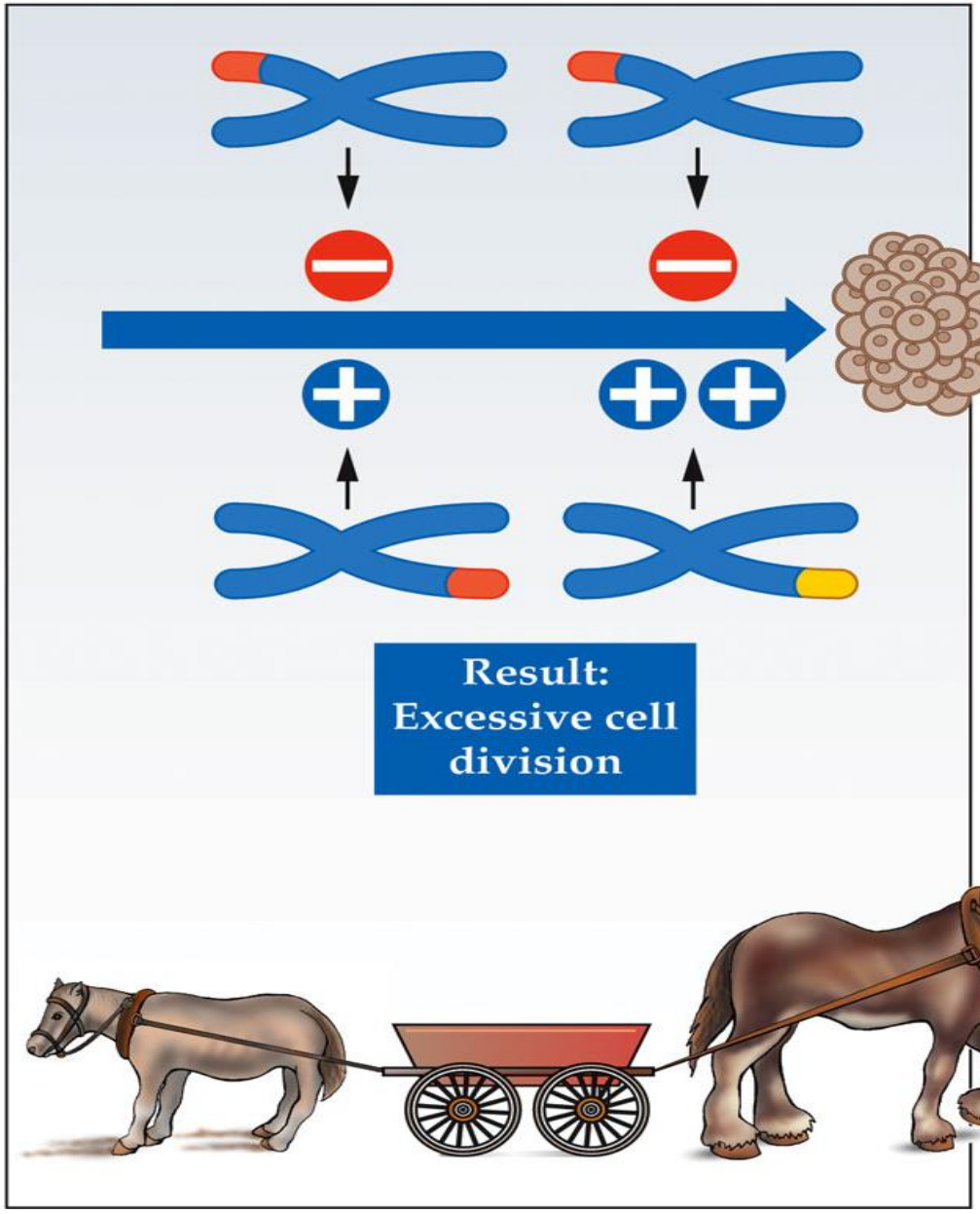
2. *The growth-inhibiting tumor suppressor genes*

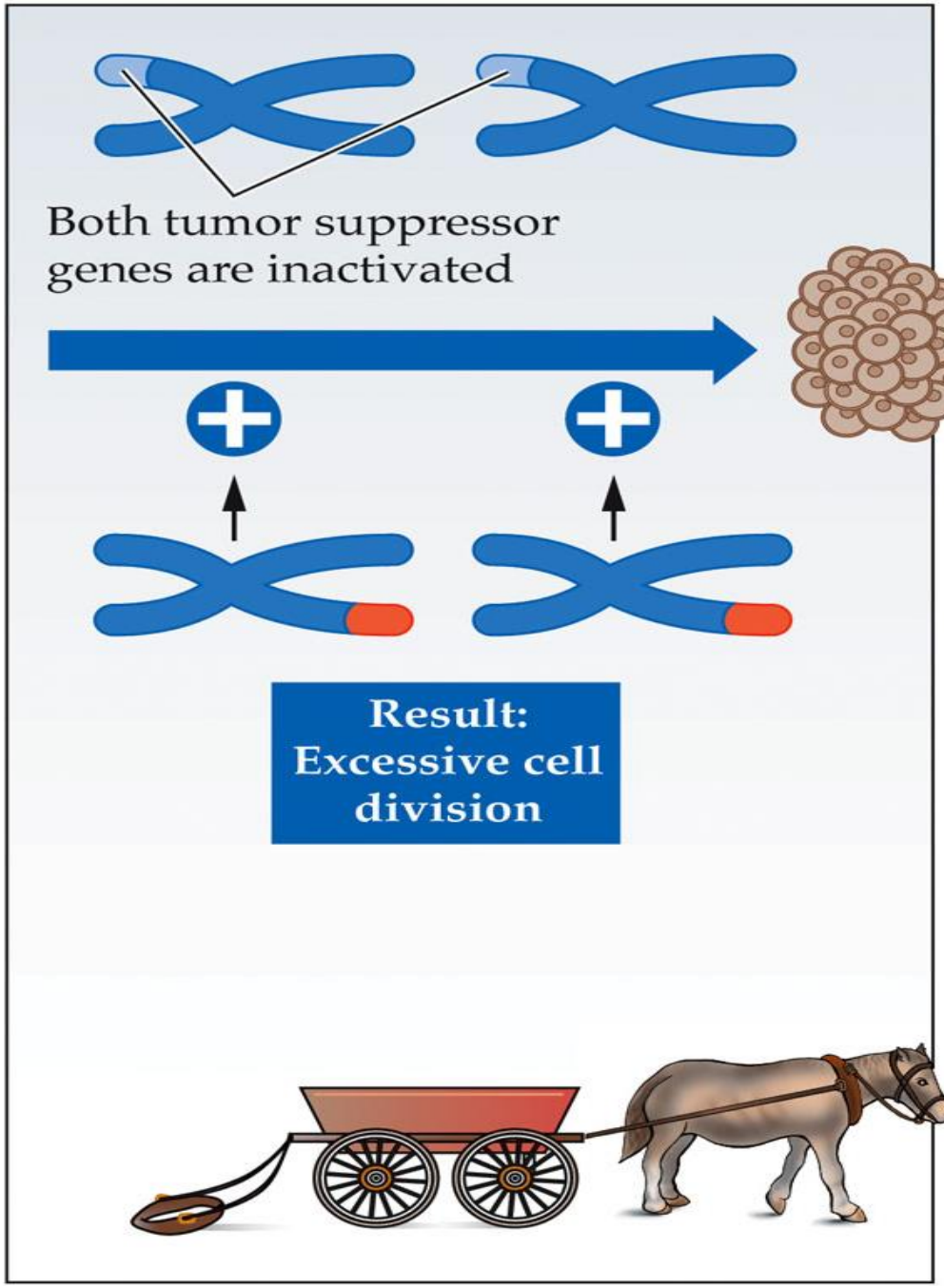
3. *Genes that regulate programmed cell death (apoptosis)*

4. *Genes involved in DNA repair-are the principal targets of genetic damage.*



DISCOVER BIOLOGY, **Second Edition, Figure 11.7 (Part 1)**


Result:
Excessive cell
division


Both tumor suppressor genes are inactivated
Result: Excessive cell division

- Mutant alleles of proto-oncogenes are considered dominant because they transform cells despite the presence of a normal counterpart

TUMOR SUPPRESSOR GENES: *RECESSIVE ONCOGENES*

- In contrast, both normal alleles of the tumor suppressor genes must be damaged for transformation to occur,

- so this family of genes is sometimes referred to as *recessive oncogenes*

- Genes that regulate apoptosis may be dominant, as are protooncogenes, or they may behave as tumor suppressor genes.

Tumor suppressor genes :2 general groups, PROMOTERS & CARETAKERS

Promoters

- The traditional tumor suppressor genes, such as ***RB*** or ***p53***,

- Mutation of the gene leads to transformation by releasing the brakes on cellular proliferation.

Caretaker

- Responsible for processes that ensure the integrity of the genome, such as DNA repair.

- **Mutation of caretaker genes does not directly transform cells by affecting proliferation or apoptosis.**

- *DNA repair genes affect cell proliferation or survival indirectly by influencing the ability of the organism to repair nonlethal damage in other genes…….*

- A disability in the DNA repair genes can predispose to mutations in the genome => *Neoplastic Transformation.*

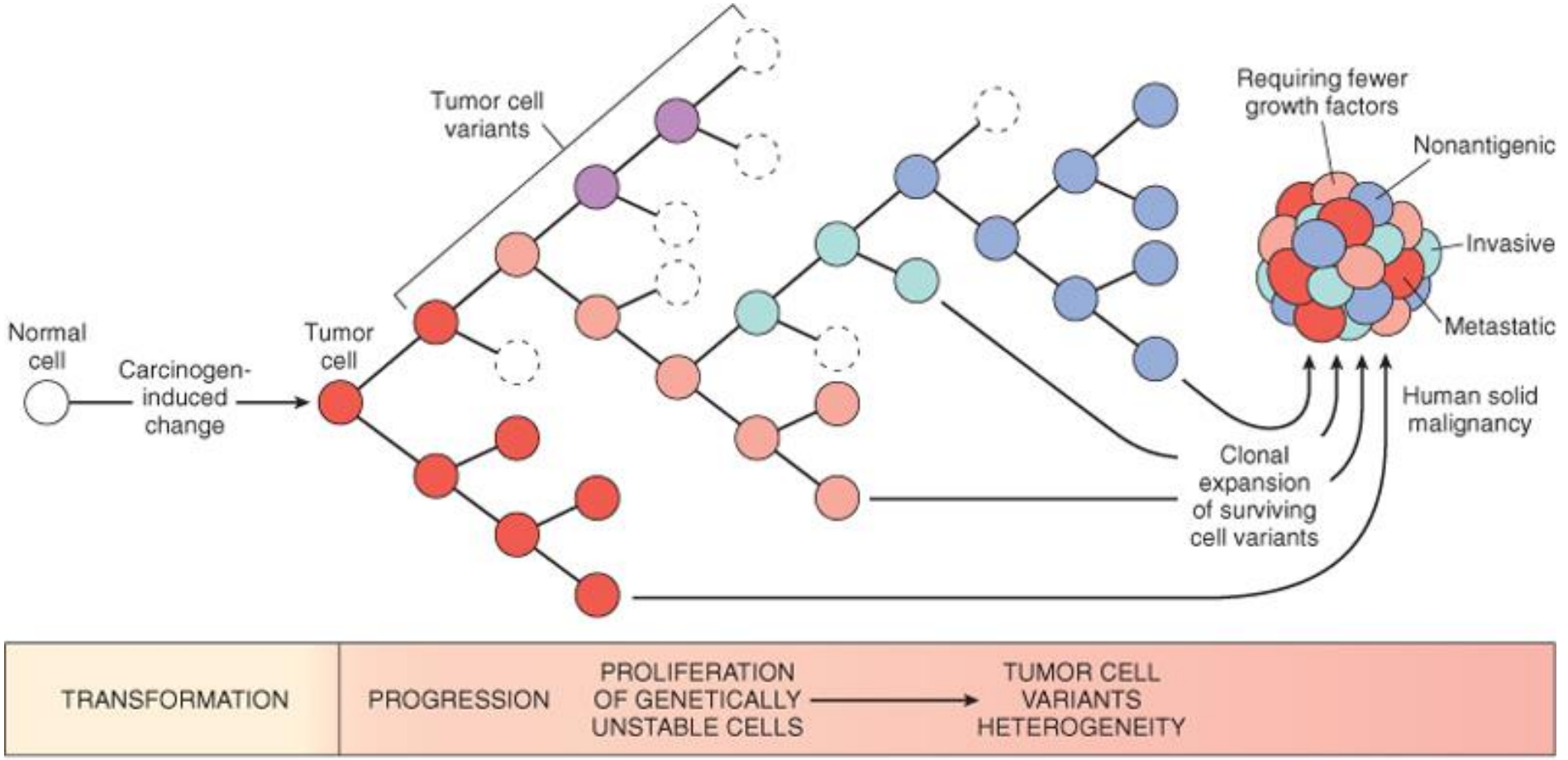
- As tumor suppressor genes.

Carcinogenesis is a multistep process at both the phenotypic and the genetic levels

- Several phenotypic attributes,
- Such as excessive growth, local invasiveness, and the ability to form distant metastases.
- characteristics acquired stepwise fashion, *tumor progression*.

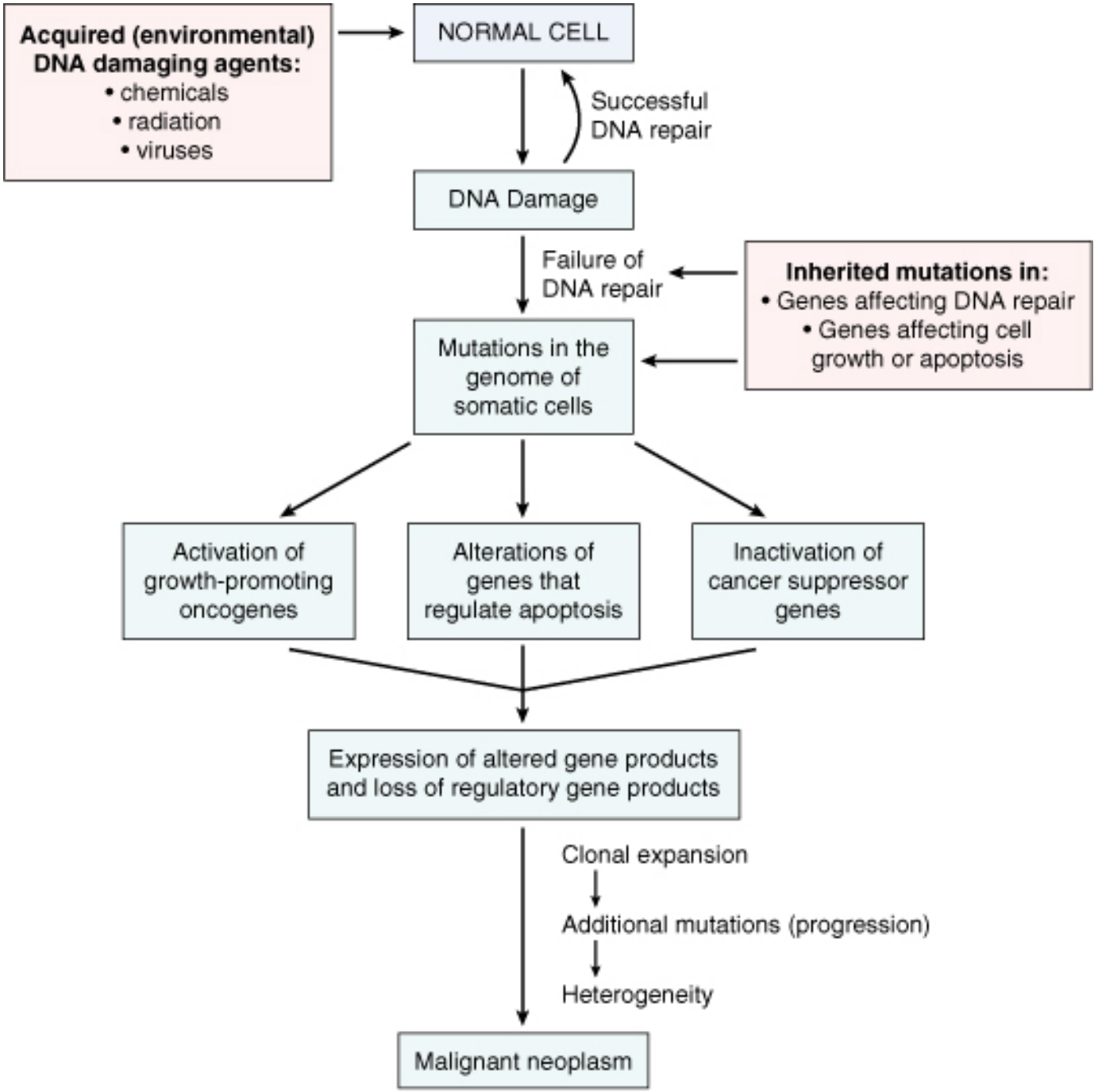
- At the molecular level, progression results from accumulation of genetic lesions that in some instances are favored by defects in DNA repair.

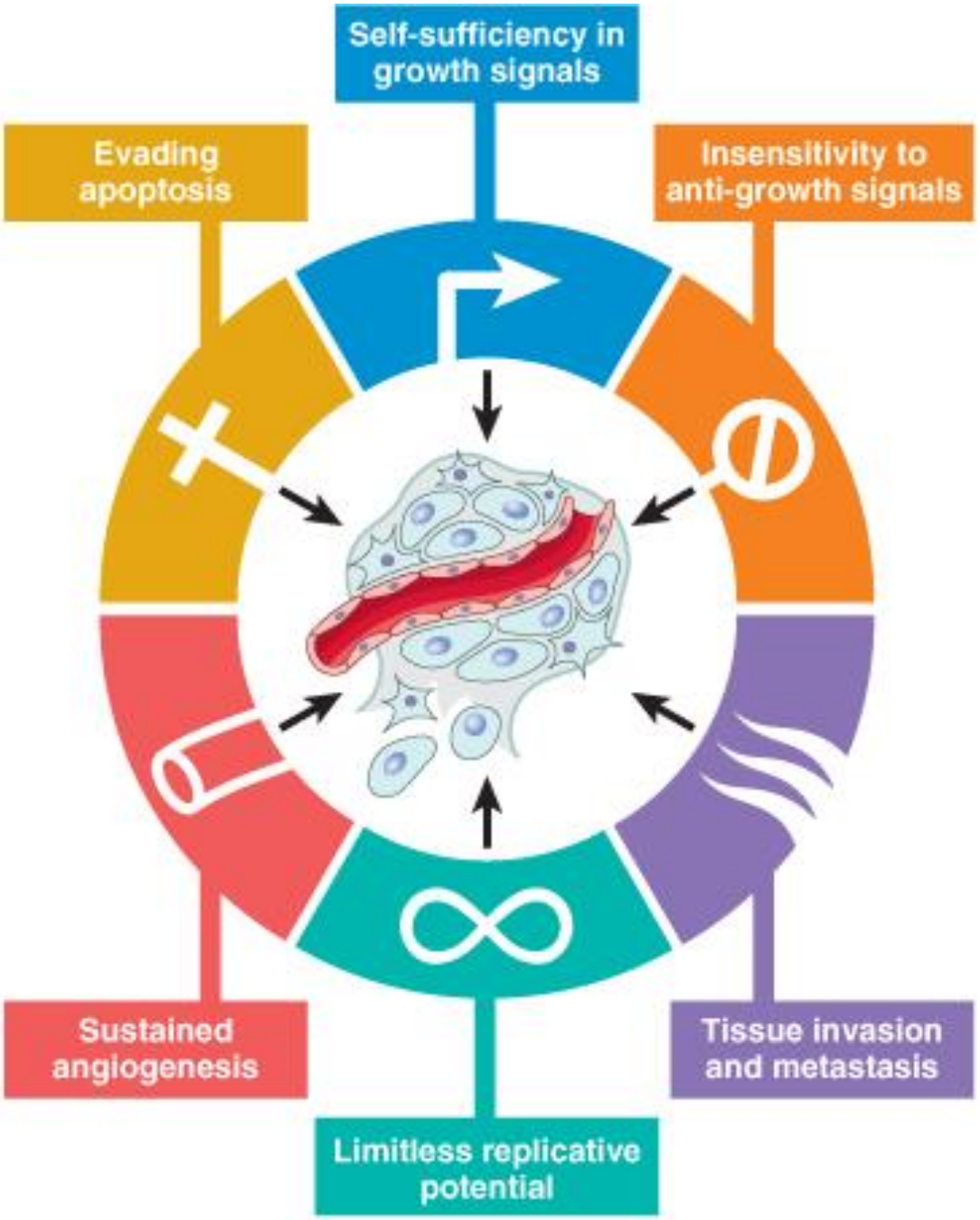
Tumor progression and generation of heterogeneity. New subclones arise from the descendants of the original transformed cell by multiple mutations



ESSENTIAL ALTERATIONS FOR MALIGNANT TRANSFORMATION

- Past two decades, hundreds of cancer-associated genes have been discovered.
- *p53*, are commonly mutated
- *c-ABL*, are affected only in certain leukemias.
- Each of the cancer genes has a specific function, the dysregulation of which contributes to the origin or progression of malignancy.





Seven fundamental changes in cell physiology that together determine malignant phenotype

1. *Self-sufficiency in growth signals*: Tumors have the capacity to proliferate without external stimuli,

2. *Insensitivity to growth-inhibitory signals*: may not respond to molecules that are inhibitory to the proliferation of normal cells (TGF-β)

3. *Evasion of apoptosis* consequence of *p53* inactivation

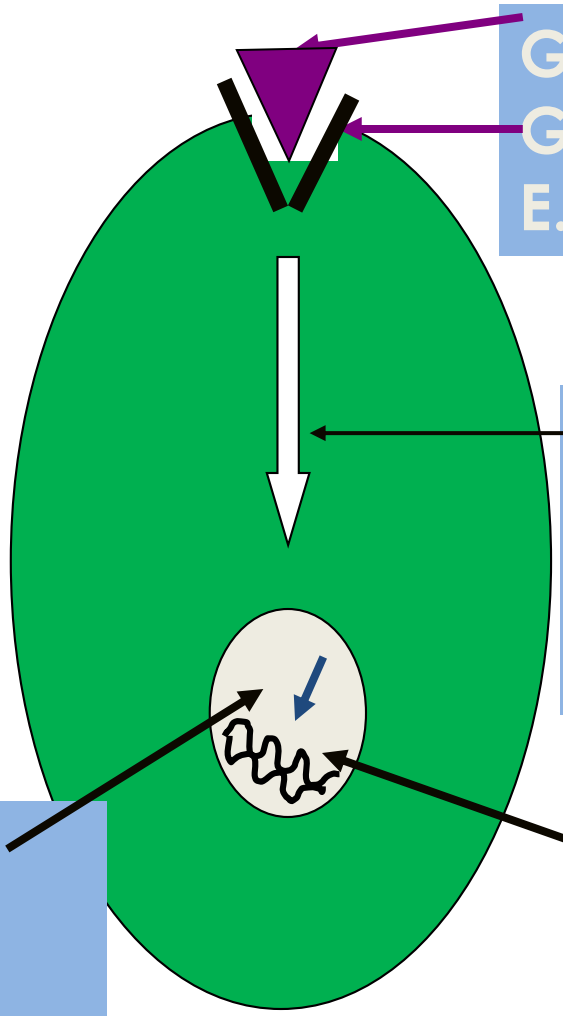
4. *Defects in DNA repair*: Tumors may fail to repair DNA damage caused by carcinogens or unregulated cellular proliferation.

5. *Limitless replicative potential*: unrestricted proliferative capacity, associated with maintenance of telomere length and function.

6. *Sustained angiogenesis*: Tumors are not able to grow without formation of a vascular supply, which is induced by various factors, the most important being (VEGF).

7. *Ability to invade and metastasize*: Tumor metastases are the cause of the vast majority of cancer deaths

Relationship B/W gene products of proto oncogene



Growth factors eg IGF
Growth factor receptors
E.g. erb-2

Signal transducing factors
E,g. cytoplasmic kinases

DNA binding proteins concerned with transcription

cell cycle proteins e.g. cyclin D

Physiologic conditions, cell proliferation can be readily resolved into the following steps:

- The binding of a growth factor to its specific receptor on the cell membrane

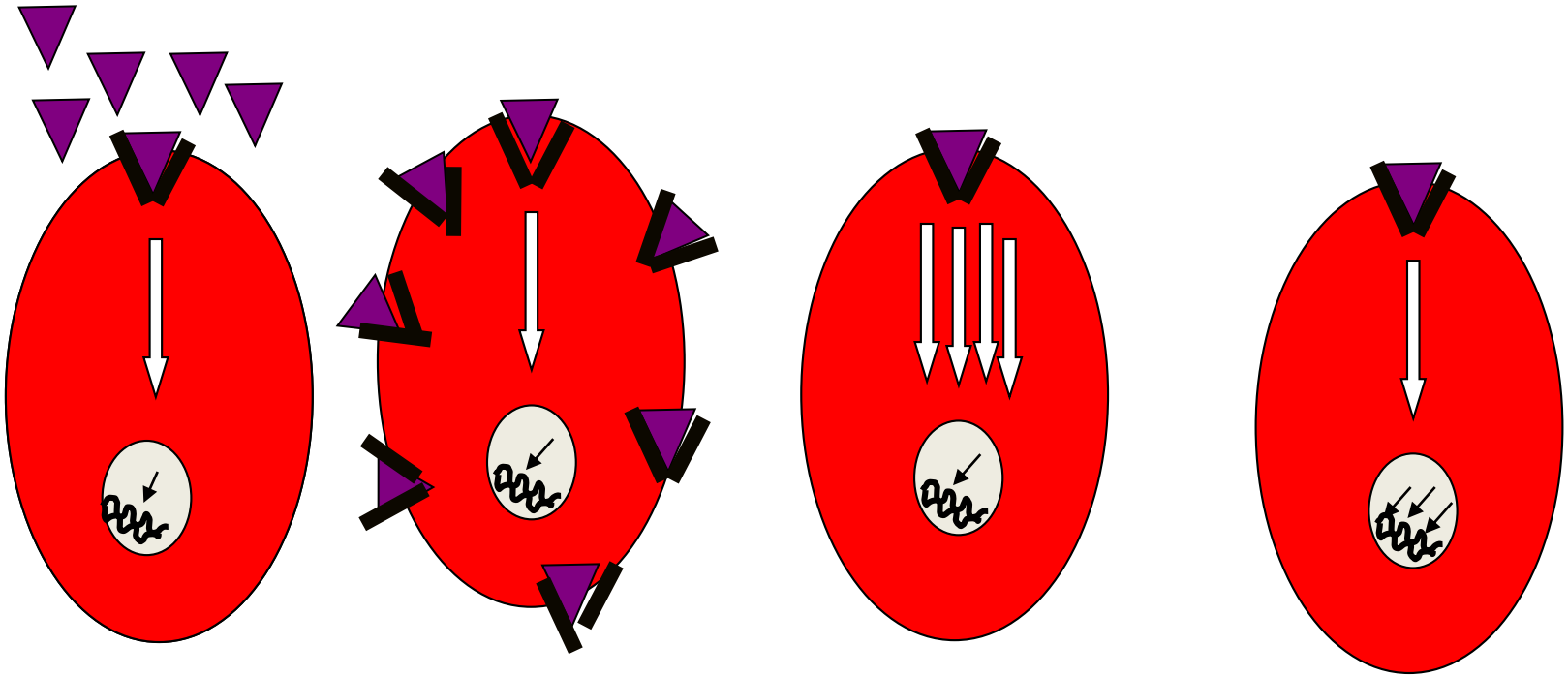
- Transient and limited activation of the growth factor receptor, => activates several signal-transducing proteins

- Transmission of the transduced signal across the cytosol to the nucleus via second messengers

- Induction and activation of nuclear regulatory factors that initiate DNA transcription

- Entry and progression of the cell into the cell cycle, resulting ultimately in cell division

NEOPLASTIC CELLS



Increased In growth factor

Increased In growth factor **receptors**

Increased in signal transduction

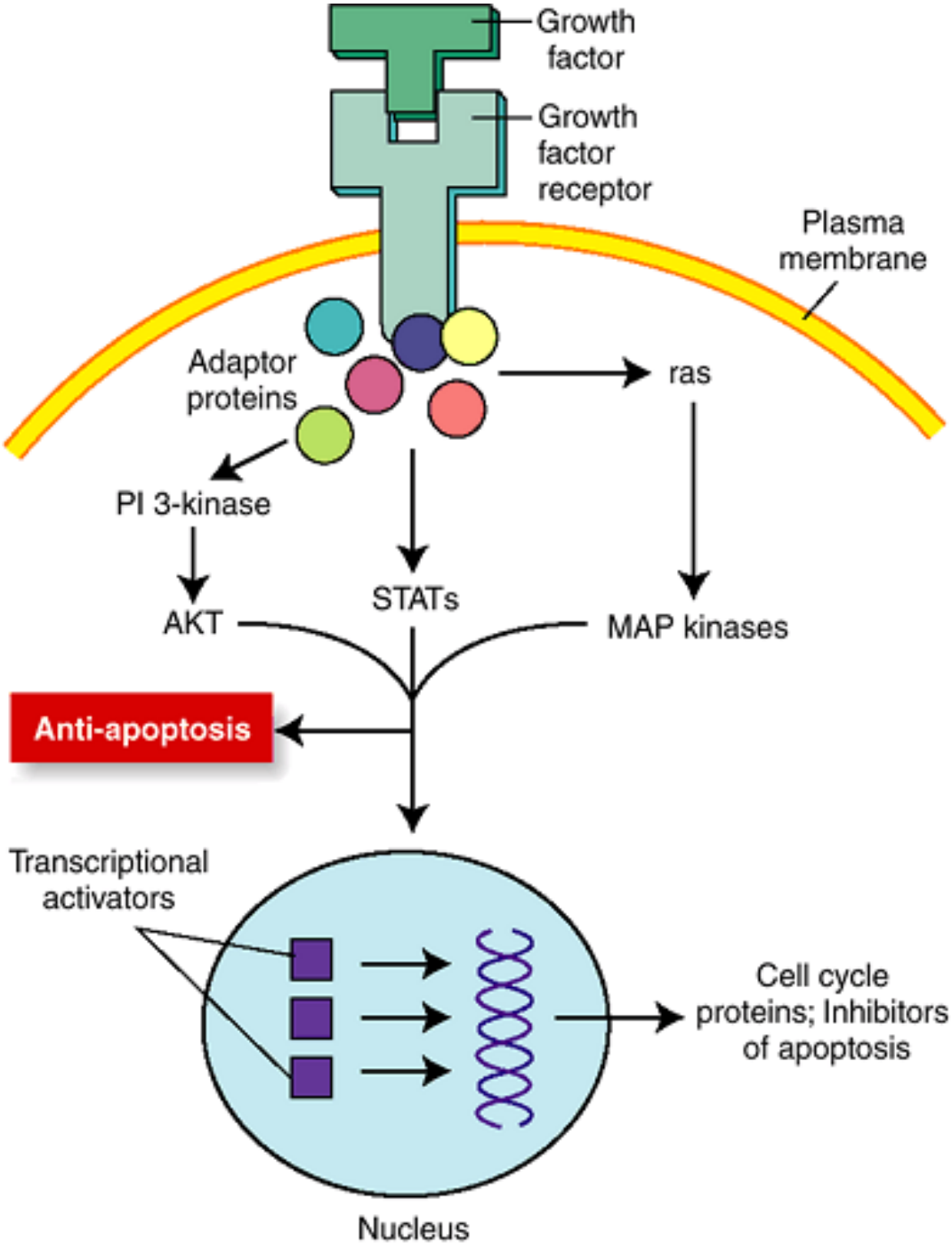
Increase in activation of transcription

Self-Sufficiency in Growth Signals

Oncogenes–Growth Promoting Genes.

Functional Category	Oncogene	Action	Tumors
Growth factor	*Sis* *int*, *hst*	(PDGF) (FGF like)	Glioma Breast, esophagus
Growth factor receptor	*erb–B* *erb–B2 (Her2/neu)*	(EGFR) (EGFR–like)	Breast, ovary Breast, ovary
Signal transduction/relay factors	*Ret* *src* *abl*	Tyrosine Kinase	Thyroid Sarcoma CML;t (9;22)
	N–ras	(GTP binding)	Leukemias
	Ki–ras	(GTP binding)	Lung, pancreas, colon

Transcription factors	***c–myc* *n–myc* *L–myc***	**(Activate growth promoting genes)**	**Leukemia, breast, colon Neuroblastoma Lung**
Cell cycle control	*bcl–1* (PRADI) *mdm–2*	(Codes cyclin–D1) (p53 antagonist)	Breast, squamous cancer Sarcomas
Apoptosis block	*bcl–2*	(Inhibits programmed cell death)	B cell lymphomas


Growth factor
Growth factor receptor
Plasma membrane
Adaptor proteins
ras
PI 3-kinase
STATs
AKT
MAP kinases
Anti-apoptosis
Transcriptional activators
Cell cycle proteins; Inhibitors of apoptosis
Nucleus

Tumor Suppressor (Growth Inhibitory) and Repair Genes

Functional Category	Gene	Tumors
Cell cycle brakes	*P53*	Bladder, lung, ovary
	RB	Retinoblastoma, bone, lung
	MTS1 (p16)	Melanoma, ovary
Other inhibitors	*NF–1* (ras antagonist)	Neurofibroma
	BRCA1	Hereditary breast cancer
	BRCA2	Hereditary breast cancer
	WT–1	Wilms' tumor
	APC	Colon
Mismatch repair	*MSH2 LH1*	Colon, endometrium
	PMS1, PMS2	
Apoptosis inducer	*p53*	Bladder, lung, ovary

GROWTH FACTORS

- Autocrine action
- Paracrine action
- Many cancer cells acquire growth self-sufficiency,
- Platelet-derived growth factor (PDGF) and
- Transforming growth factor α (TGF-α).

- Many Glioblastomas secrete PDGF and express the PDGF receptor
- Sarcomas make TGF-α & its receptor.

- In many instances, the products of other oncogenes (*RAS*) cause overexpression of growth factor genes.

- Consequently the cell may be forced to secrete large amounts of growth factors (TGF-α)

GROWTH FACTOR RECEPTORS

- Several oncogenes encode
- Mutations and pathologic overexpression
- Mutant receptor proteins deliver continuous mitogenic signals to cells, even in the absence of the growth factor in the environment.

- More common than mutations is overexpression of growth factor receptors.

- This overexpression can render cancer cells hyperresponsive to normal levels of the growth factor, a level that would not normally trigger proliferation.
- (EGF) receptor family.

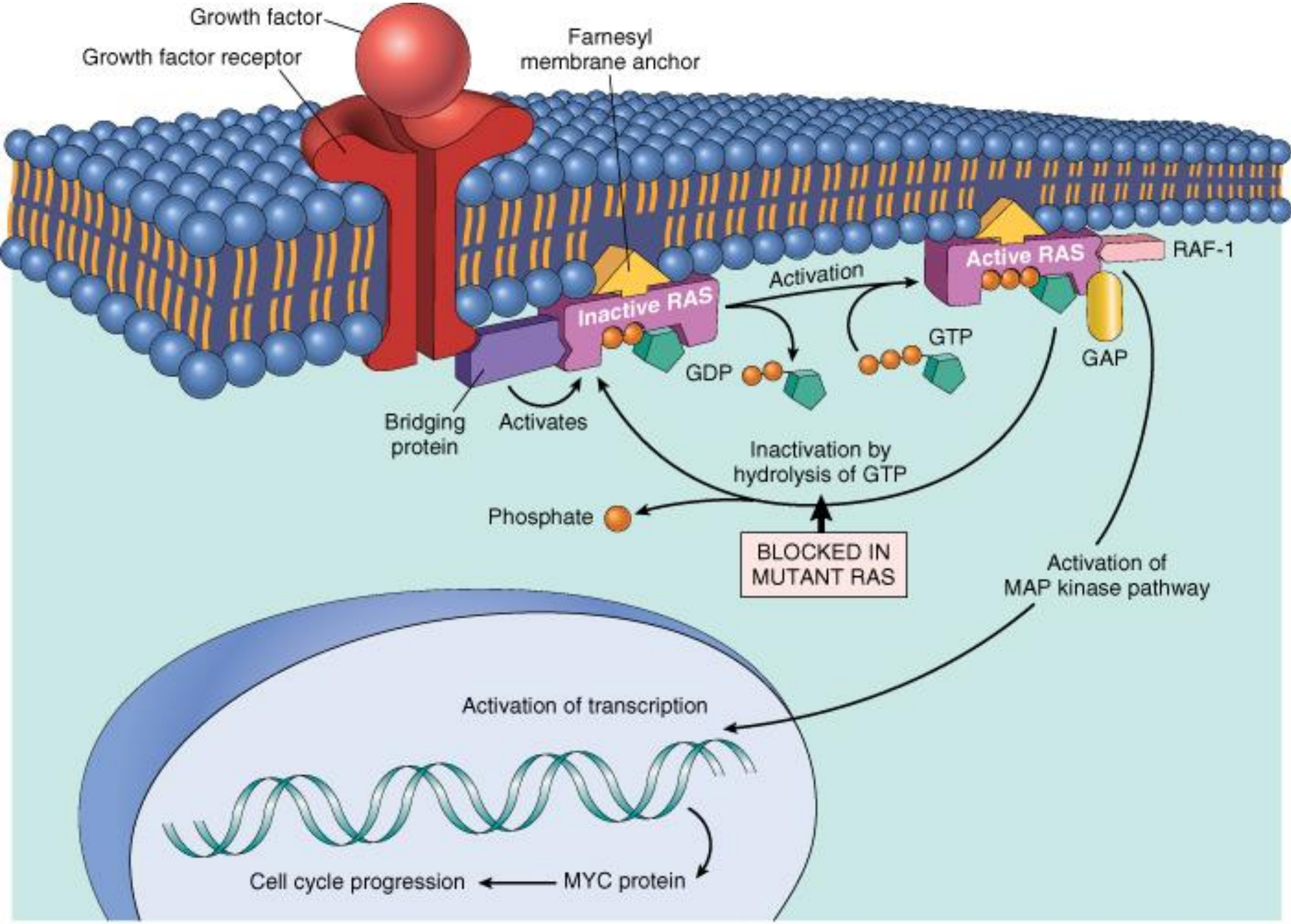
- *ERBB1*, the EGF receptor, is overexpressed in 80% of squamous cell carcinomas of the lung

- *HER2/NEU (ERBB2)*, is amplified in 25% to 30% of breast cancers and adenocarcinomas of the lung, ovary, and salivary glands.

- High level of *HER2/NEU* protein in breast cancer cells => poor prognosis.

- Clinical benefit derived from blocking the extracellular domain of this receptor with anti- *HER2/NEU* antibodies.

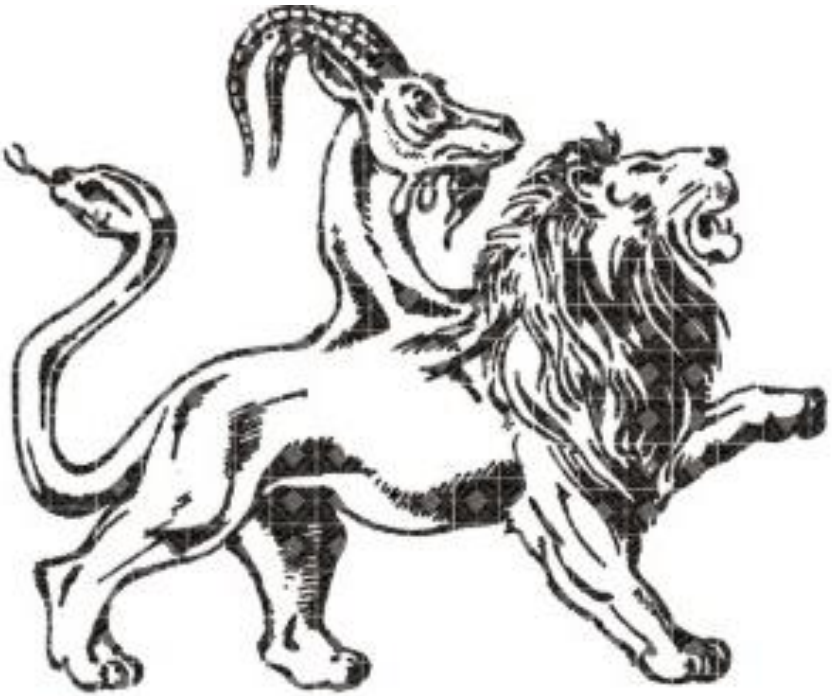
- Treatment of breast cancer with anti-HER2 antibody is an elegant example of "bench to bedside" medicine



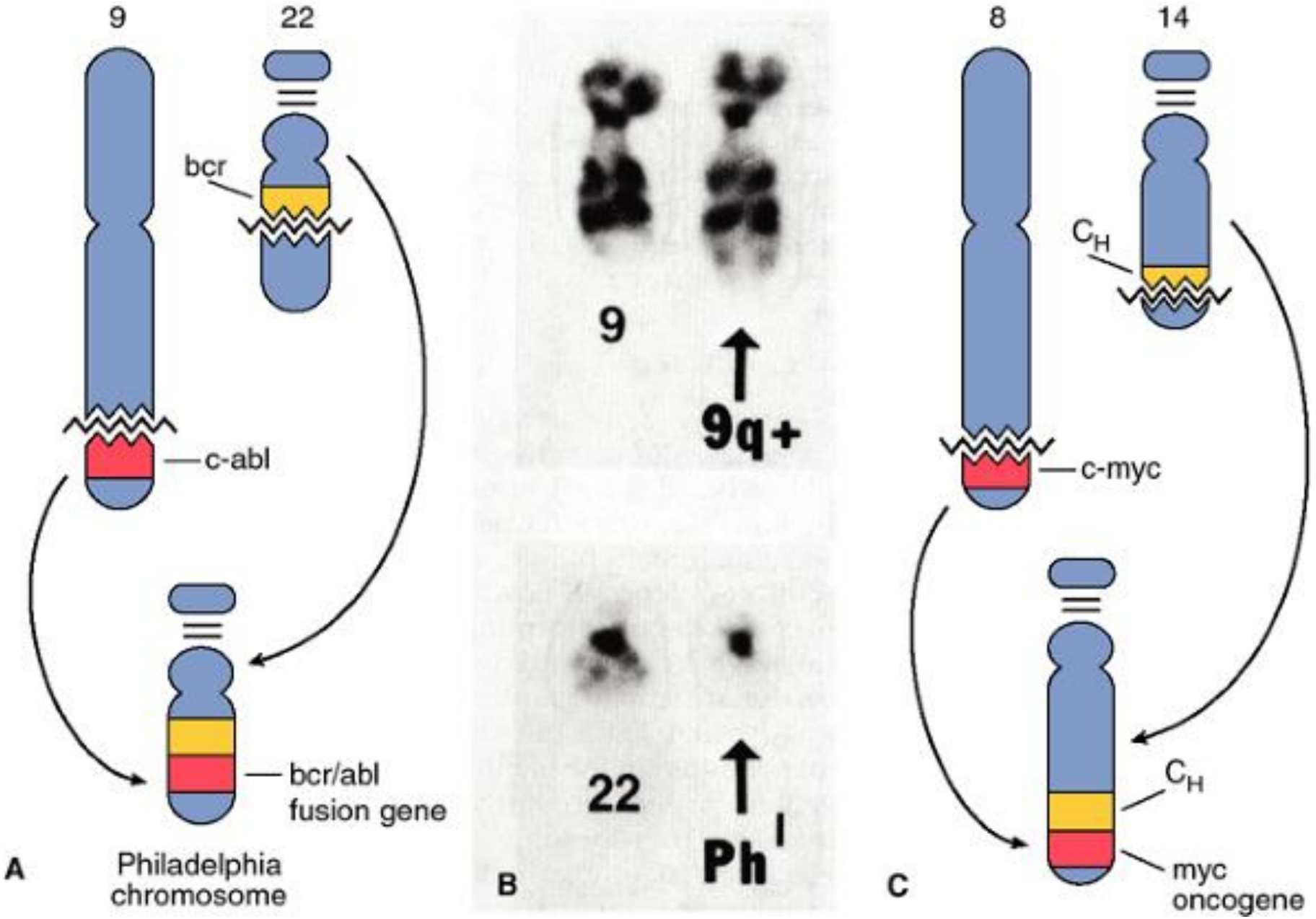
SIGNAL-TRANSDUCING PROTEINS

- A relatively common mechanism
- These signaling molecules couple growth factor receptors to their nuclear targets.
- Inner leaflet of the plasma membrane,
- Receive signals from activated growth factor receptors
- Transmit them to the nucleus.
- *RAS* and *ABL*.

- Most common oncogene abnormality in human tumors
- 30% of all human tumors contain mutated versions of the *RAS* gene.
- Colon & pancreatic cancers, *RAS* mutations even higher.
- Binds [GTP] &[GDP]),
- Normal RAS proteins flip back and forth between an excited signal-transmitting state and a quiescent state.



CHIMERA

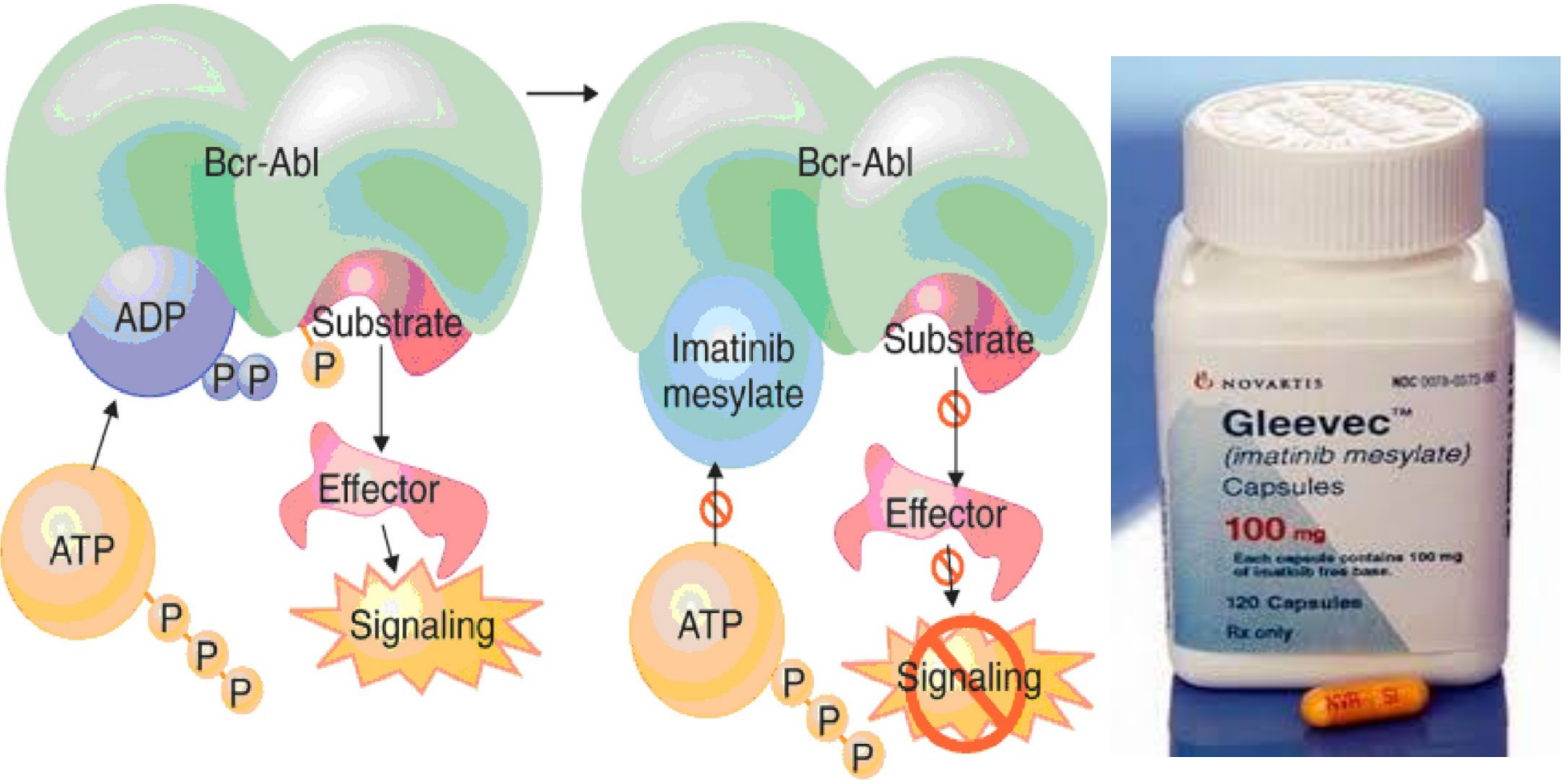

9
22
bcr
c-abl
bcr/abl
fusion gene
A
Philadelphia
chromosome
9
9q+
22
Ph
B
8
14
C_H
c-myc
C_H
myc
oncogene
C

- The *ABL* protooncogene has tyrosine kinase activity
- CML and certain acute leukemias, *ABL* gene is translocated from its normal abode on chromosome 9 to chromosome 22,
- Where it fuses with part of the breakpoint cluster region (*BCR*) gene

- The *BCR-ABL* hybrid gene has potent tyrosine kinase activity, including the *RAS-RAF* cascade

- Dramatic clinical response of patients with chronic myeloid leukemia after therapy with an inhibitor of *ABL* kinase called STI 571 imatinib mesylate (Gleevec);

- This is another example of rational drug design


Bcr-Abl
ADP
P P
Substrate
P
Effector
ATP
P P P
Signaling
Bcr-Abl
Imatinib mesylate
Substrate
Effector
ATP
P P P
Signaling
NOVARTIS
Gleevec™
(imatinib mesylate)
Capsules
100 mg
120 Capsules
Rx only

NUCLEAR TRANSCRIPTION FACTORS

- Ultimately, all signal transduction pathways enter the nucleus
- Growth autonomy of mutations affecting genes that regulate transcription of DNA.
- *MYC* gene is involved most commonly in human tumors.
- MYC protein is induced rapidly when quiescent cells receive a signal to divide.

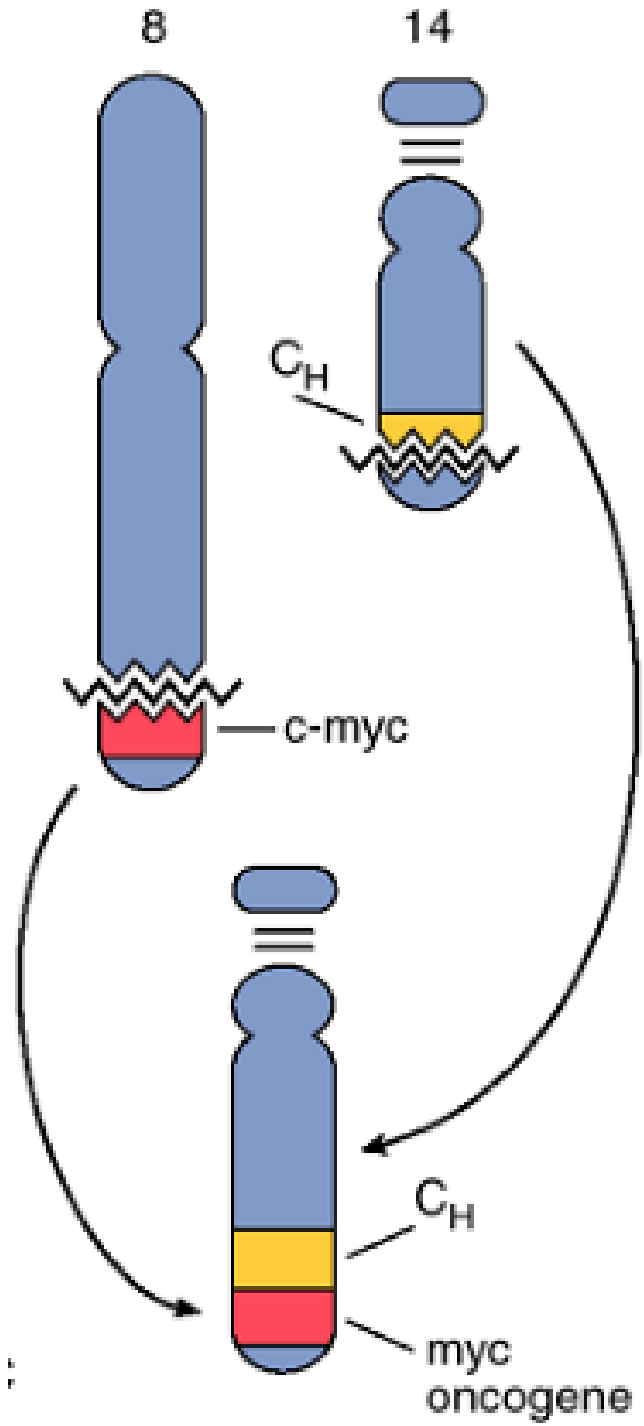
- The MYC protein binds to the DNA, causing transcriptional activation of several growth-related genes, including (CDKs),
- Whose product drives cells into the cell cycle
- In normal cells, MYC levels decline to near basal level when the cell cycle begins.
- In contrast, oncogenic versions of the *MYC* gene are associated with persistent expression or overexpression, contributing to sustained proliferation.

The MYC protein can either activate or repress the transcription of other genes

- Activated;: several growth-promoting genes, including cyclin-dependent kinases (CDKs), whose products drive cells into the cell cycle

- Repressed :: CDK inhibitors (CDKIs).

- Thus, MYC promotes tumorigenesis by increasing expression of genes that promote progression through the cell cycle and repressing genes that slow or prevent progression through the cell cycle.



Burkitt lymphoma

chromosomal breaks involve the long arms of chromosomes 8 and 14.

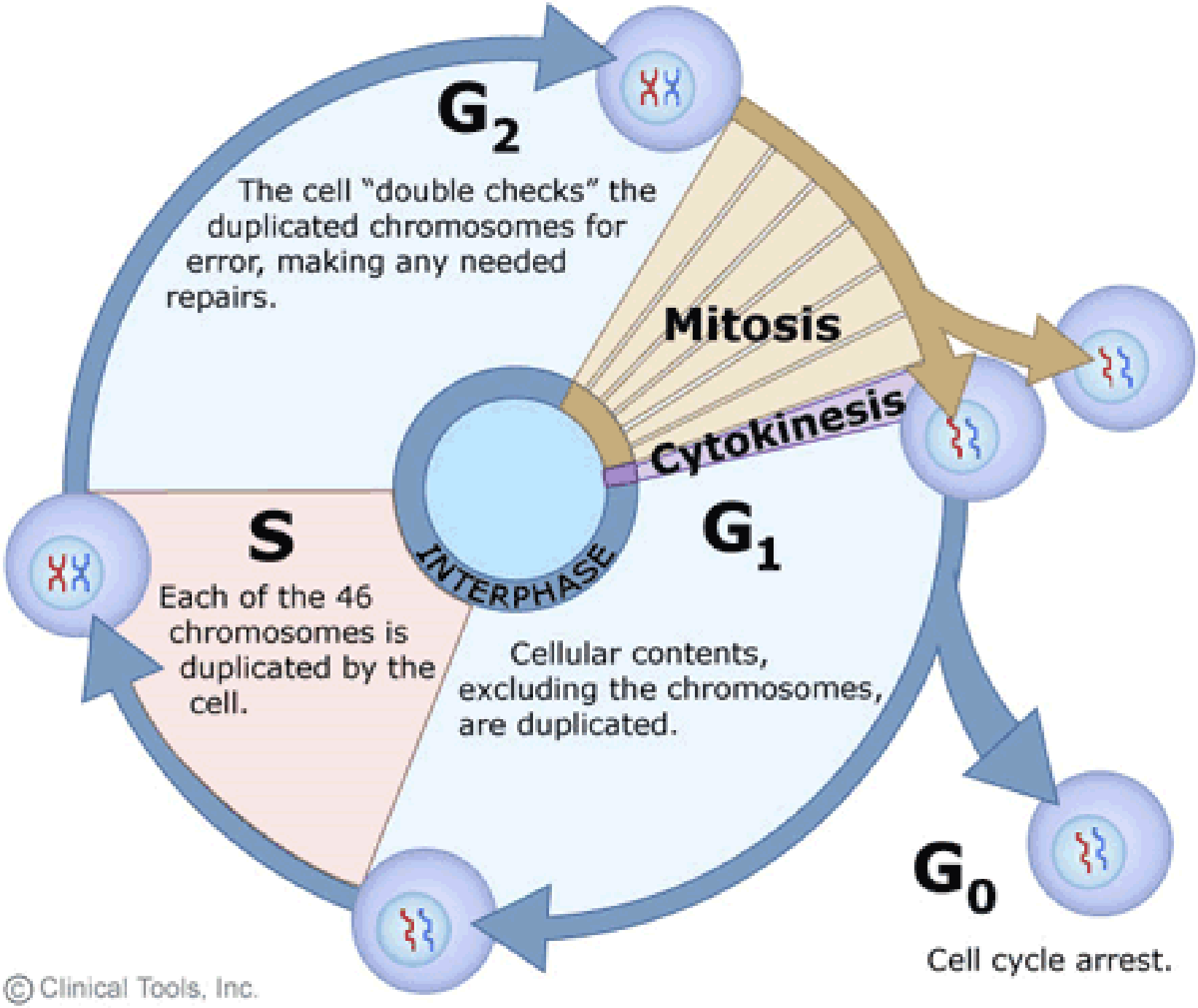
The c-myc gene on chromosome 8 is translocated to a region on chromosome 14 adjacent to the gene coding for the constant region of an immunoglobulin heavy chain (C_H).

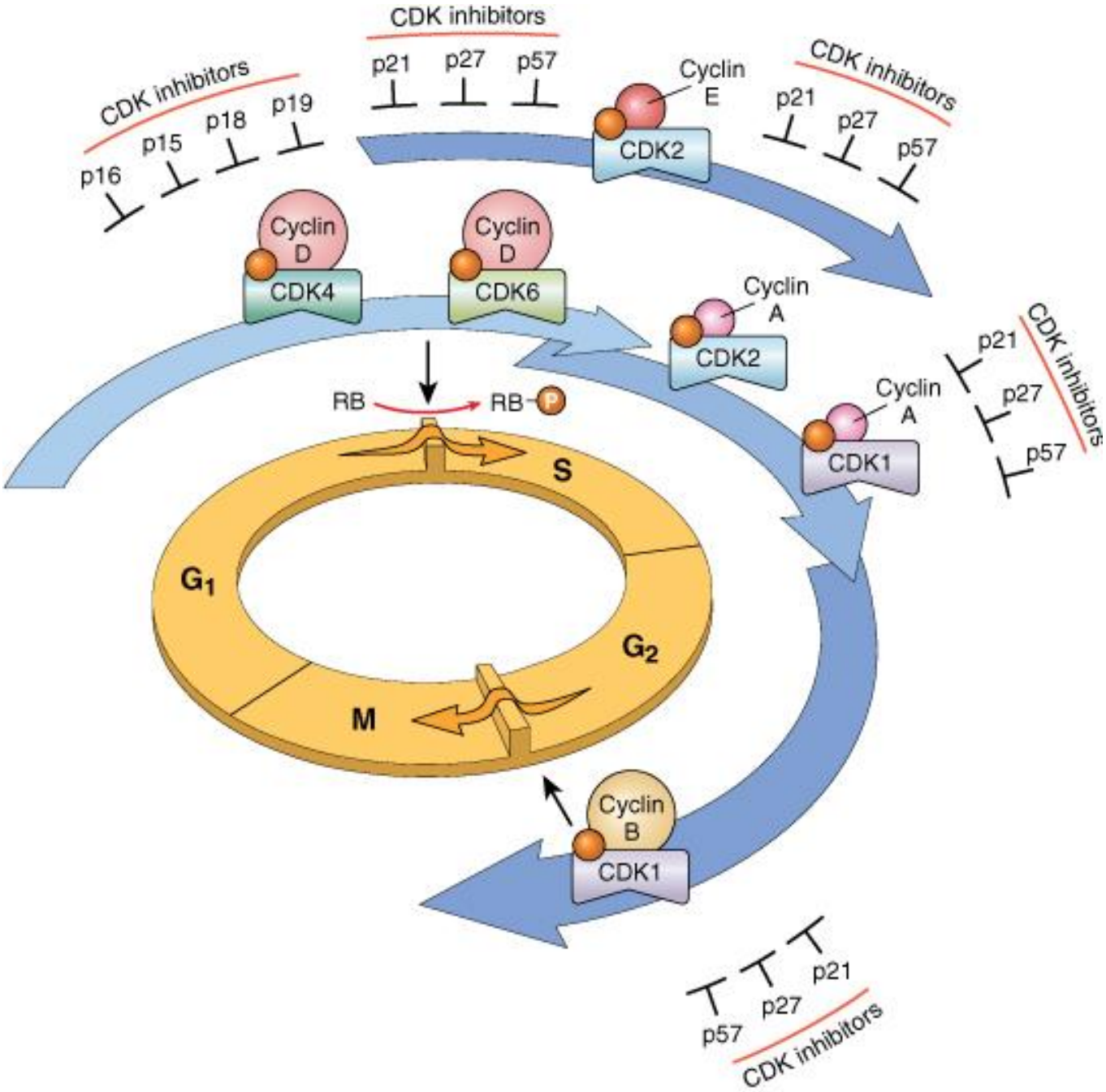
- Dysregulation of the *MYC* gene resulting from a t(8;14) translocation occurs in Burkitt lymphoma, a B-cell tumor;
- *MYC* is amplified in breast, colon, lung, and many other cancers;
- The related *N-MYC* and *L-MYC* genes are amplified in neuroblastomas and small cell cancers of lung.

CYCLINS AND CYCLIN-DEPENDENT KINASES

- The ultimate outcome of all growth-promoting stimuli is the entry of quiescent cells into the cell cycle.
- Orderly progression of cells through the various phases of the cell cycle is orchestrated by CDKs
- After they are activated by binding with another family of proteins called *cyclins*
- The CDK-cyclin complexes phosphorylate crucial target proteins and are expressed constitutively during the cell cycle but in an inactive form

- Because of the cyclic nature of their production and degradation, these proteins have been termed *cyclins*.
- The cell cycle may be seen as a relay race
- While cyclins arouse the CDKs,
- Their inhibitors, silence the cdks
- And exert negative control over the cell cycle





- Mutations that dysregulate the activity of cyclins and CDKs would favor cell proliferation.
- Mishaps affecting the expression of cyclin D or CDK4 seem to be a common event in neoplastic transformation.
- The cyclin D genes are overexpressed breast, esophagus, liver, and a subset of lymphomas.
- Amplification of the *CDK4* gene occurs in melanomas, sarcomas, and glioblastomas.
- Mutations affecting cyclin B and cyclin E and other CDKs much less frequent

Mechanisms of Gene Activation & Inactivation

- Neoplastic transformation => activation (or derepression) of growth promoter genes or inactivation or loss of suppressor genes.

- **Activation** (functional concept) => normal action of growth regulation is diverted into oncogenesis.
- The resultant activated proto-oncogene is referred to as an **activated oncogene** (or a mutant oncogene, if structurally changed), or simply as a **cellular oncogene (c-*onc*)**

Activation and inactivation by several mechanisms

(1) **Mutation,** including single nucleotide loss or substitution, codon loss, gene deletion or more major chromosomal loss;

(2) **Translocation** to a different part of the genome where regulatory influences may favor inappropriate expression or repression;

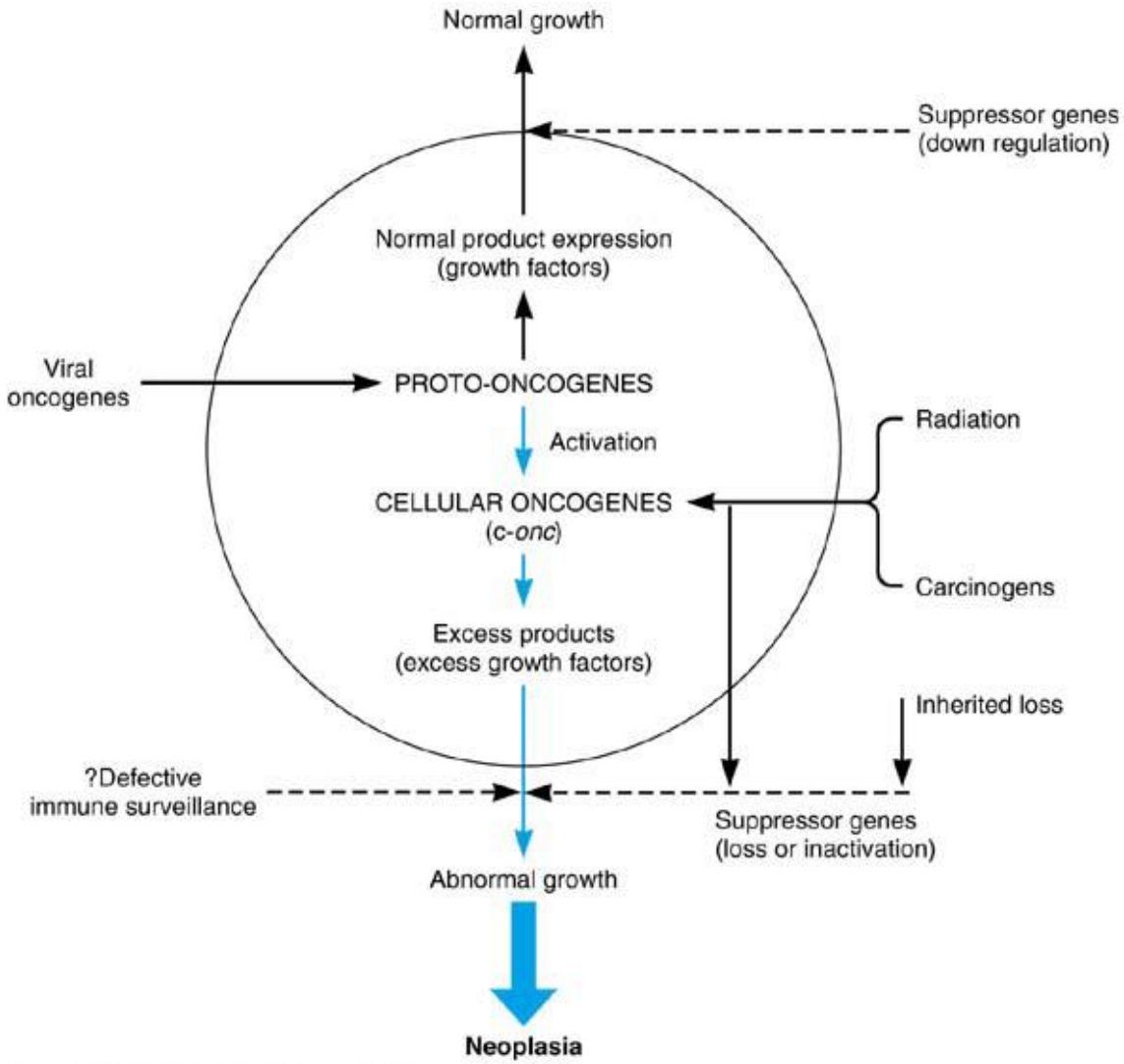
(3) Insertion of an oncogenic virus at an adjacent site

(4) Amplification (production of multiple copies of the proto-oncogenes), which appear as additional chromosome bands

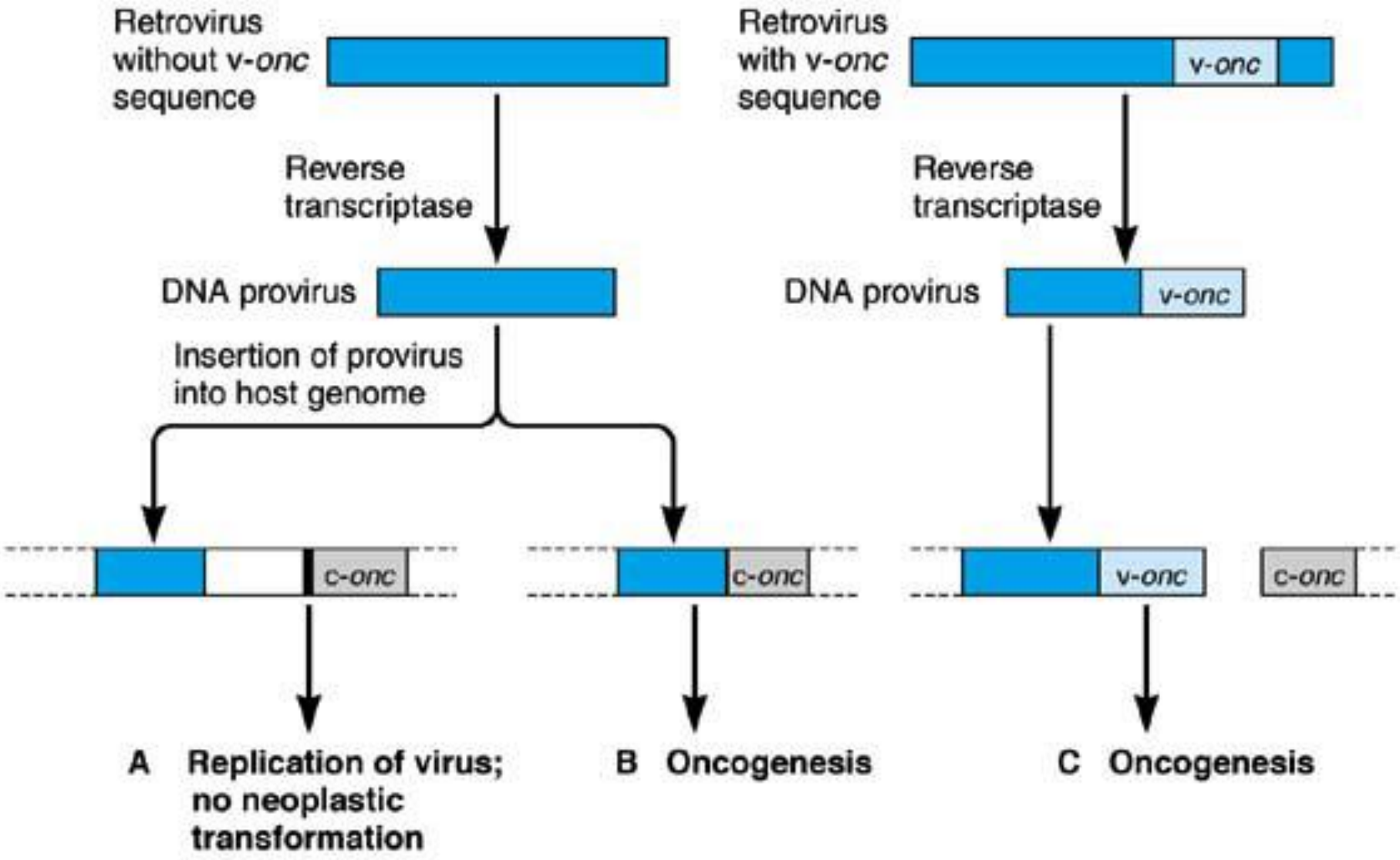
(5) Introduction of viral oncogenes or

(6) Derepression (loss of suppressor control).

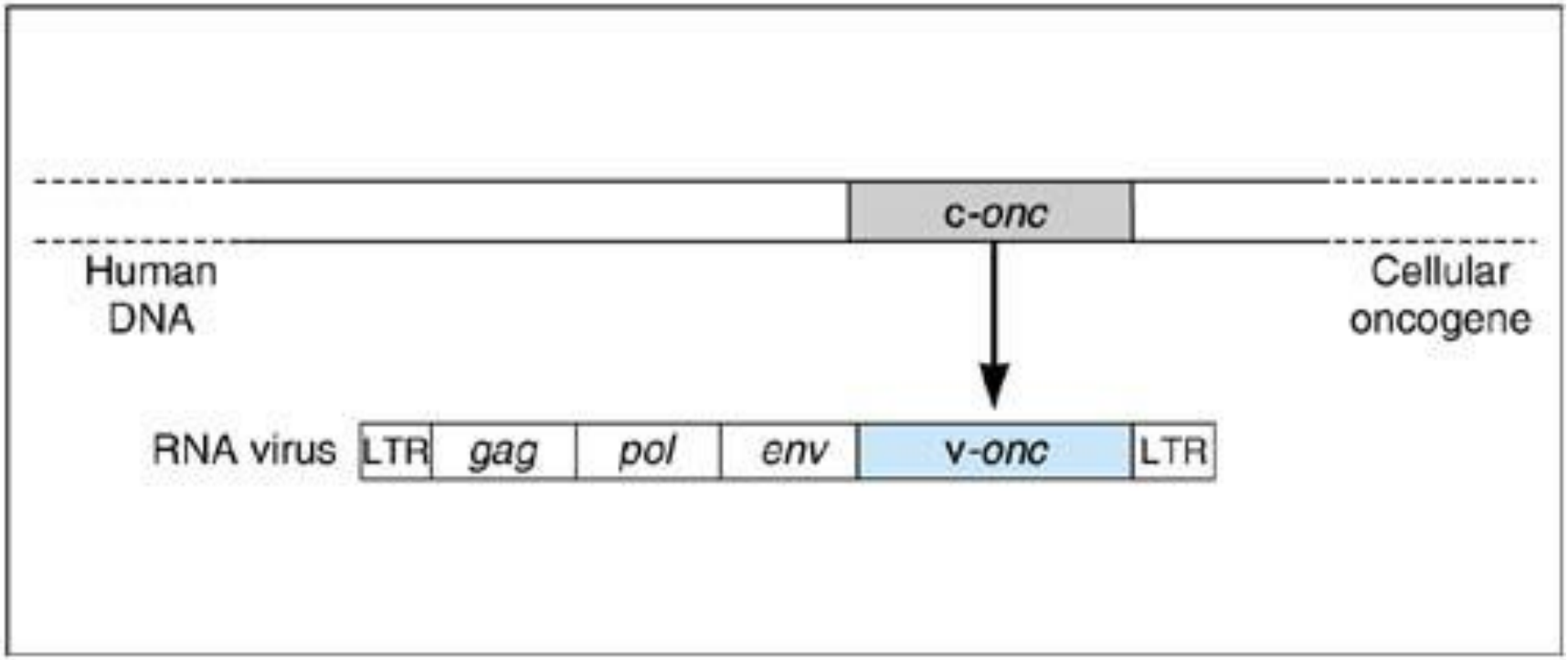
Relationship of cellular oncogenes and suppressor genes to normal growth and neoplasia



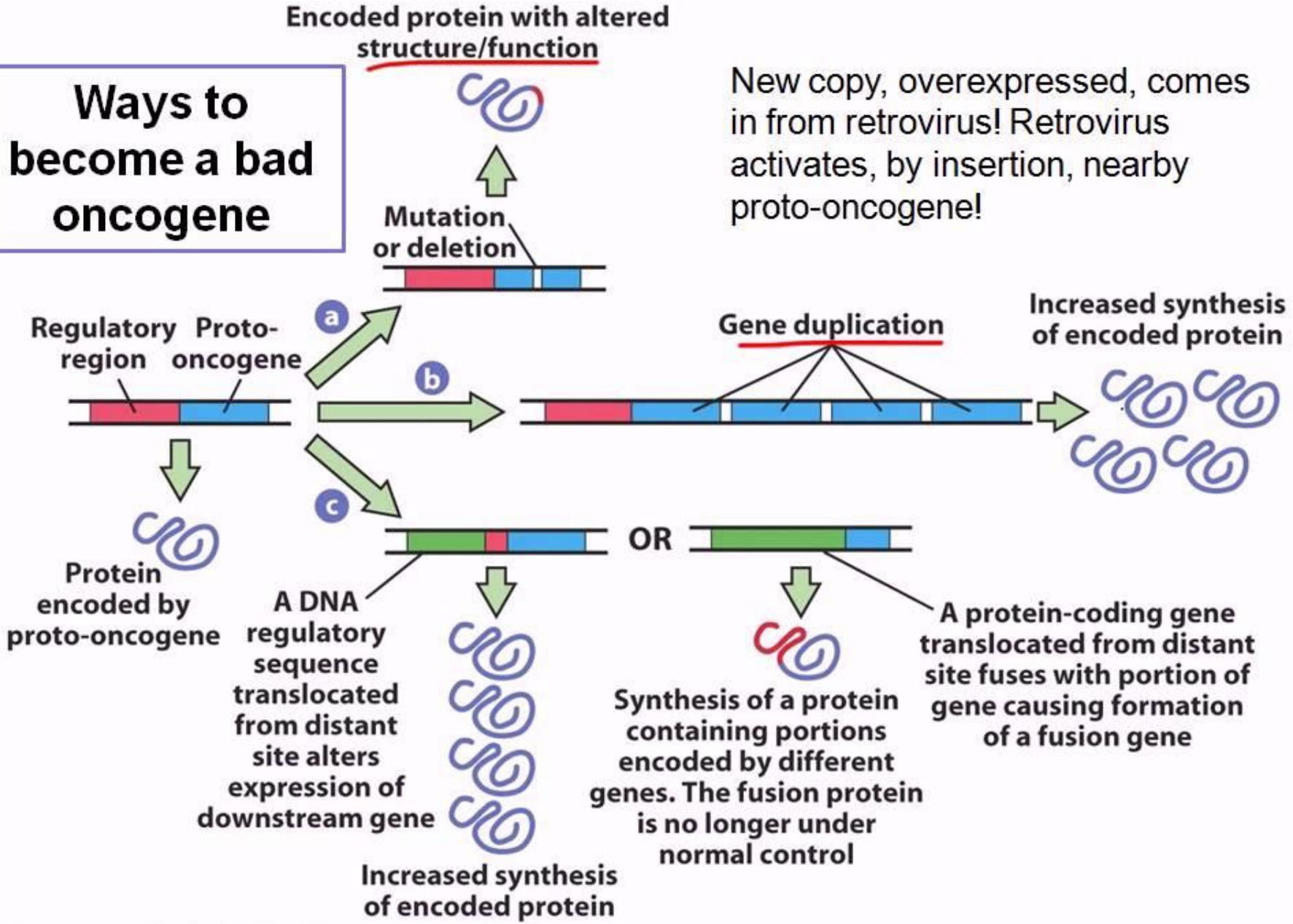
Viral Oncogene Hypothesis



?In the course of evolution, RNA viruses acquired the cellular oncogene from animal cells by genetic recombination

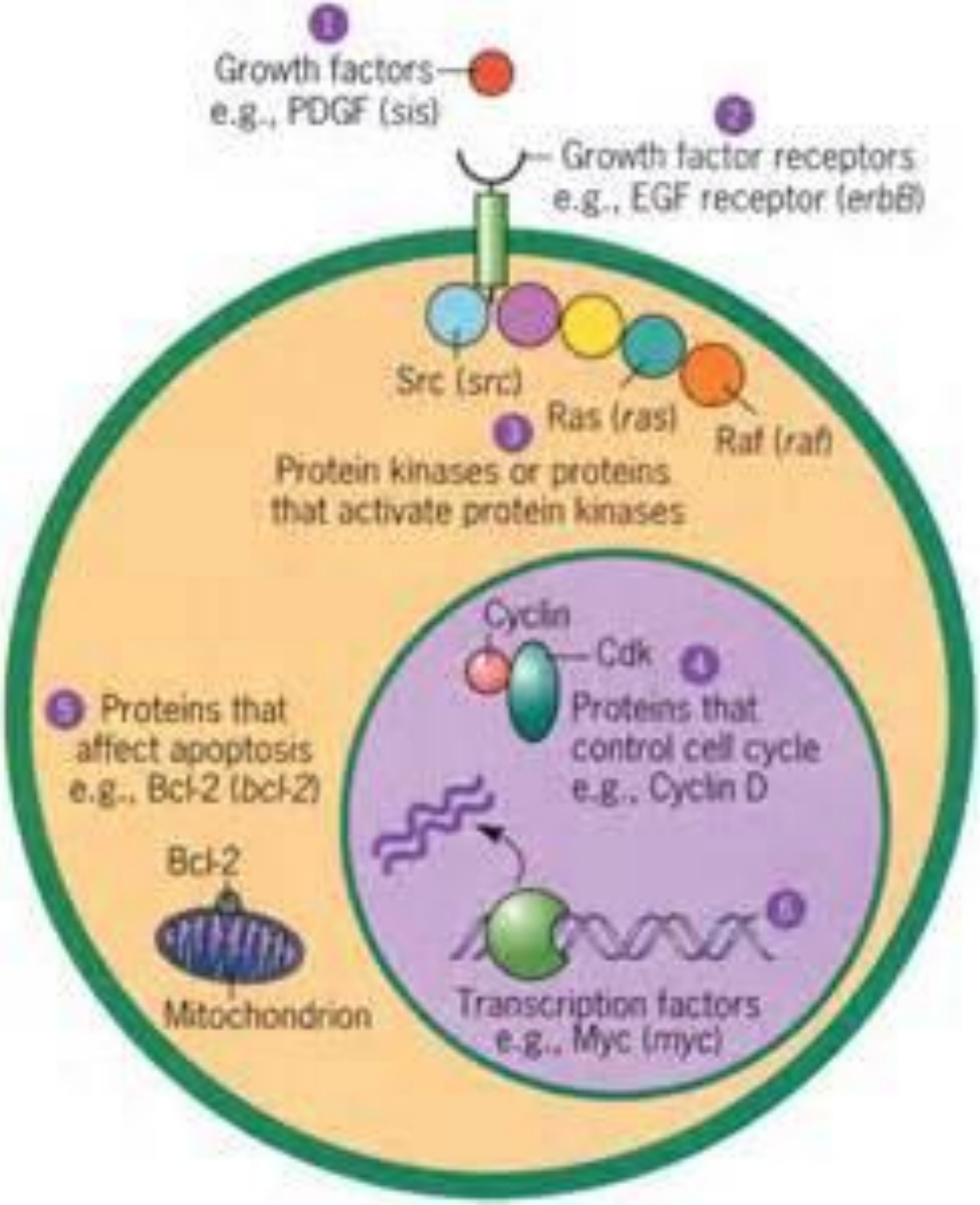


Ways to become a bad oncogene



New copy, overexpressed, comes in from retrovirus! Retrovirus activates, by insertion, nearby proto-oncogene!

Figure 16-12 Cell and Molecular Biology, 4/e (© 2005 John Wiley & Sons)


1
Growth factors
e.g., PDGF (sis)
2
Growth factor receptors
e.g., EGF receptor (erbB)
Src (src)
Ras (ras)
Raf (raf)
3
Protein kinases or proteins
that activate protein kinases
Cyclin
Cdk
4
Proteins that
control cell cycle
e.g., Cyclin D
5
Proteins that
affect apoptosis
e.g., Bcl-2 (bcl-2)
Bcl-2
Mitochondrion
6
Transcription factors
e.g., Myc (myc)

Have a good day