Chapter 19

The Genetics of Cancer

Sections to study

19.3 How cell division is normally controlled

19.1 Characteristics of cancer cells

19.2 The genetic basis of cancers

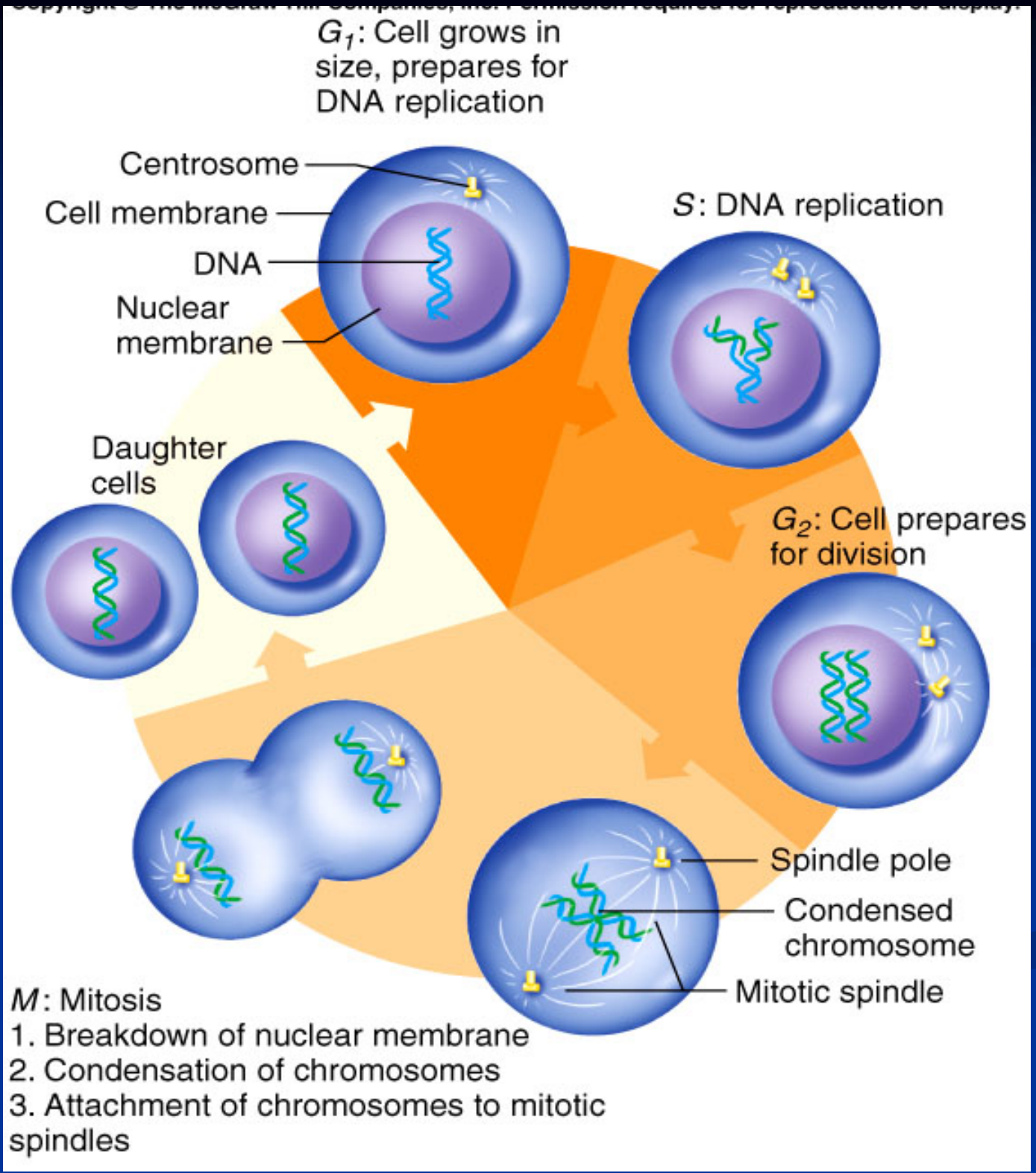
19.4 How mutations cause cancer phenotypes

19.5 Personalized cancer treatment

19.3 How cell division is normally controlled

Cell division

- Mitosis
- Cytokinesis



How do cells know when to divide?

- **Extracellular signals**: Steroids, peptides, and proteins that act over long or short distances, collectively known as hormones.
- **Cell-bound signals**: Such as histocompatibility proteins. Cells in the immune system communicate via these signals.

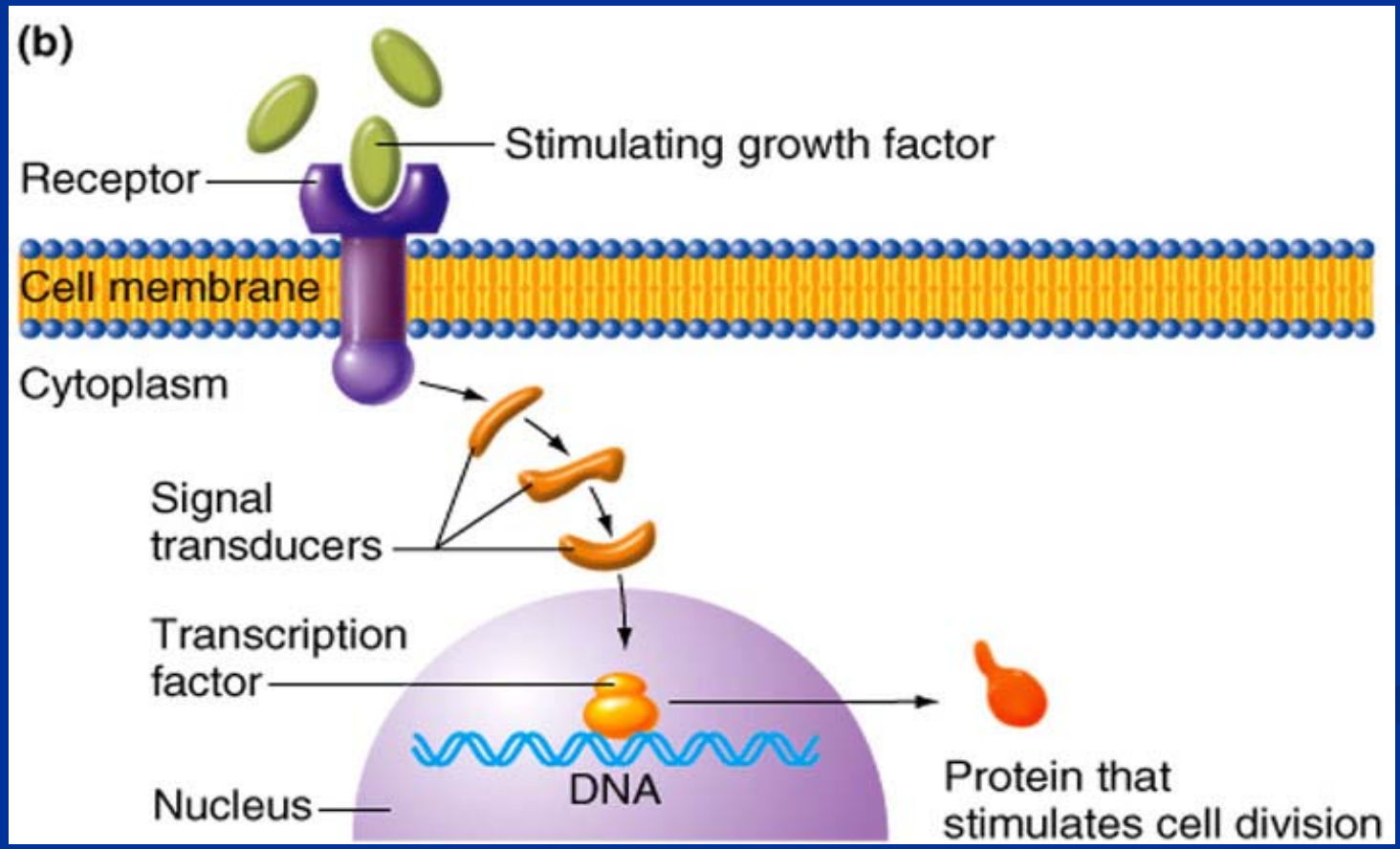
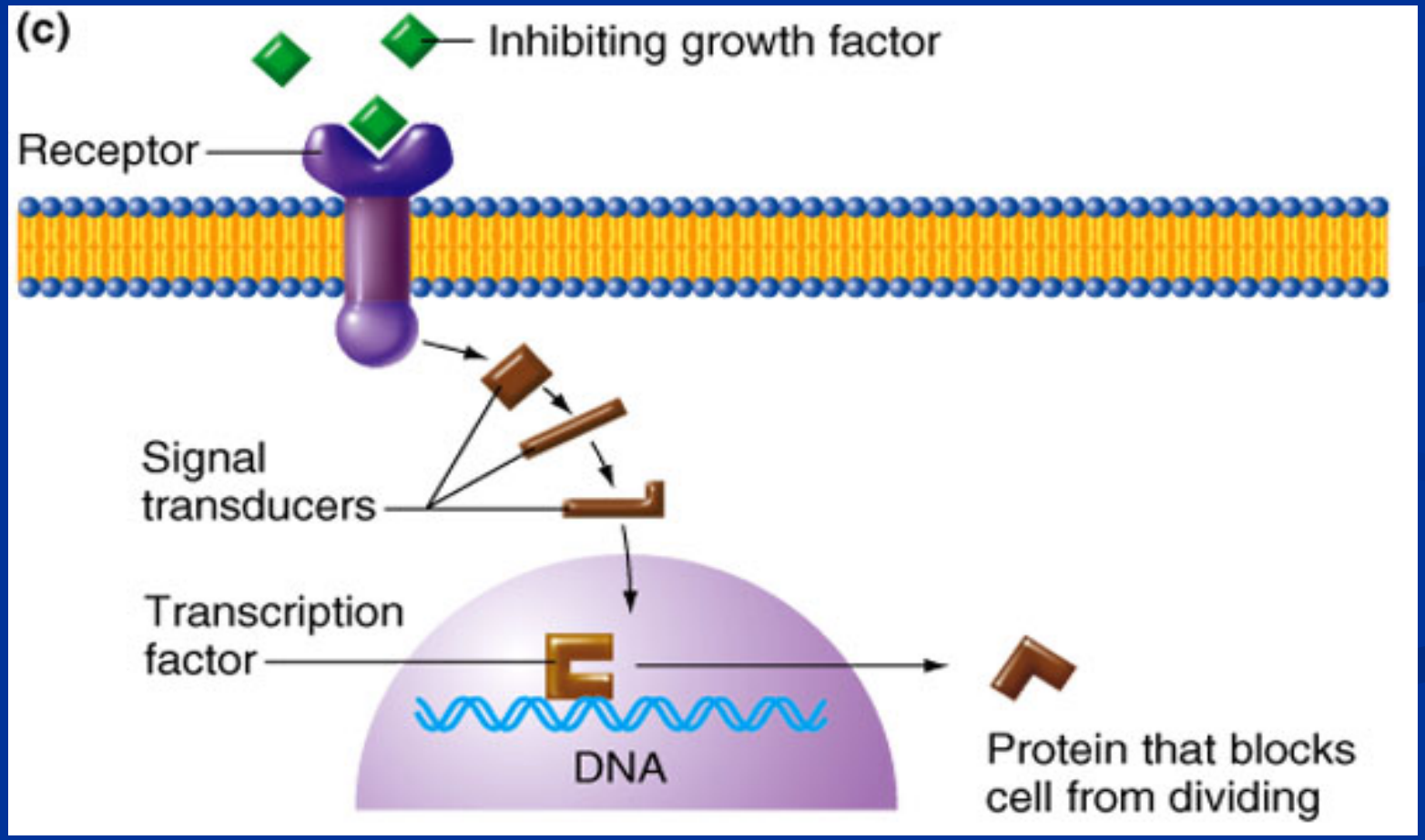


Fig. 19.11

Each signal transduction pathway/system has four components

The activation or inhibition of intracellular targets after growth factor binding is called signal transduction.

1. **Growth factors** – hormones and cell-bound signals that stimulate or inhibit cell proliferation.
2. **Receptors** – membrane-bound proteins that accept signals.
3. **Signal transducers** relay messages.
4. **Transcription factors** activate the expression of genes.



The small GTPase RAS is involved in growth factor signaling

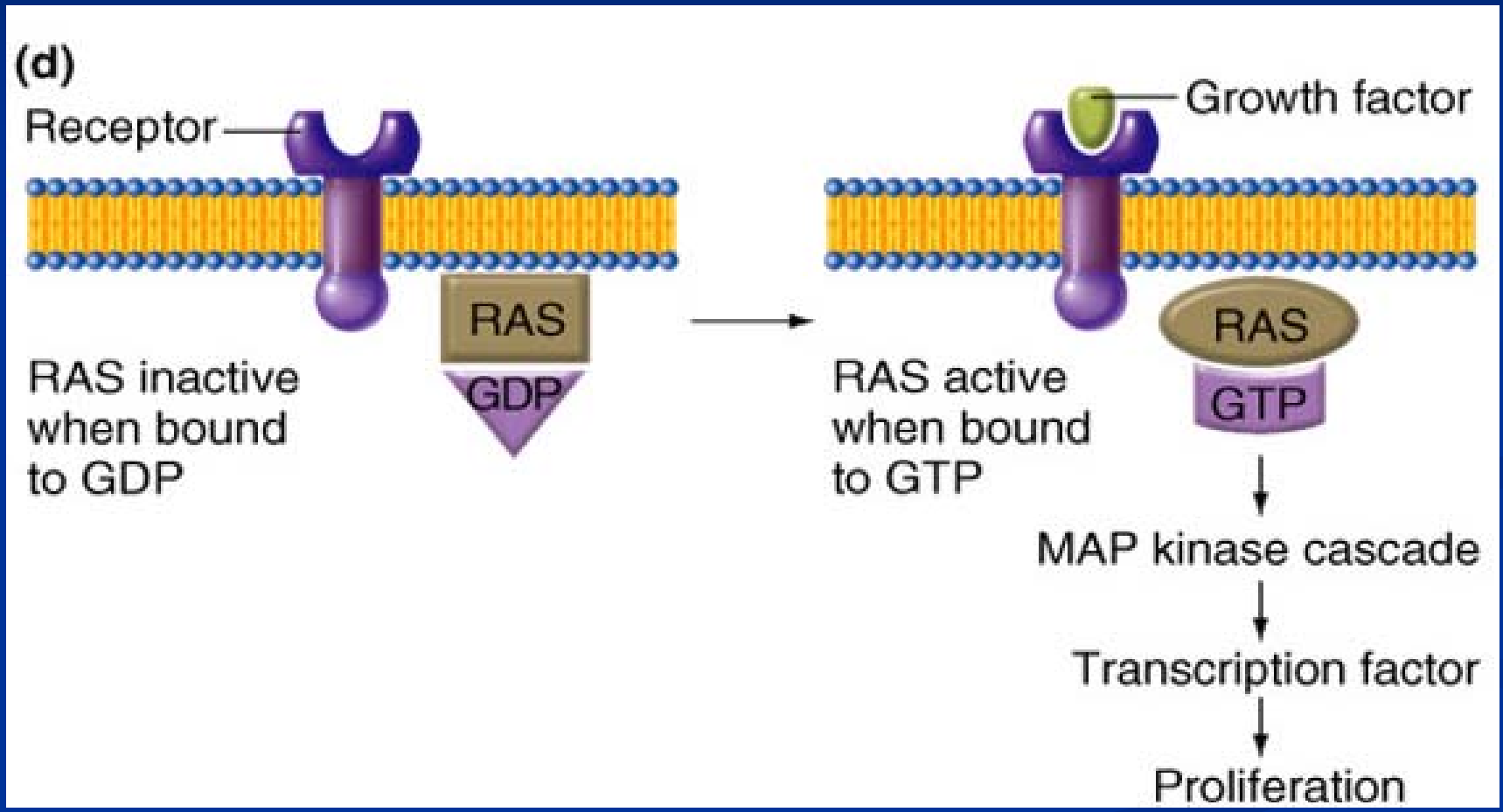
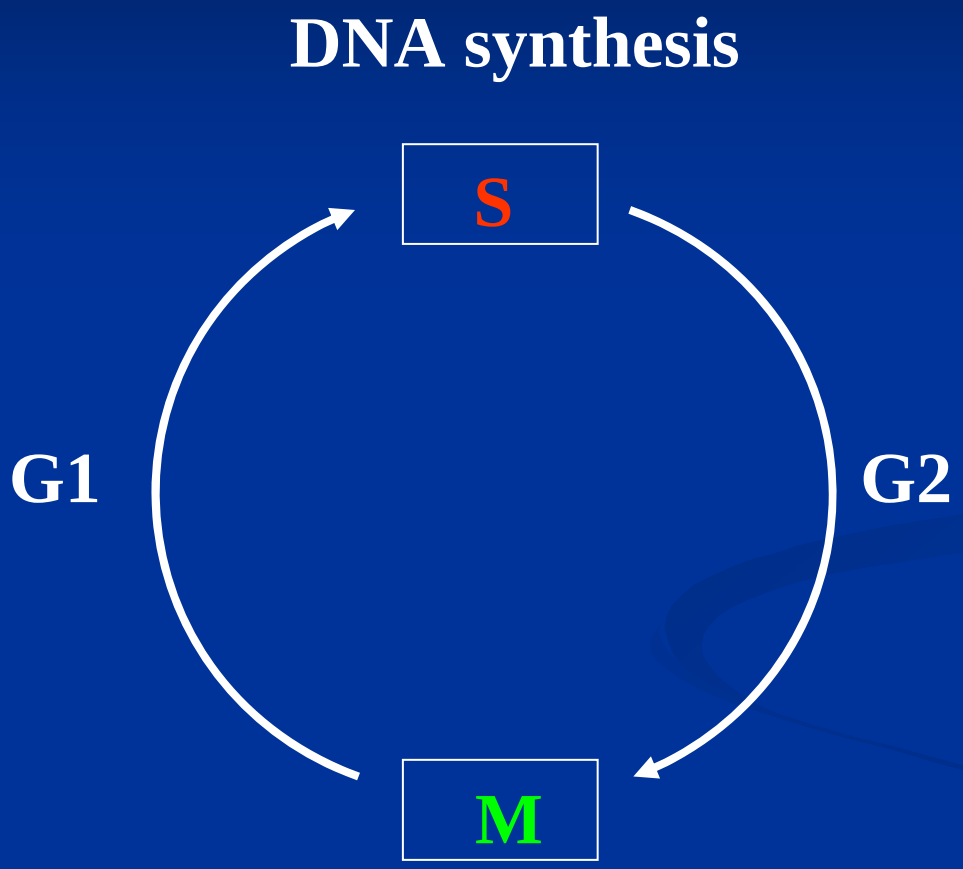


Fig. 19.12

Cell cycle and its regulation



The length of cell cycle varies with each organism

Fertilized *Xenopus* egg 

0.5 hr

Cultured fibroblast 

24 hr

Saccharomyces cerevisiae 

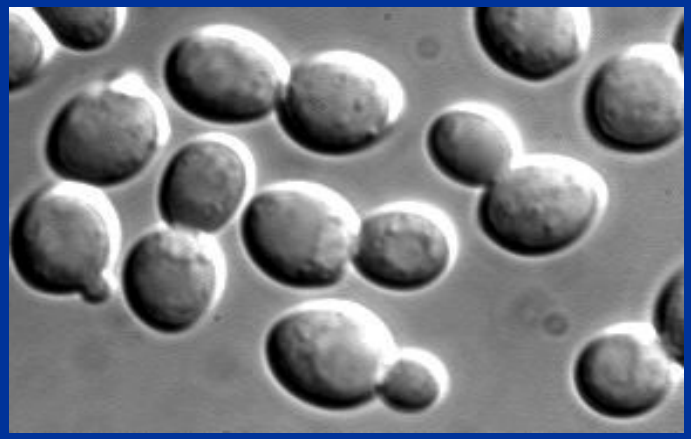
2 hr

Schizosaccharomyces pombe 

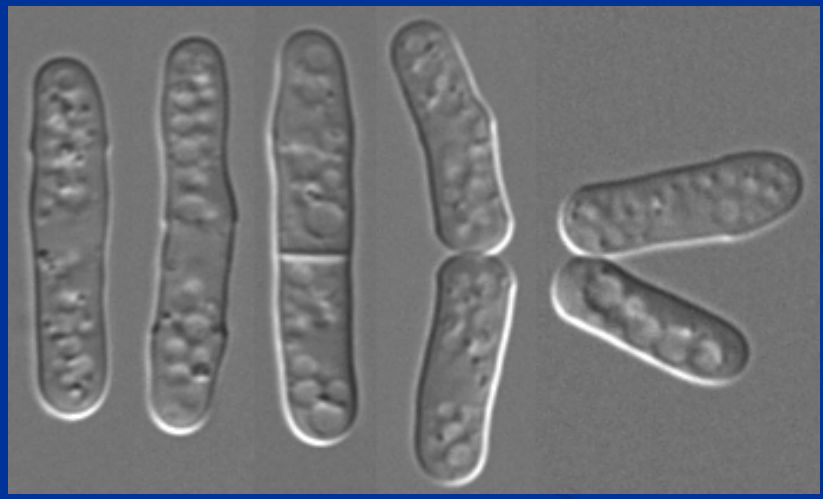
2.5 hr

Experiments with yeast helped identify genes that control cell division

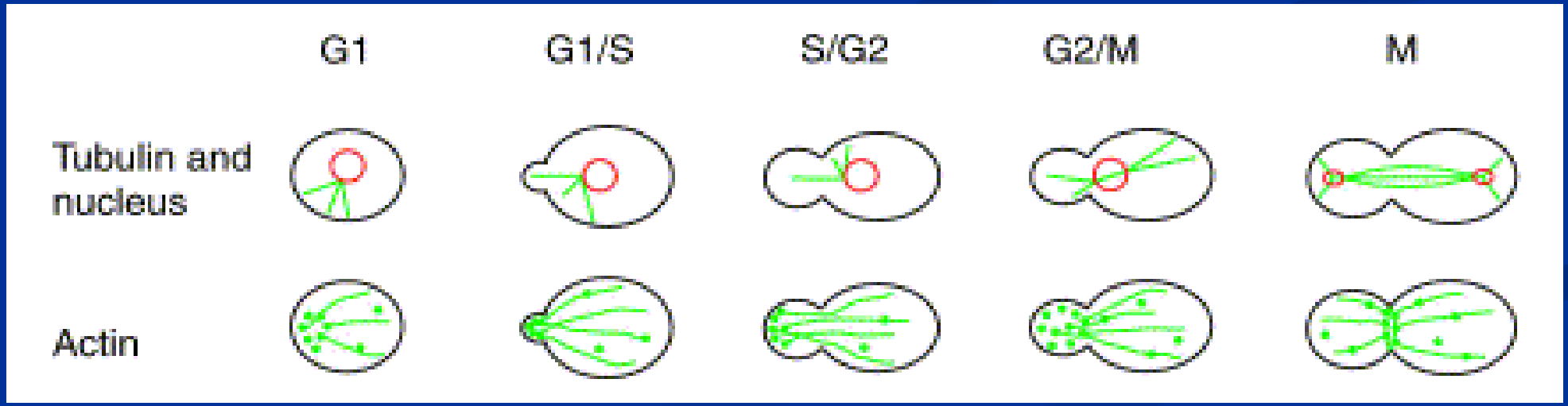
The budding yeast
Saccharomyces cerevisiae



The fission yeast
Schizosaccharomyces pombe



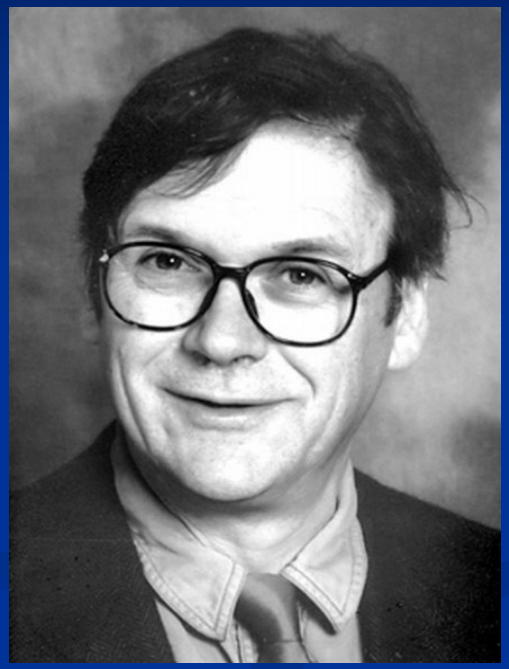
- Properties of yeast
  - Grow as haploid or diploid organisms
    - Can identify recessive mutations in haploids
    - Complementation analysis in diploids
  - Budding – daughter cell arises on the surface of mother cell and grows in size during cell cycle. Helps determine stage of cell cycle
- Powerful genetics



The 2001 Nobel Prize in Physiology or Medicine

Leland H. Hartwell
Isolated cell division
cycle *cdc* mutants
in the budding yeast

Paul M. Nurse
Found *cdc2*
in the fission yeast

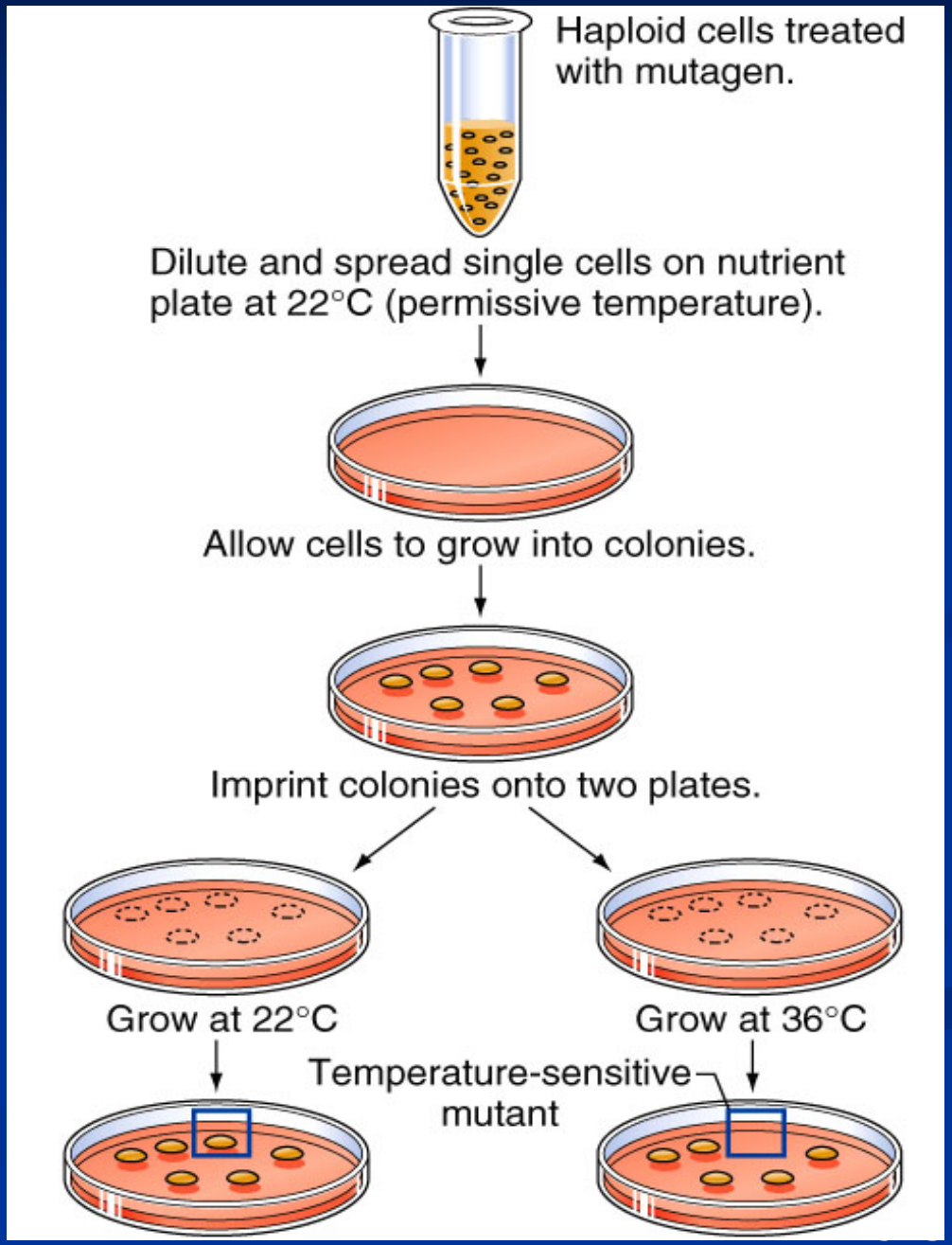


Tim Hunt
Found cyclins
in sea urchin

Isolation of temperature-sensitive mutants in yeast

- Mutants grow normally at permissive temperature, but lose gene function at restrictive temperature.
- Several dozens of cell cycle mutants have been isolated.

Leland H. Hartwell



A cell-cycle mutant of yeast

- (a) Growth at permissive temperature displays buds of all sizes.
- (b) Growth at restrictive temperature shows cells arrested with a large bud.

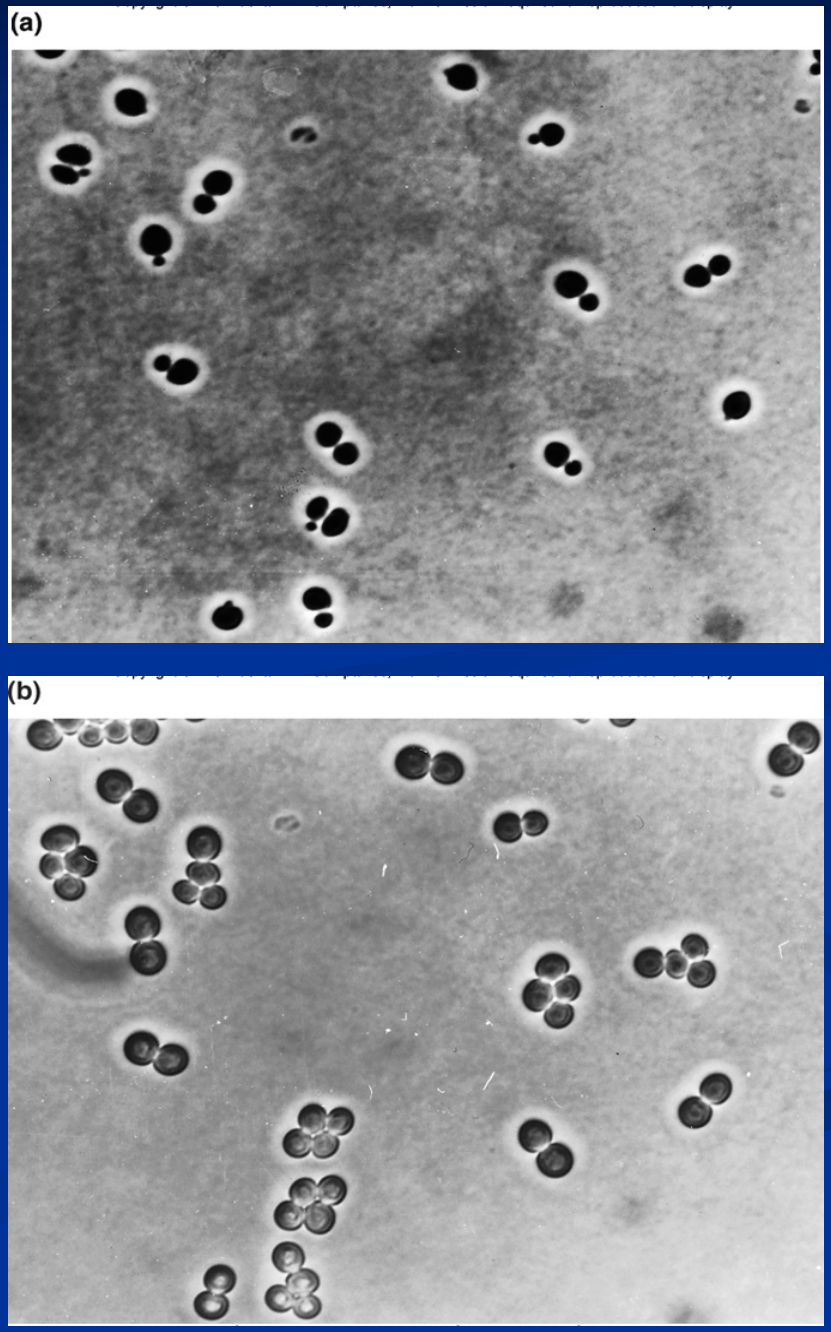


Fig. A

Wild-type and *cdc* mutant cells several hours after incubation at the restrictive temperature

Wild-type

cdc8

cdc24

cdc10

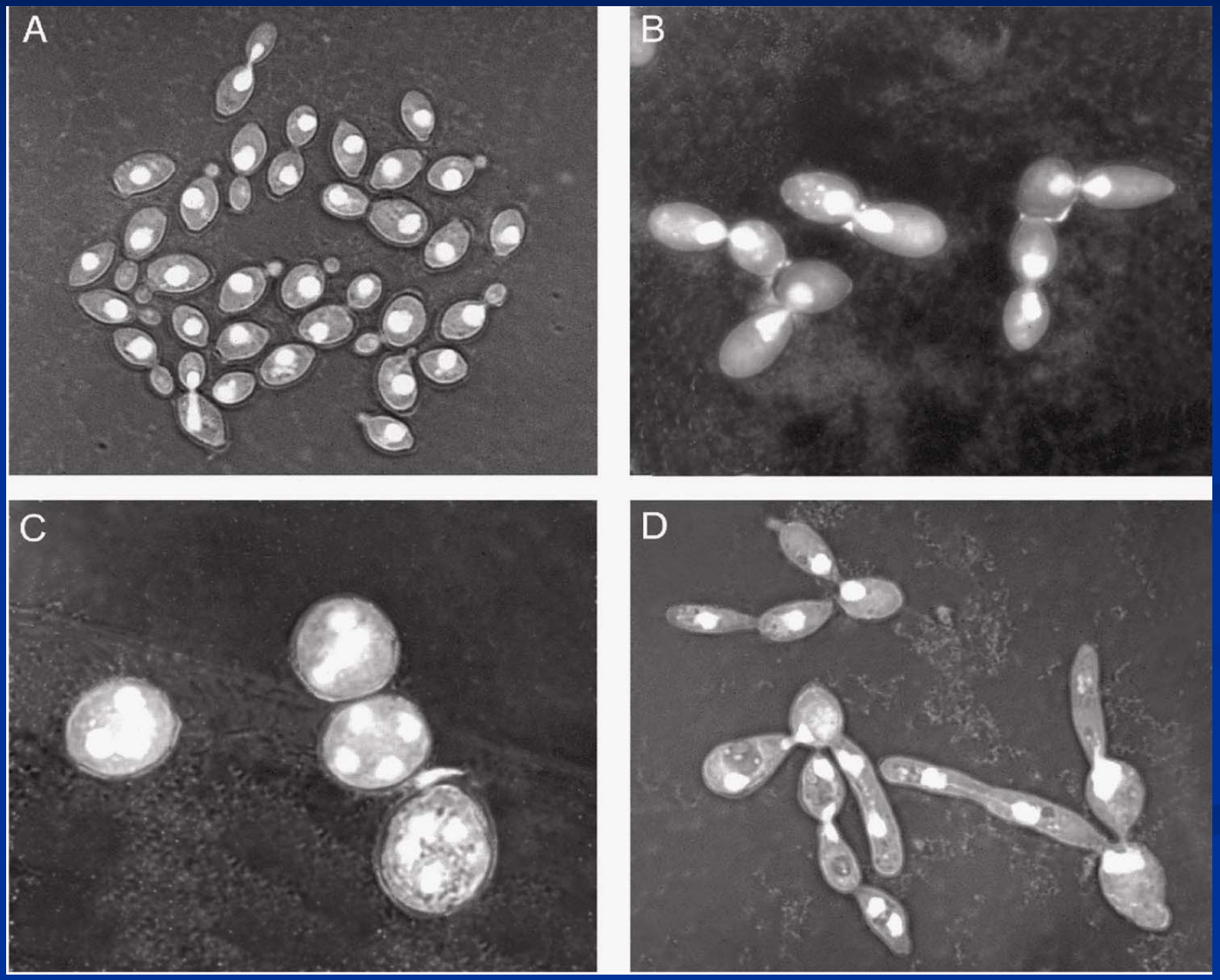
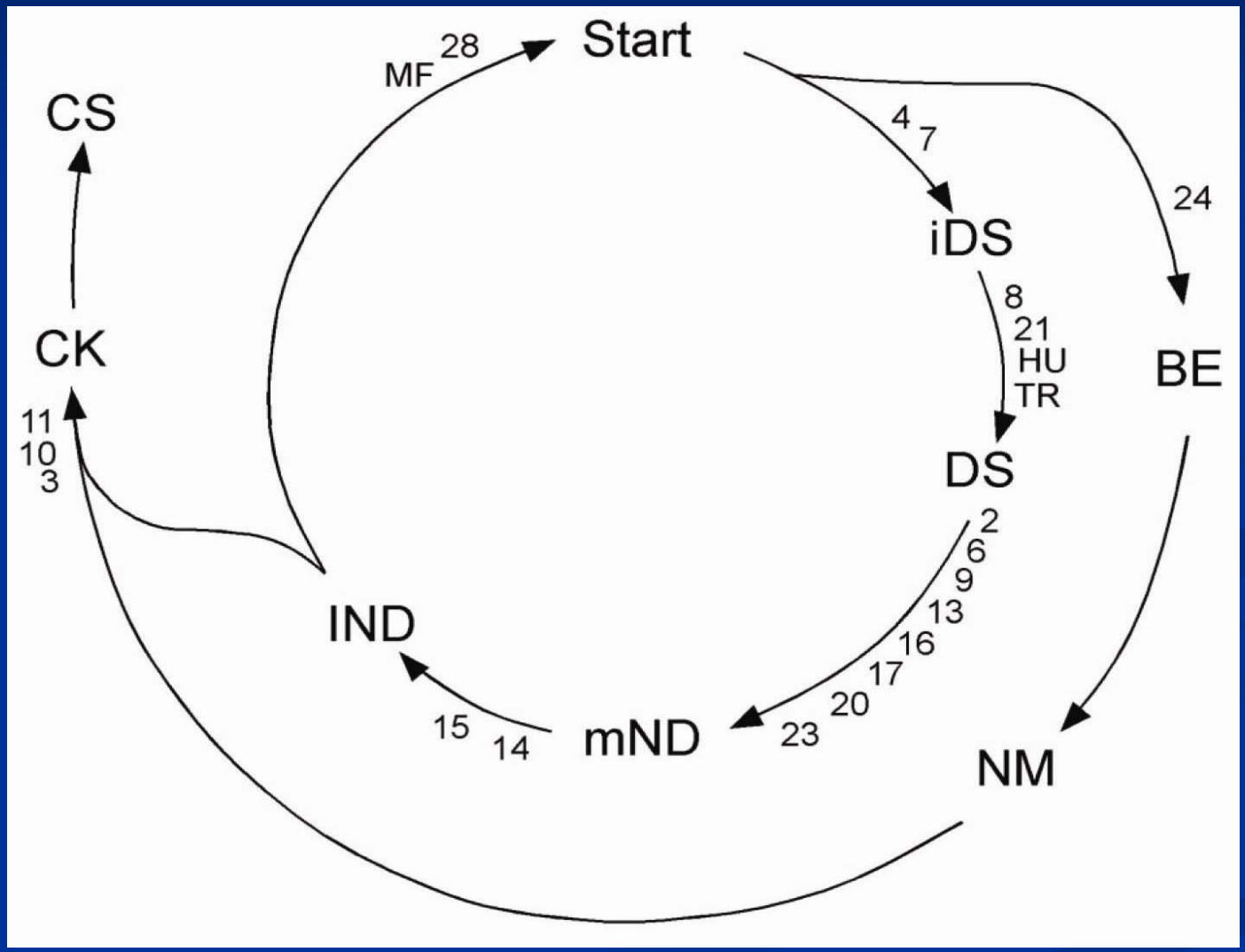


Figure from
Lee Hartwell

A pathway of gene-controlled events in *S. cerevisiae* cell cycle



BE=bud emergence, NM=nuclear migration, CK=cytokinesis, CS=cell separation, iDS=initiation of DNA synthesis DS=DNA synthesis, mND=medial nuclear division, lND=late nuclear division, MF=mating factor,

Some important cell-cycle and DNA repair genes

TABLE 19.1 Some Important Cell-Cycle and DNA Repair Genes

Genes	Gene Products and Their Function
CDKs	Enzymes known as cyclin-dependent protein kinases that control the activity of other proteins by phosphorylating them
CDC28	A CDK discovered in the yeast *Saccharomyces cerevisiae* that controls several steps in the *S. cerevisiae* cell cycle
CDC2	A CDK discovered in the yeast *Schizosaccharomyces pombe* that controls several steps in the *S. pombe* cell cycle; also the designation for a particular CDK in mammalian cells
CDK4	A CDK of mammalian cells important for the G_1-to-S transition
CDK2	A CDK of mammalian cells important for the G_1-to-S transition
cyclins	Proteins that are necessary for and influence the activity of CDKs
cyclinD	A cyclin of mammalian cells important for the G_1-to-S transition
cyclinE	A cyclin of mammalian cells important for the G_1-to-S transition
cyclinA	A cyclin of mammalian cells important for S phase
cyclinB	A cyclin of mammalian cells important for the G_2-to-M transition
E2F	A transcription factor of mammalian cells important for the G_1-to-S transition
RB	A mammalian protein that inhibits E2F
p21	A protein of mammalian cells that inhibits CDK activity
p16	A protein of mammalian cells that inhibits CDK activity
p53	A transcription factor of mammalian cells that activates transcription of DNA repair genes as well as transcription of *p21*
RAD9	A protein that inhibits the G_2-to-M transition of *S. cerevisiae* in response to DNA damage
E6	A protein of the HPV virus that inhibits p53
E7	A protein of the HPV virus that inhibits Rb

Cyclin-dependent kinases (CDK) control the cell cycle by phosphorylating substrate proteins

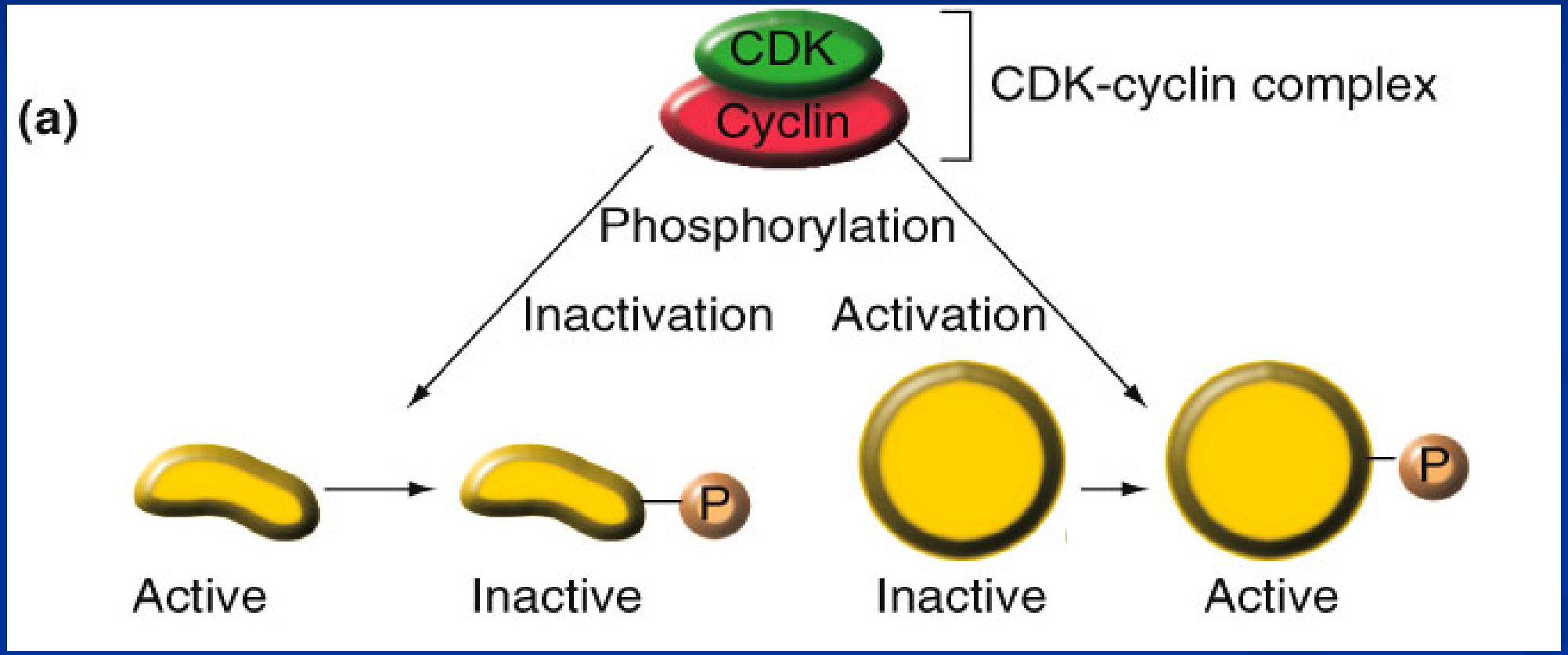


Fig. 19.13

- **Nuclear lamins**
  - **Underlie inner surface of the nuclear membrane**
  - **Probably provide structural support for nucleus**
  - **May also be site for assembly of DNA replication, transcription, RNA transport, and chromosome structure proteins**
  - **Dissolution of nuclear membrane during mitosis is triggered by CDK phosphorylation of nuclear lamins.**

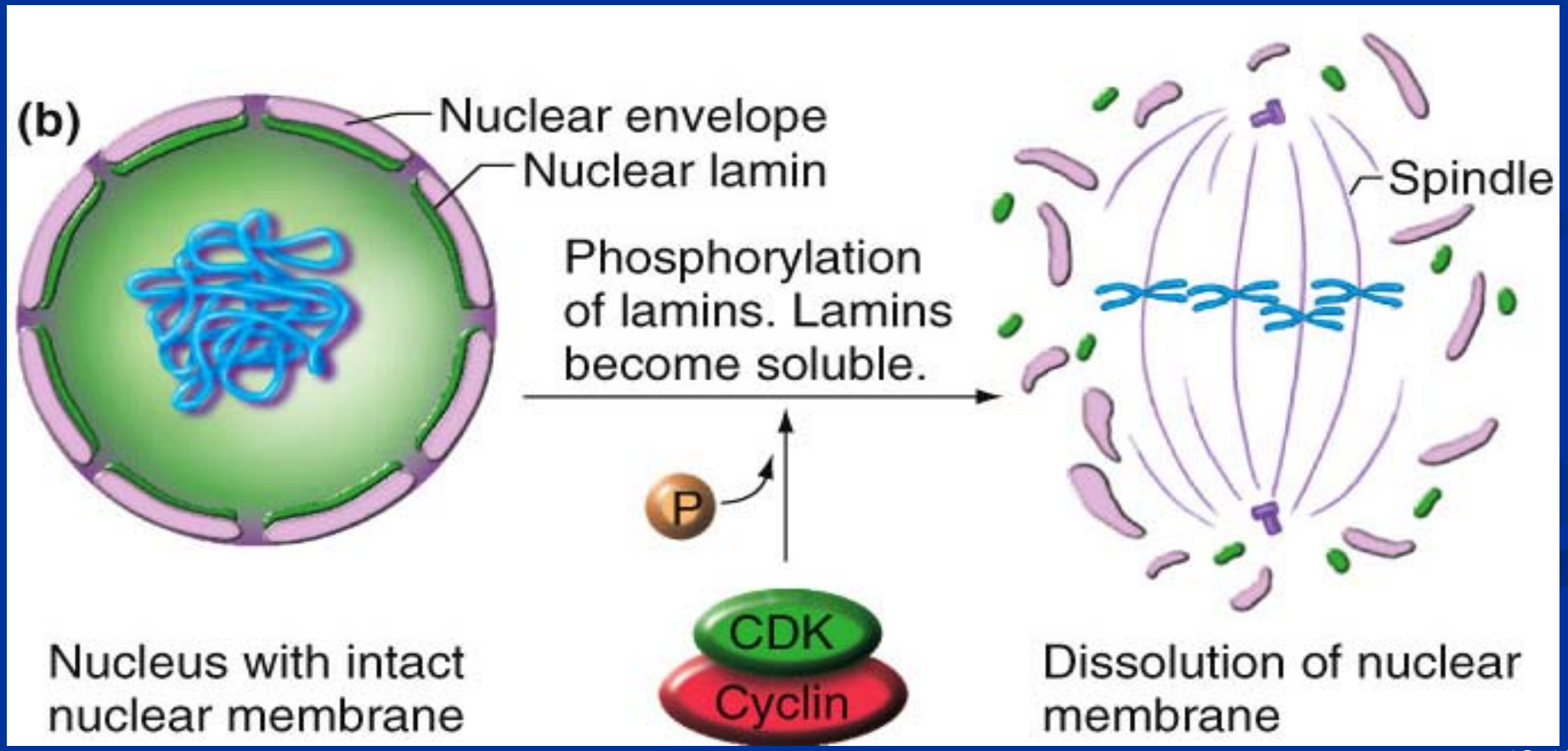
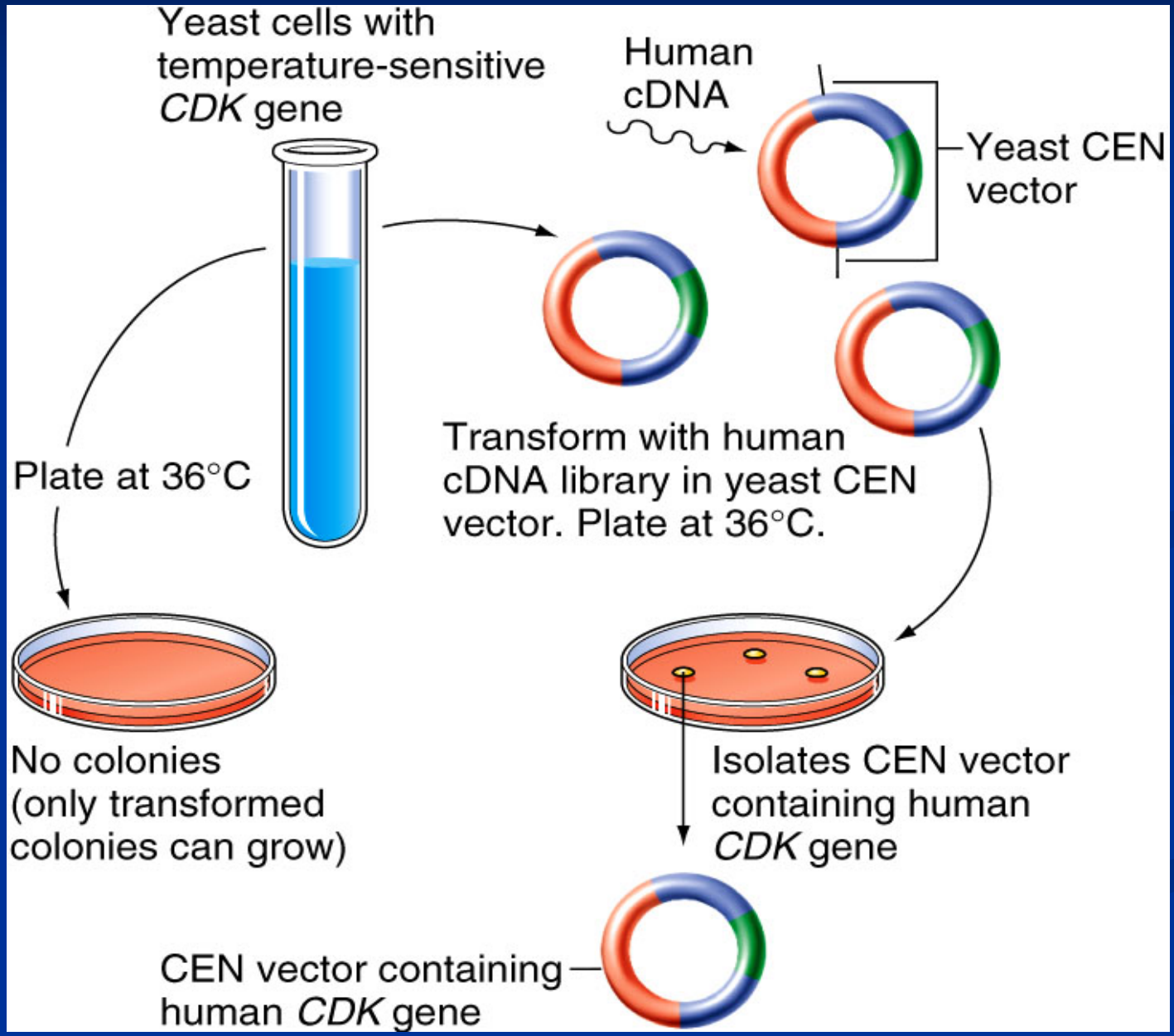


Fig. 19.13

Human CDKs and cyclins can function in yeast in place of native proteins



G1-to-S transition in human cells

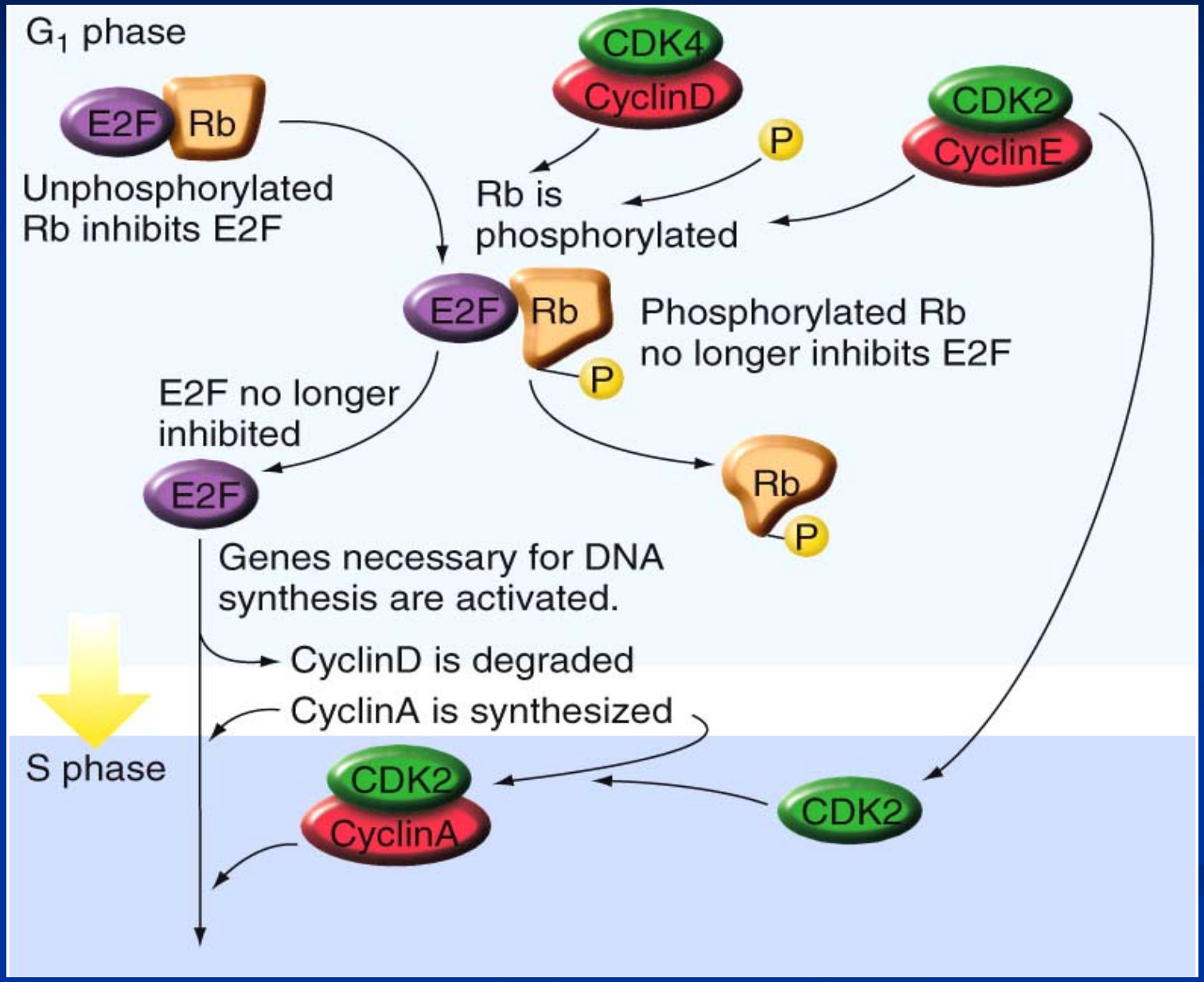


Fig. 19.15

Individuals who inherit one copy of the *RB*$^{-}$ allele are prone to cancer of the retina (retinoblastoma)

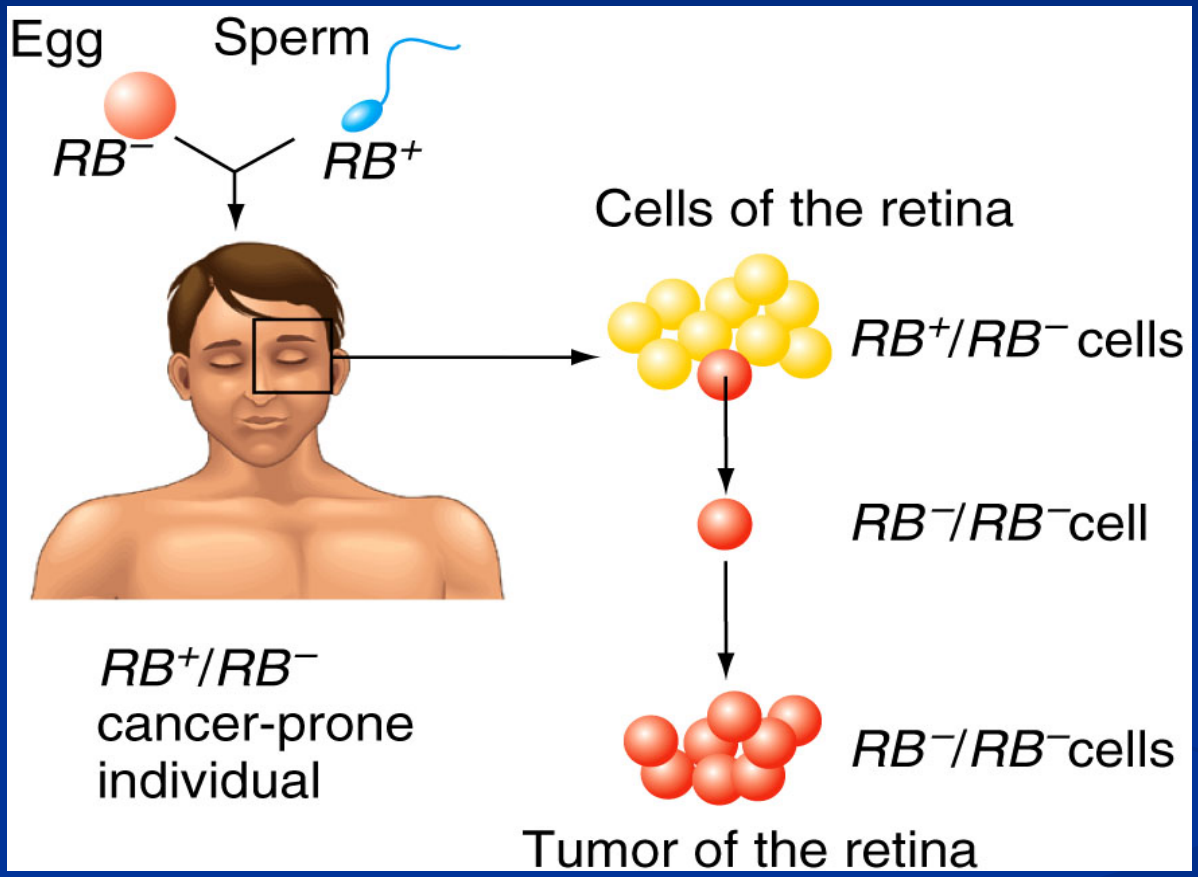
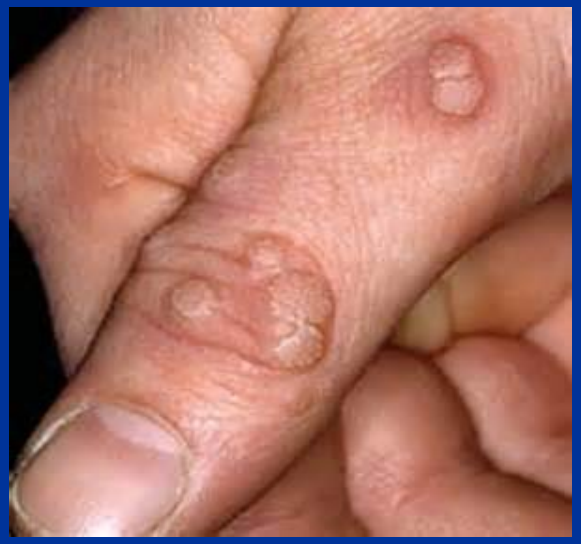


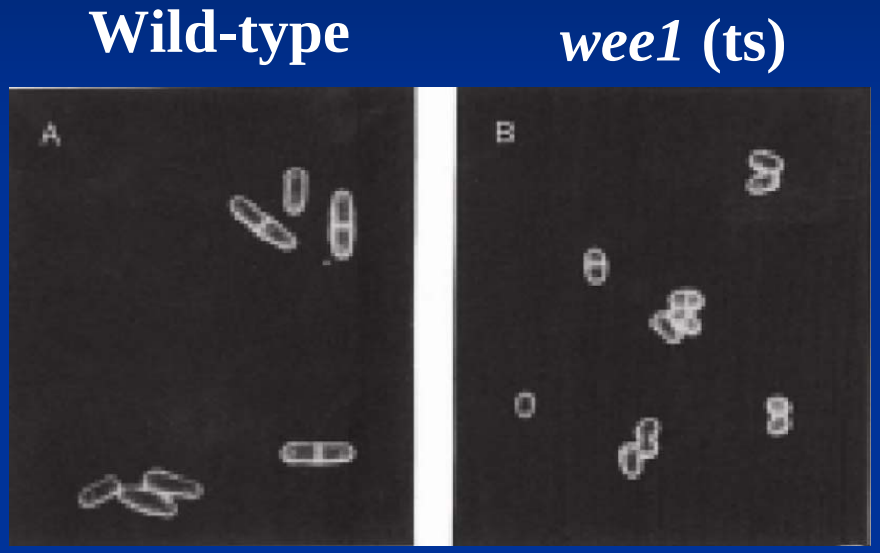
Fig. 19.23

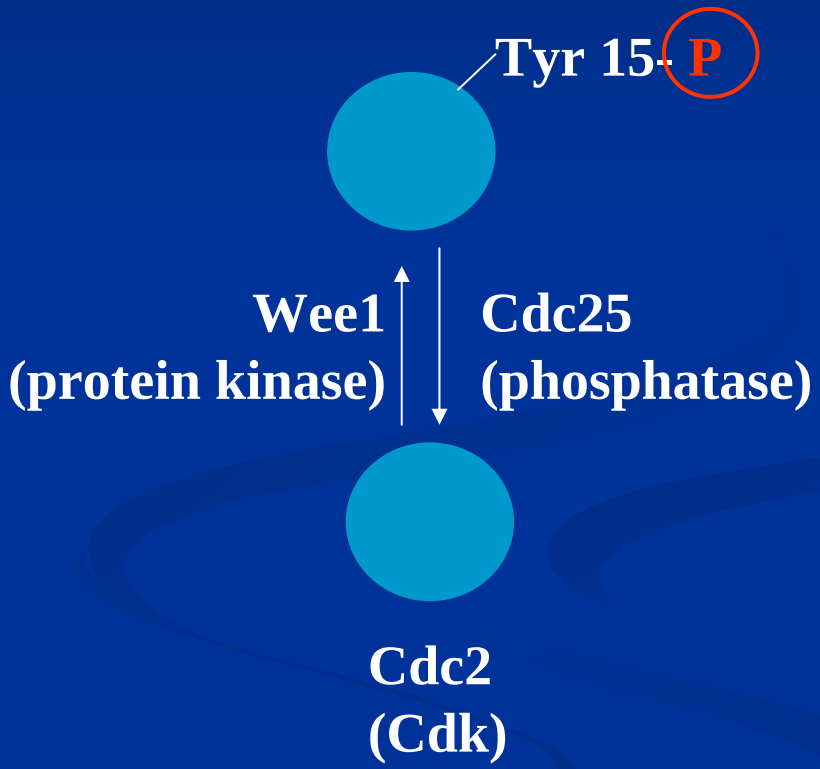
The E7 protein of human papillomavirus (HPV, 人乳头瘤病毒) inhibits Rb, leading to cell proliferation.

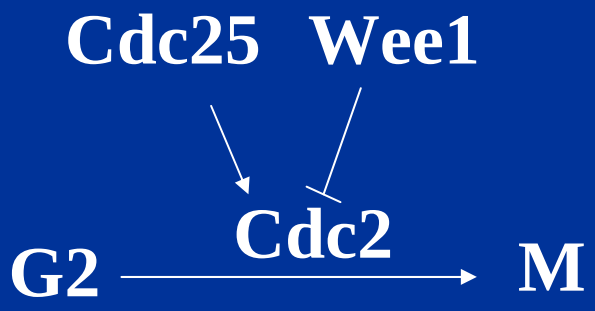


Disease	HPV type
Common warts	2, 7, 22
Plantar warts	1, 2, 4, 63
Flat warts	3, 10, 8
Anogenital warts	6, 11, 42, 44 and others[13]
Anal dysplasia (lesions)	6, 16, 18, 31, 53, 58[14]
Genital cancers	• Highest risk:[13] 16, 18, 31, 45 • Other high-risk:[13][15] 33, 35, 39, 51, 52, 56, 58, 59 • Probably high-risk:[15] 26, 53, 66, 68, 73, 82
Epidermodysplasia verruciformis	more than 15 types
Focal epithelial hyperplasia (oral)	13, 32
Oral papillomas	6, 7, 11, 16, 32
Oropharyngeal cancer	16
Verrucous cyst	60
Laryngeal papillomatosis	6, 11

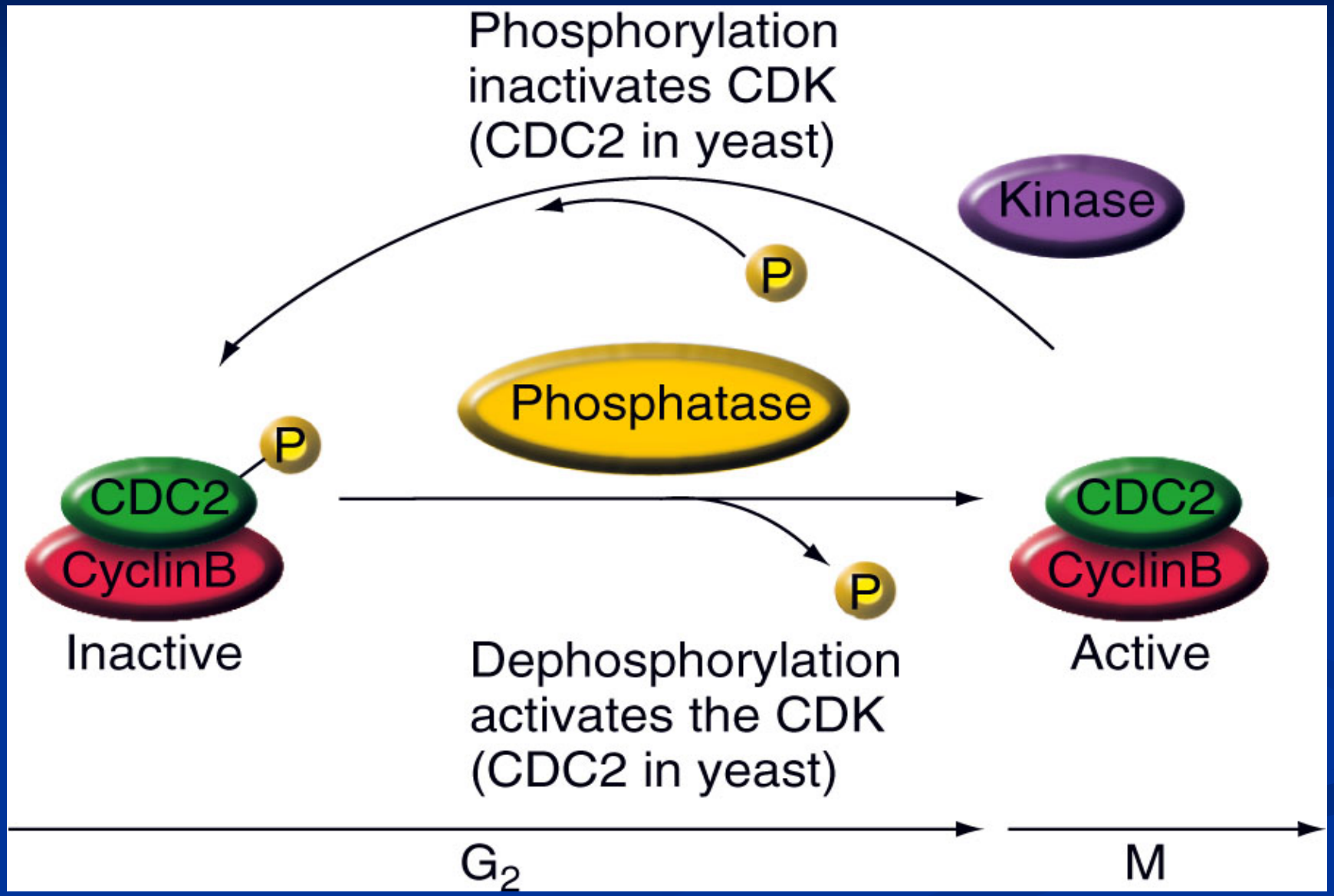
Genetic studies on G2-to-M transition in the fission yeast *S. pombe*



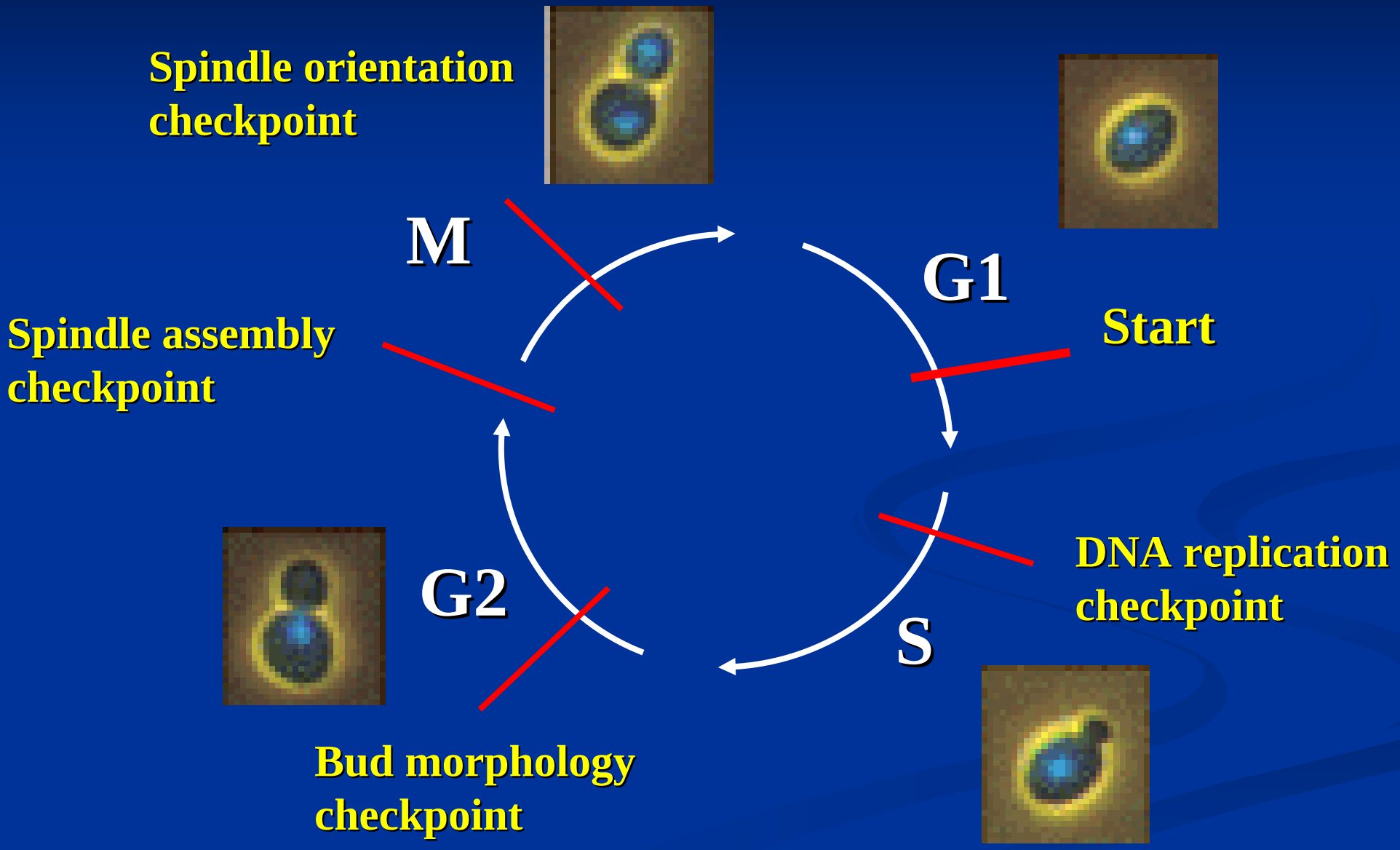




Humans make the transition from G2 to M similar to yeast



Cell-cycle checkpoints ensure genomic stability



G1-to-S checkpoint

- p53 pathway activated by ionizing radiation or UV light (causing DNA damage) delays entry into S phase.
- p53 – transcription factor, induces expression of DNA repair genes and p21 (CDK inhibitor).
- DNA is repaired before cell cycle continues.
- If DNA is badly damaged, cells commit suicide.

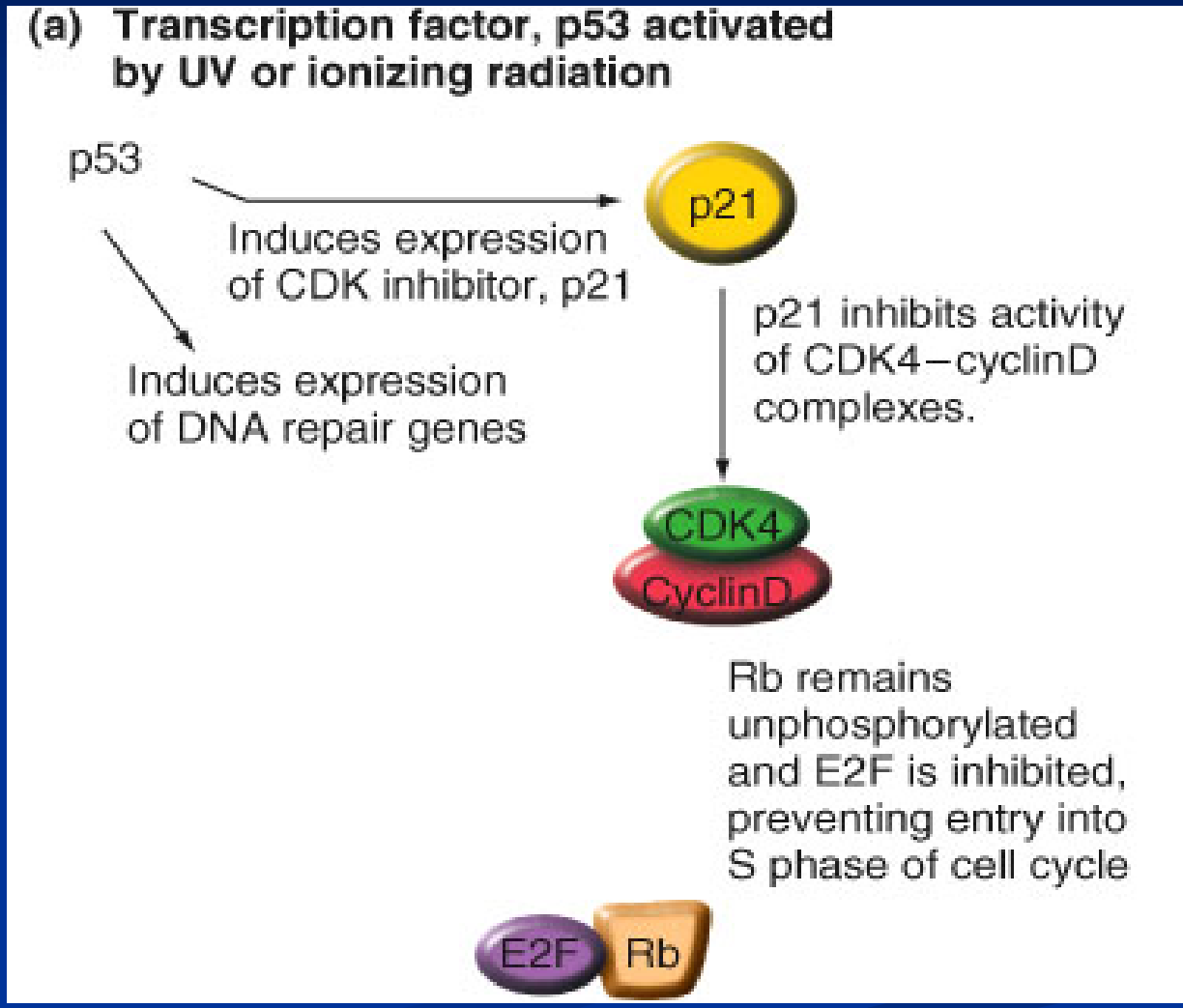
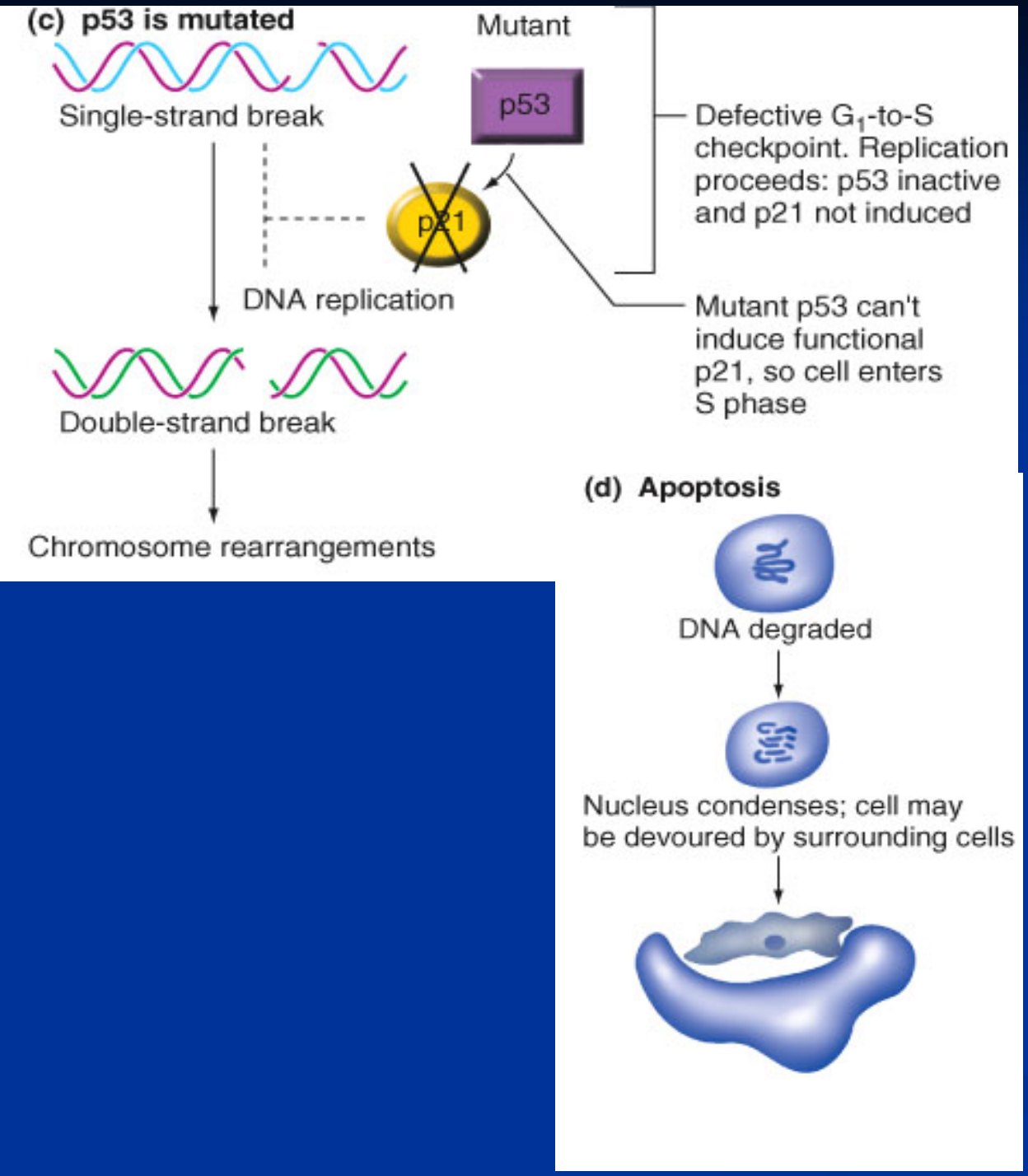


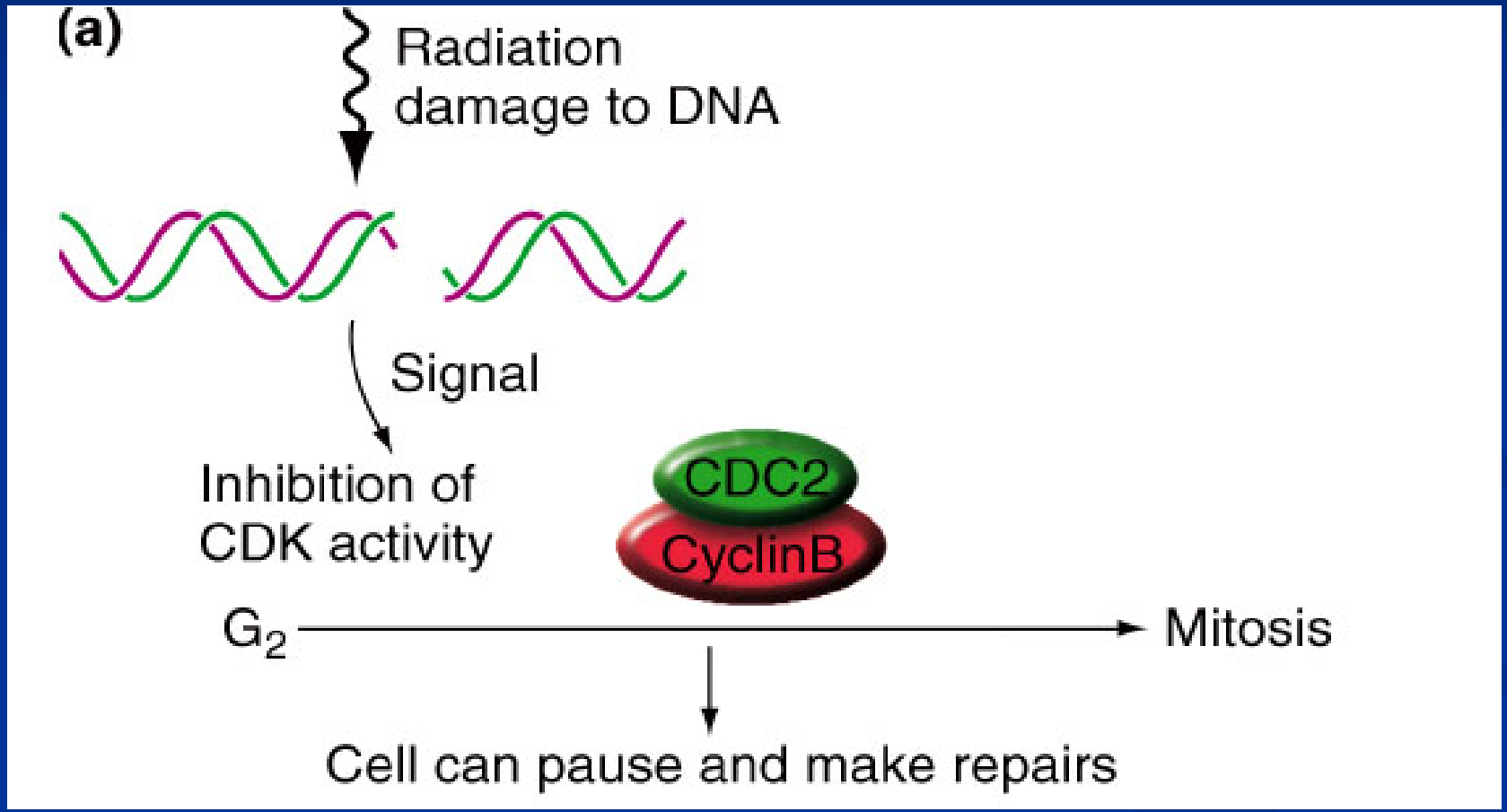
Fig. 19.16



- ***p53* mutants do not induce p21 and cell cycle is not arrested.**
- **Cells replicate damaged DNA.**
- **Cells die.**

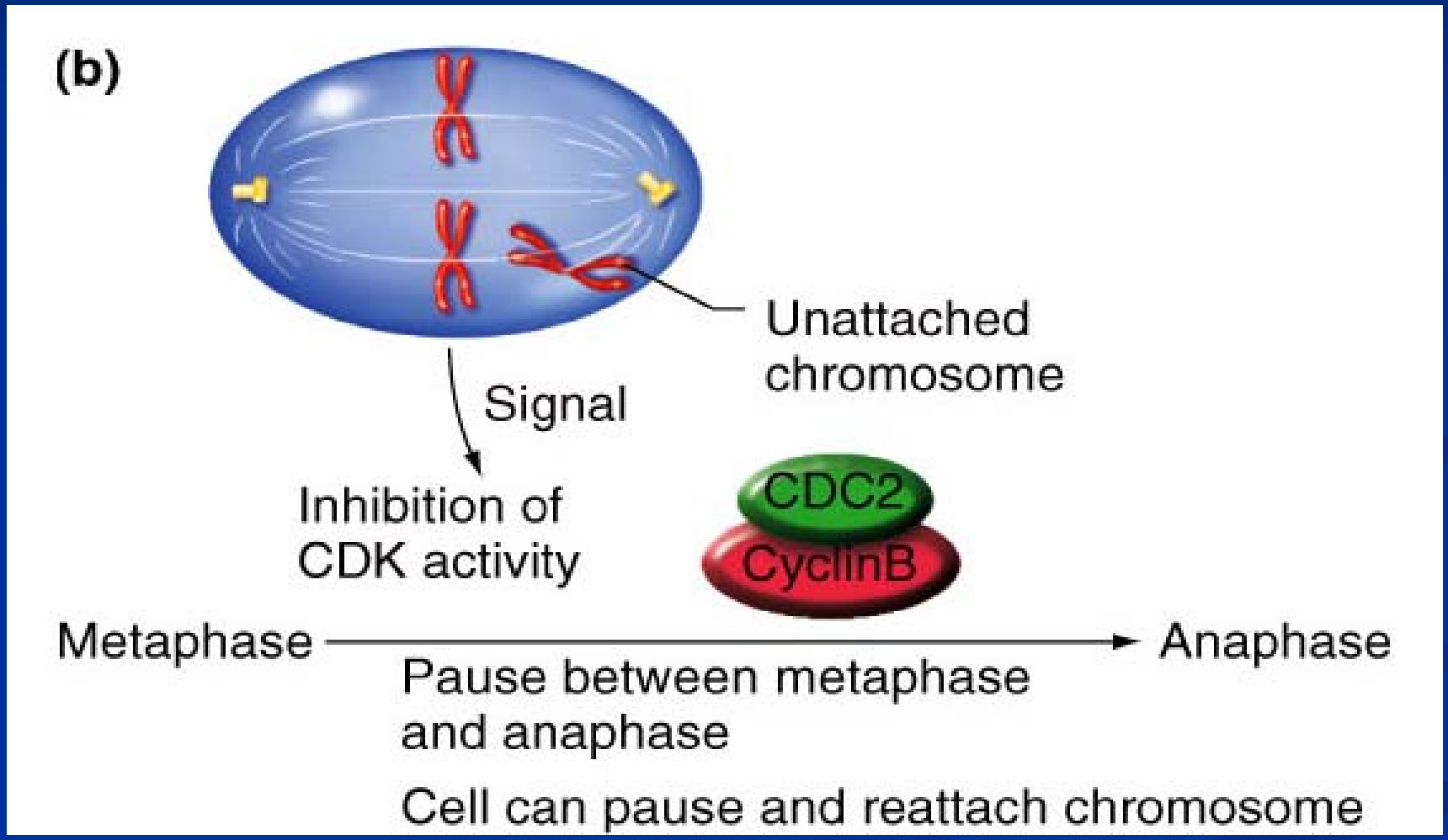
Two checkpoints act at the G_2-to-M transition

DNA damage during G2



Checkpoint in M

Spindle formation and chromosome attachment

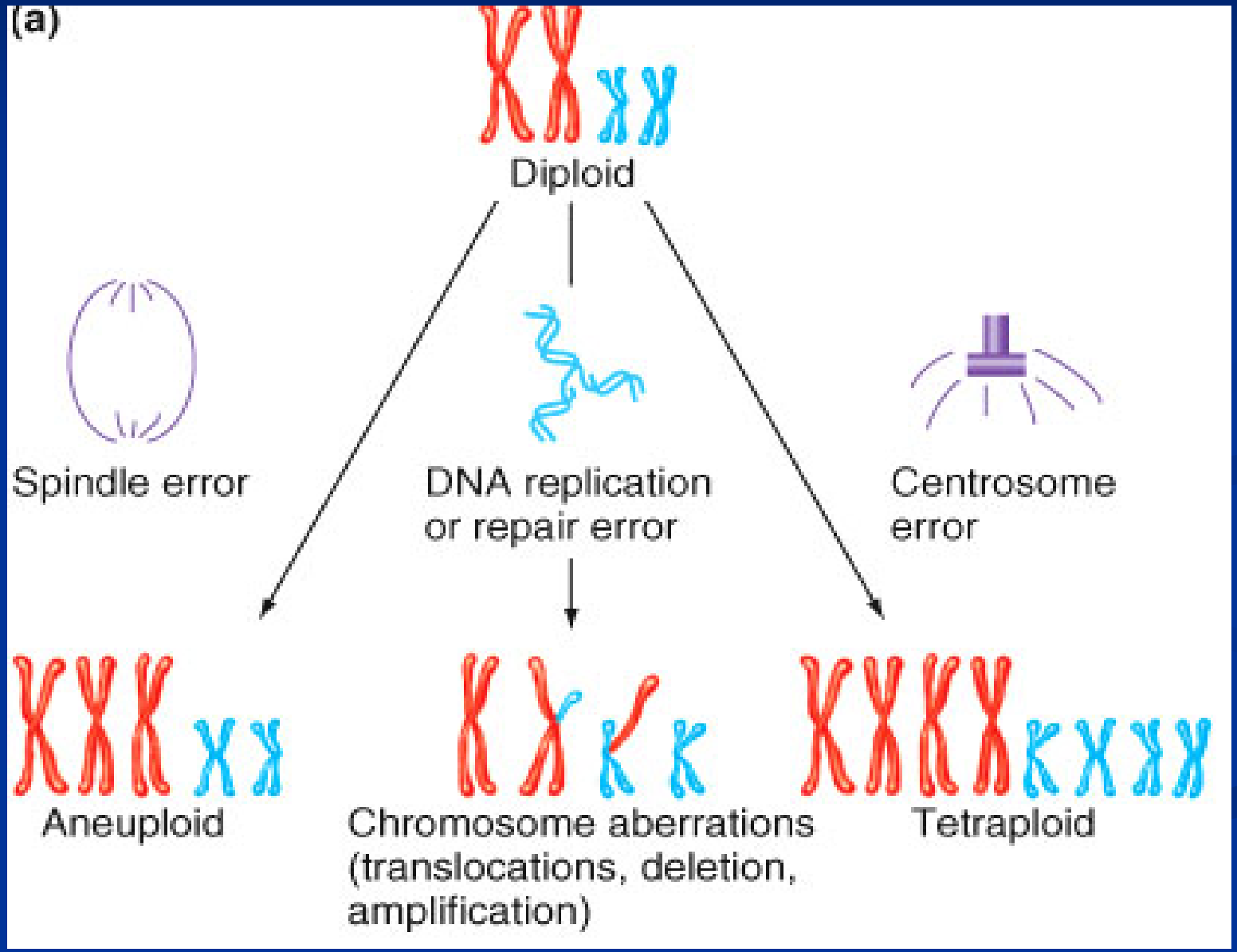


Checkpoints ensure genomic stability

Three types of genomic instability:

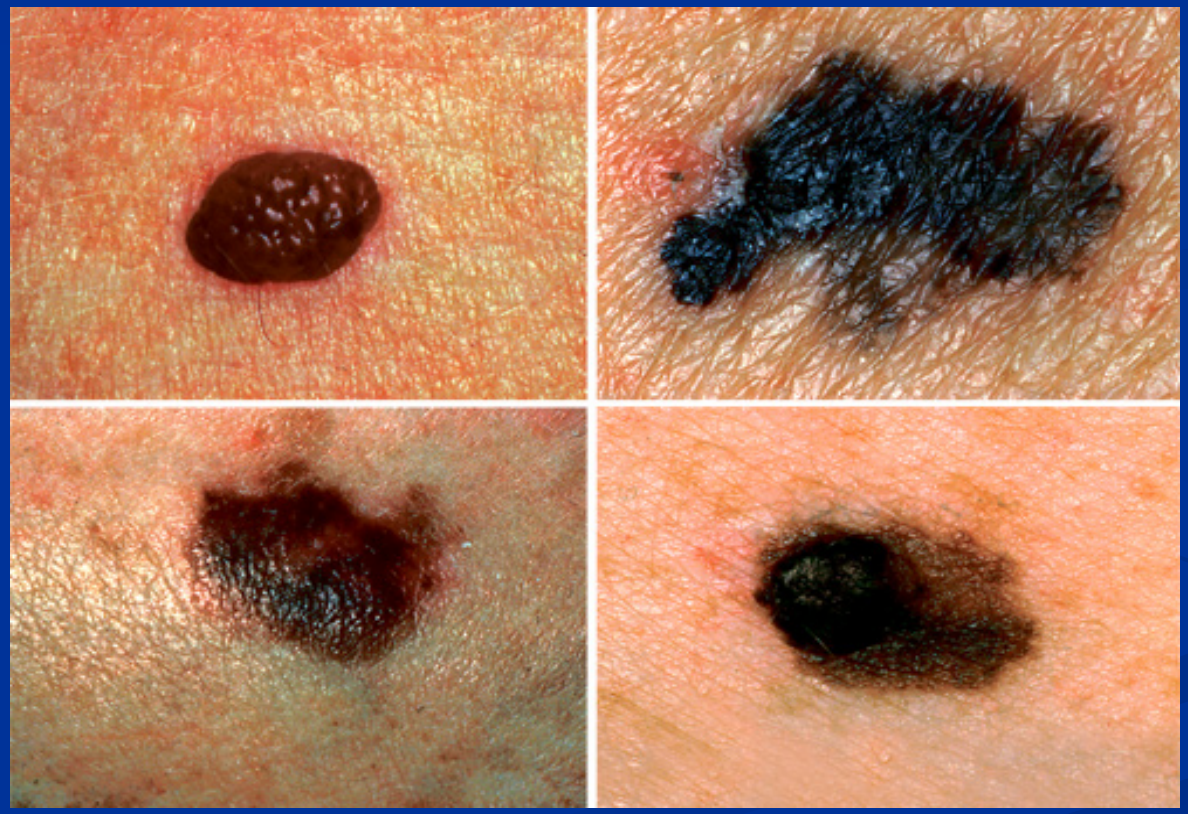
- **Chromosome aberrations**: such as deletion, duplication, and translocation.
  - Single-stranded nicks – normally repaired in G1 phase.
- **Aneuploidy**
  - Chromosome loss or gain by spindle error– normally corrected in G2-to-M checkpoint.
- **Changes in ploidy**
  - Caused by defective centrosomes or spindles.

Three classes of error lead to genomic instability in tumor cells



19.1 Characteristics of cancer cells

Cancer results when some cells in an individual organism's body divide out of control and eventually acquire the ability to spread beyond their prescribed boundaries.



Moles and skin cancer

Relative percentages of new cancers in the US

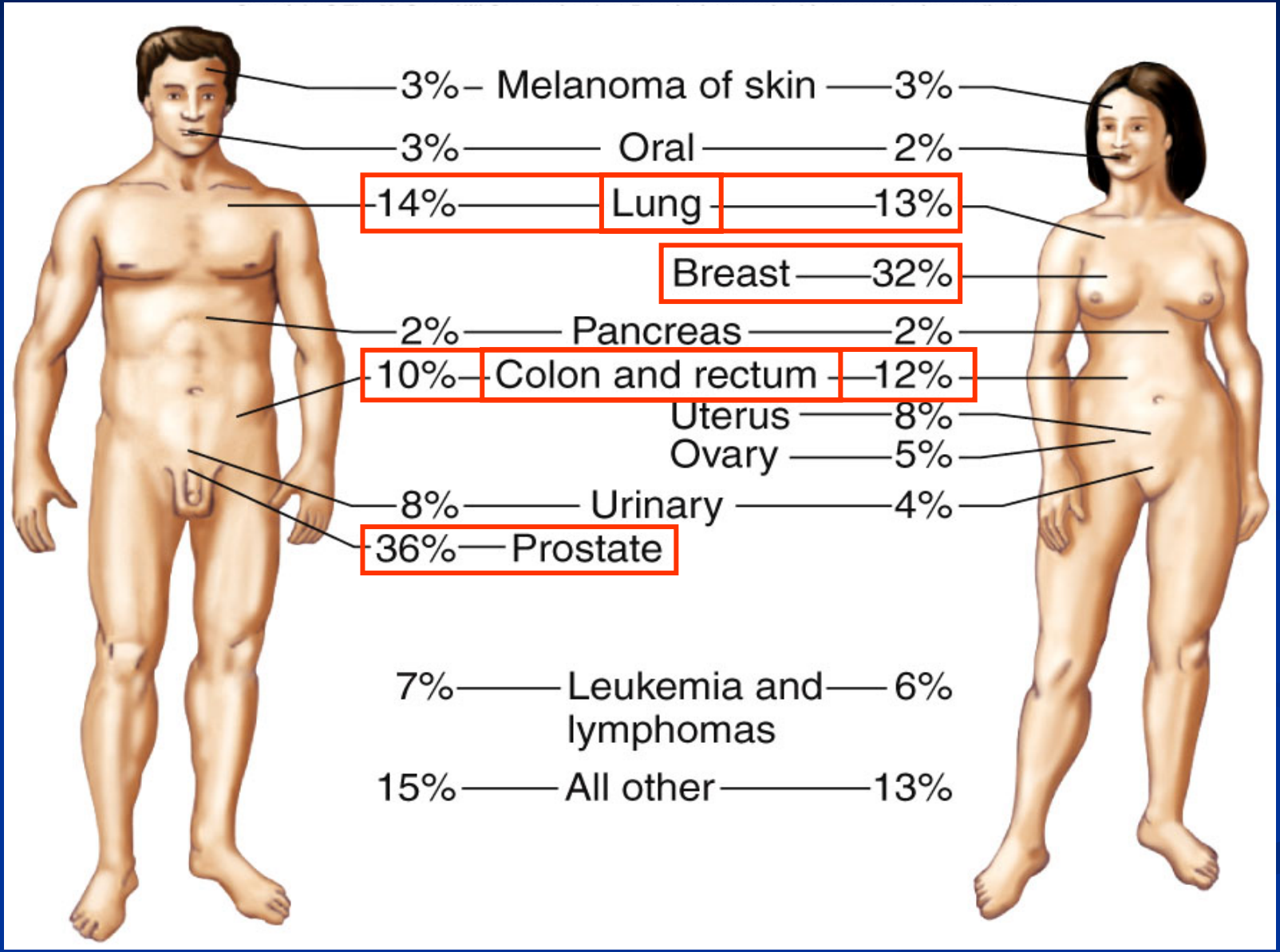


Fig 19.1

Each cancer may represent a unique property

- Cancer can develop in different tissues and organs.
  - Different cell types vary in their phenotypic responses to the same cancer-causing mutations.
- Cancers affecting the same tissue may have different origins and effects. Cancers in different patients often have unique properties.
  - Mutations in a variety of different genes that regulate cell division can help produce cancer.

Each cancer cell displays a number of phenotypes

1. Uncontrolled cell growth.
2. Genomic and karyotypic instability.
3. The potential for immortality.
4. The ability to get more nutrients and invade distant tissues.

1. Changes that produce uncontrolled cell growth

- **Autocrine stimulation** – tumor cells make their own signals to divide.
- Loss of **contact inhibition** – lost property to stop dividing when contacted by another cell.
- Loss of **gap junctions** – no channels for connecting to neighbor cell.
- Loss of **cell death** – resistance to programmed cell death.

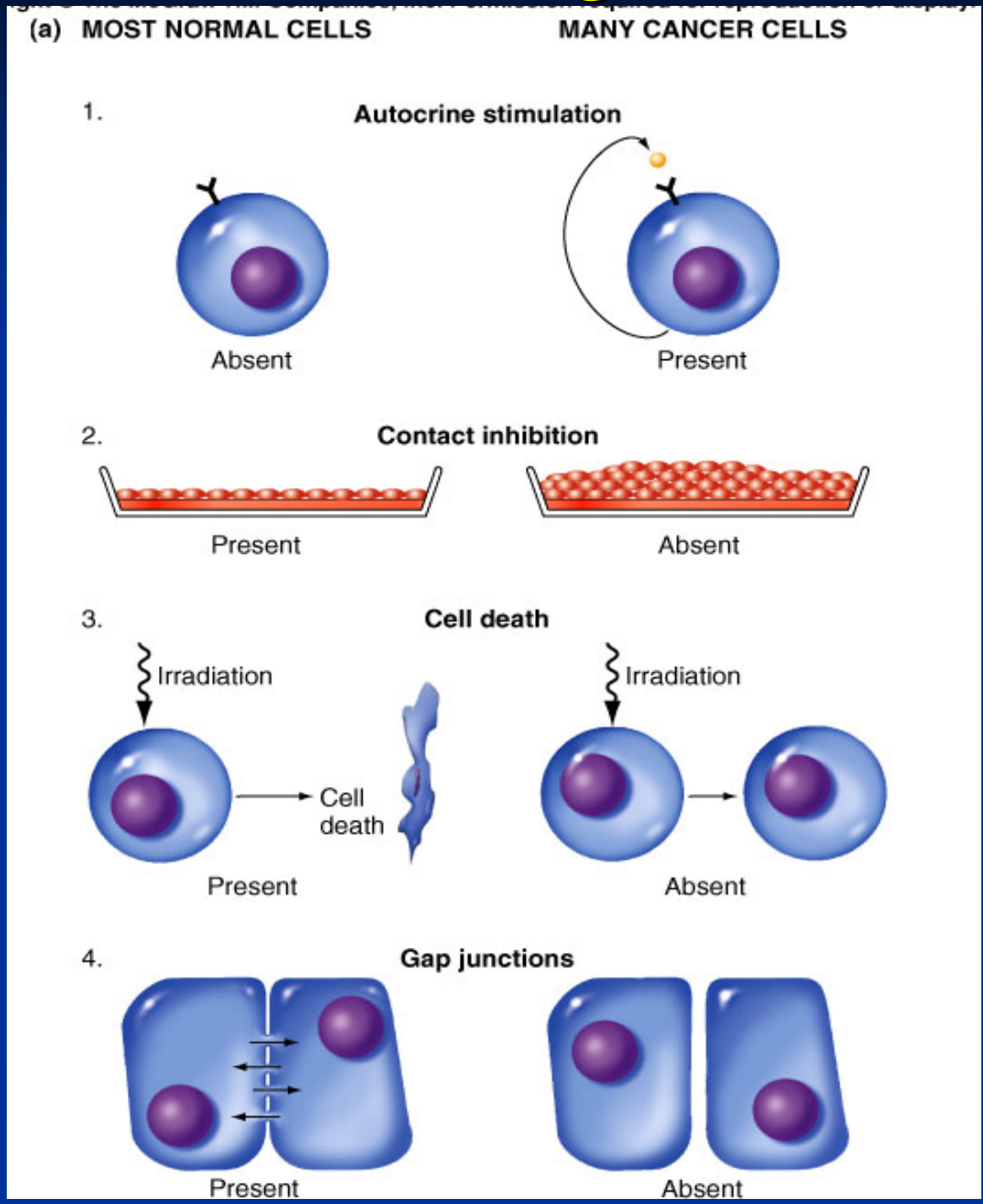
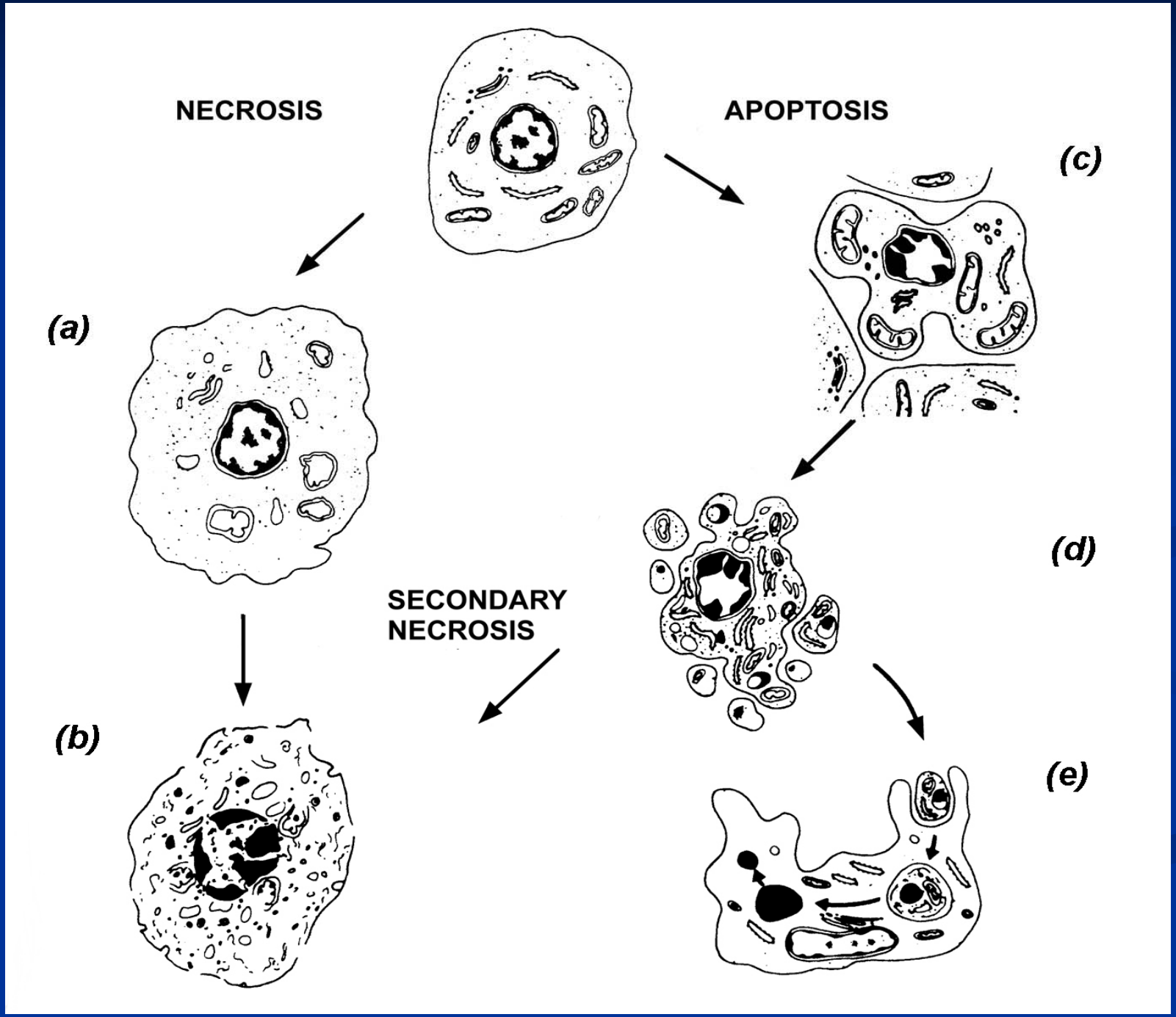
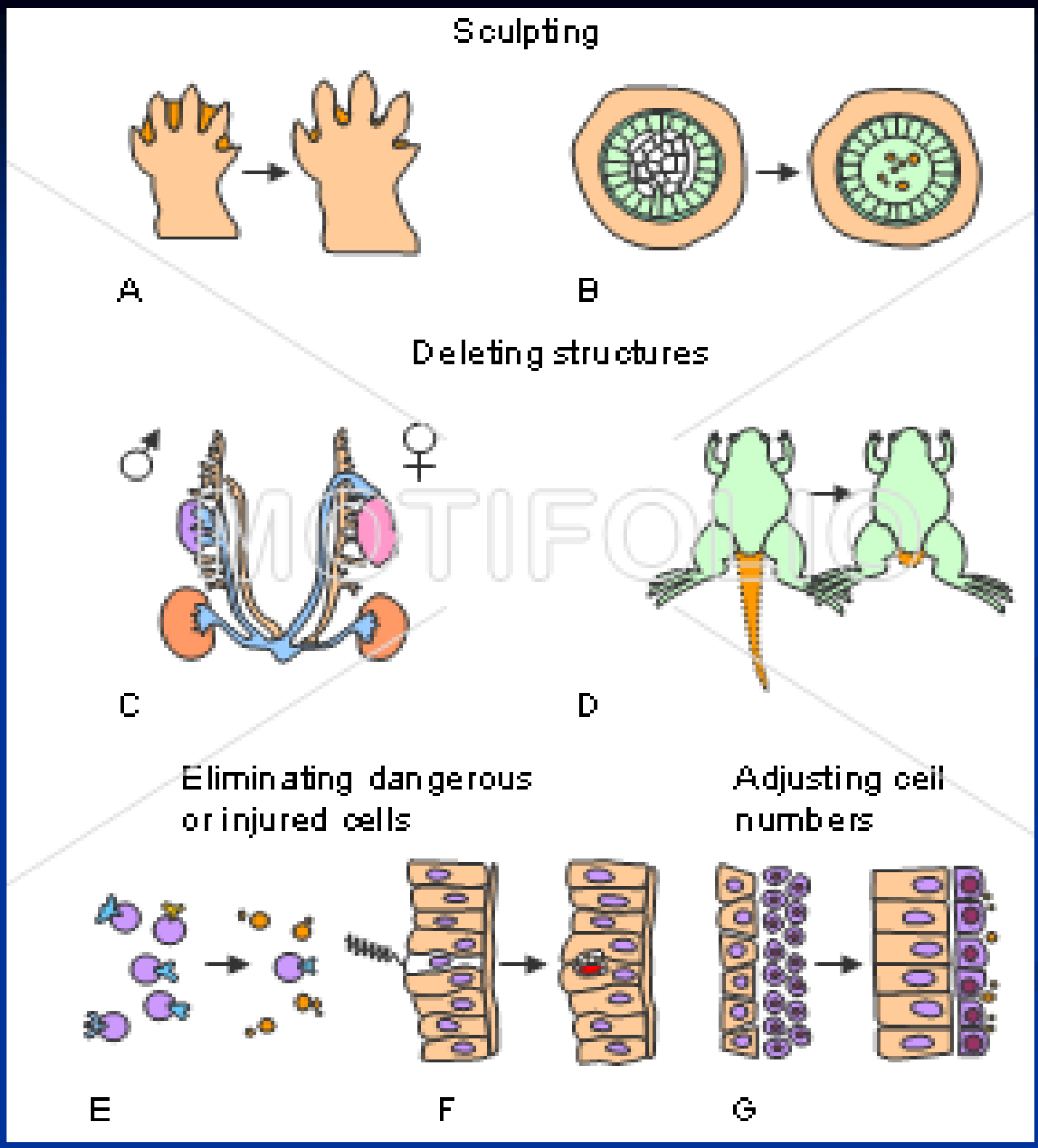


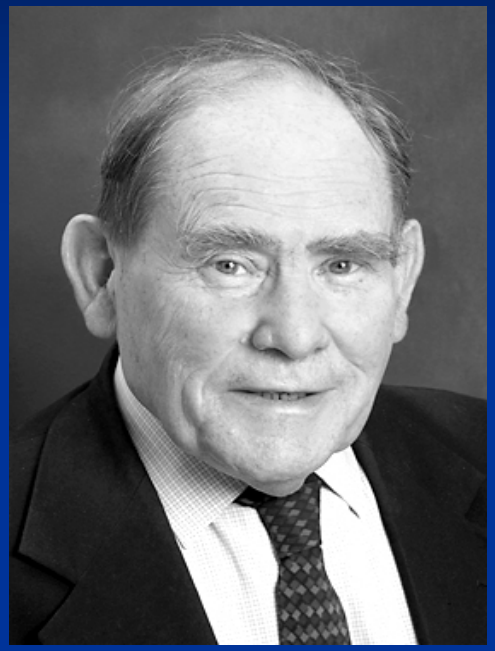
Fig. 19.2

Programmed cell death (apoptosis and necrosis)

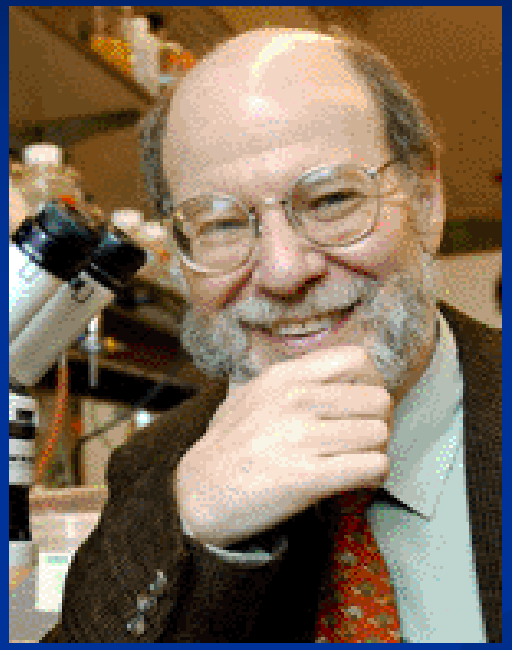



Sculpting
A
B
Deleting structures
♂
♀
C
D
Eliminating dangerous or injured cells
Adjusting cell numbers
E
F
G

The 2002 Nobel Prize in Physiology or Medicine



Sydney Brenner
Cambridge U



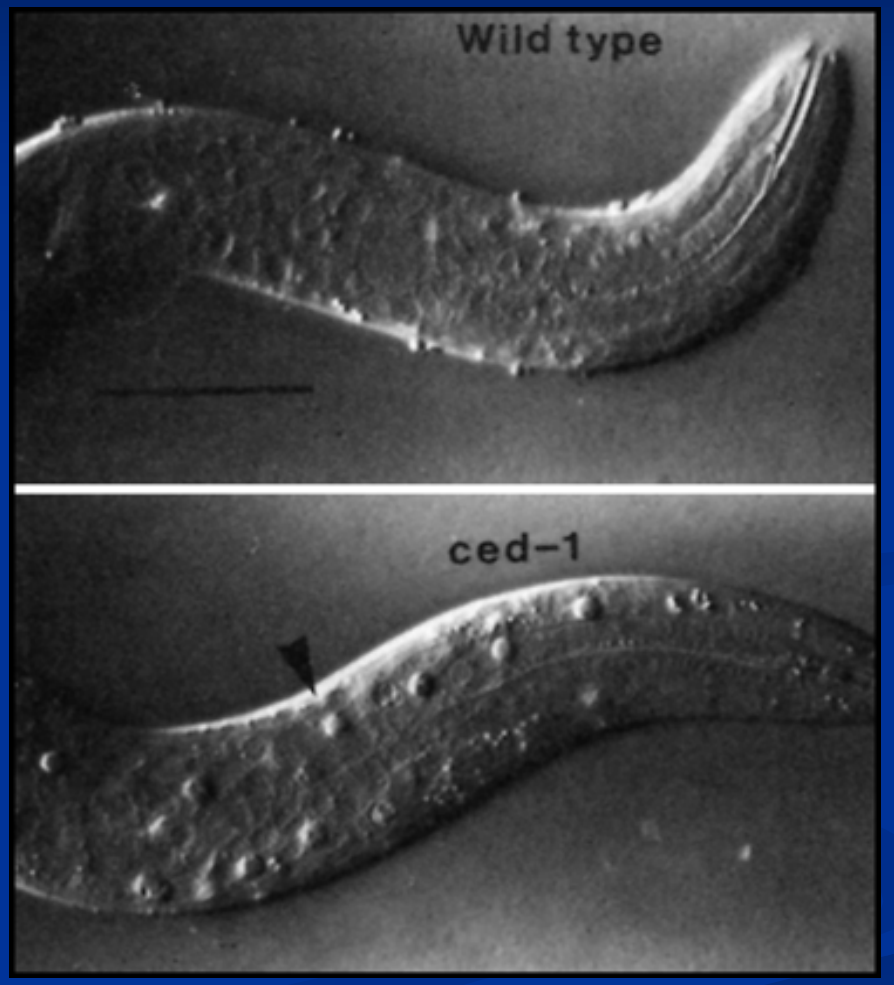
H. Robert Horvitz
MIT

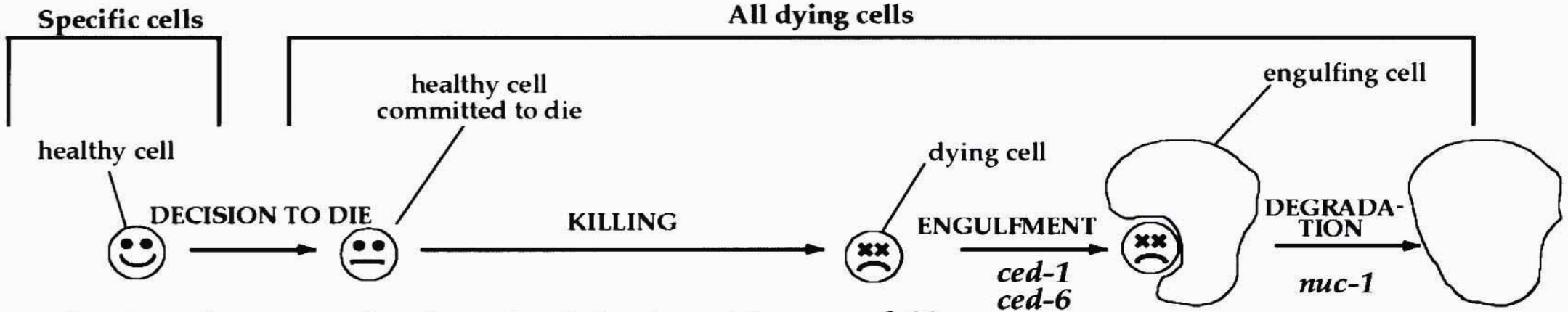
John Sulston
Cambridge U

For their discovery of genetic programs that control cell death in *C. elegans*.

Screening for cell death mutants in *C. elegans*

The nematode *C. elegans*





CES-2: bZip transcription factor
CES-1: zinc-finger transcription factor

TRA-1: zinc-finger transcription factor (Zarkower and Hodgkin)

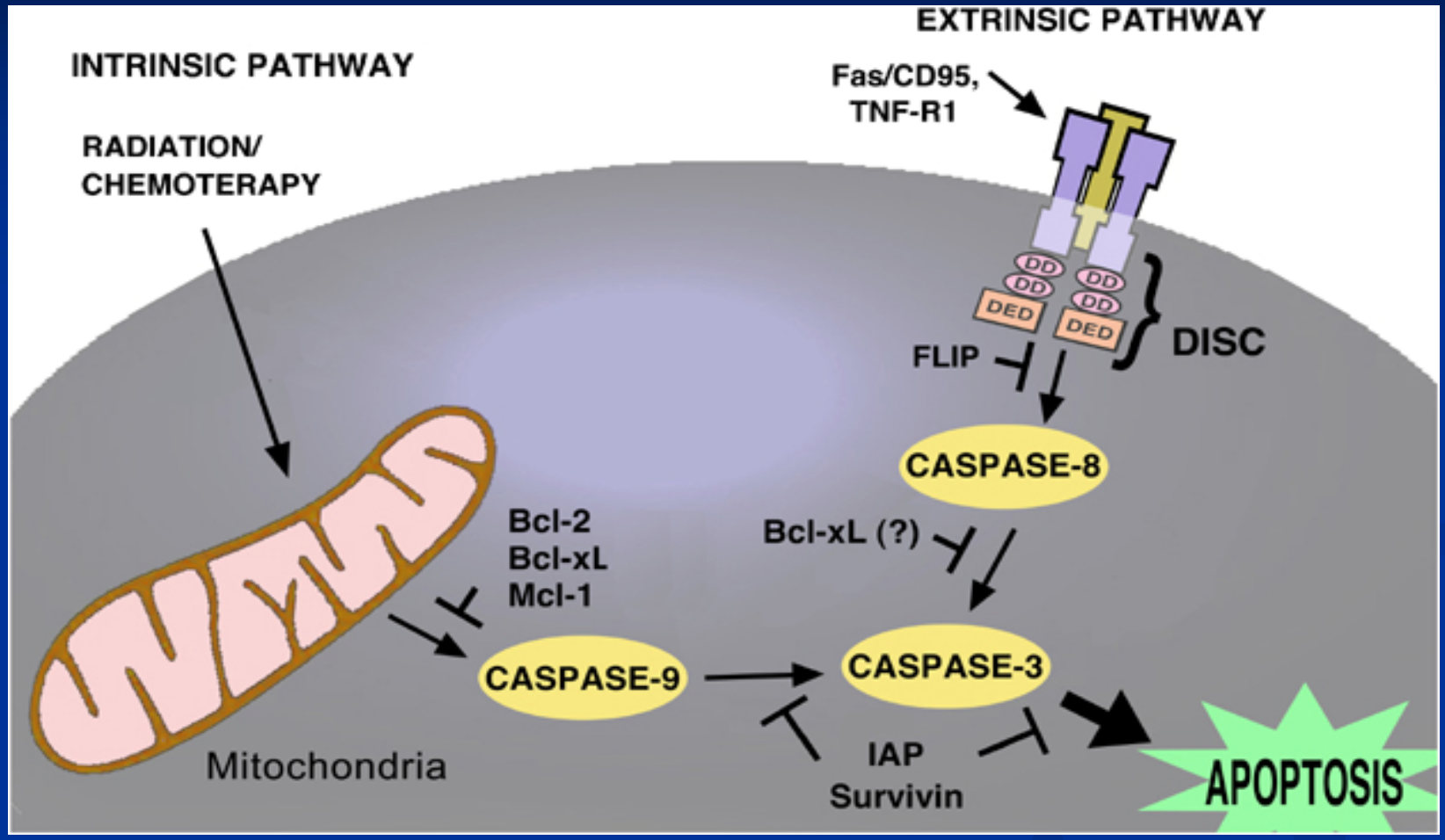
EGL-1: BH3 protein
CED-9: Bcl-2-like protein
CED-4: Apaf-1-like protein
CED-3: Caspase

CED-8: XK-like protein
CED-11: TRPC7-like protein?

CED-2: CrkII-like protein
CED-5: DOCK180-like protein
CED-10: Rac-like protein
CED-12: PH & SH3-binding motifs

CED-7: ABC transporter
CED-1: SREC-like receptor
CED-6: adaptor protein (Liu and Hengartner)

Xiaodong Wang
NIBS



2. Changes that produce genomic and karyotypic instability

- Mutation rate is much higher in cancer cells.
  - Defective in mismatch repair during DNA replication.
  - Defective in DNA damage repair caused by radiation or UV.
- Gross chromosomal rearrangements.
- Aneuploidies and polyploidies.
  - Defective mitotic apparatus.

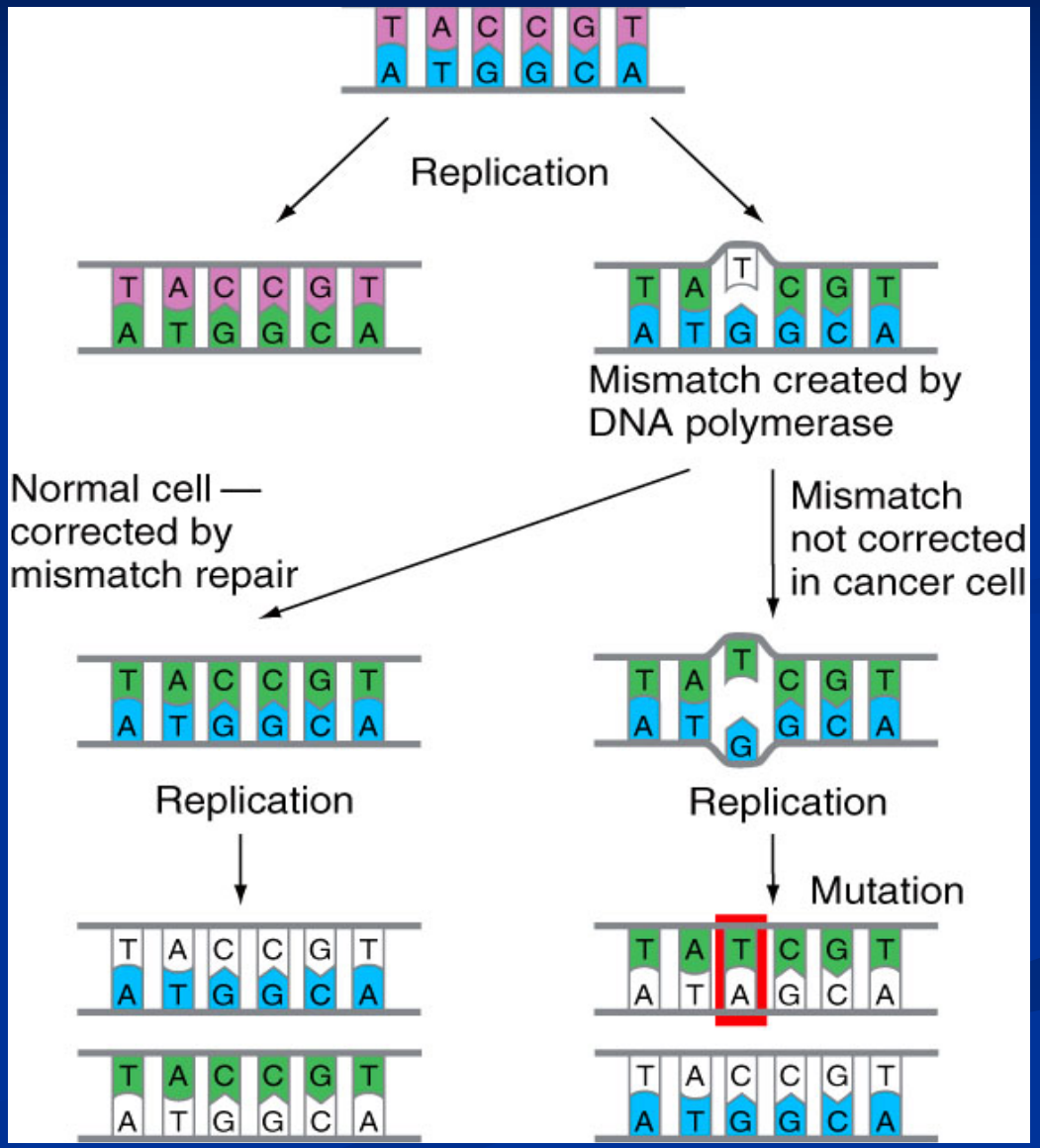
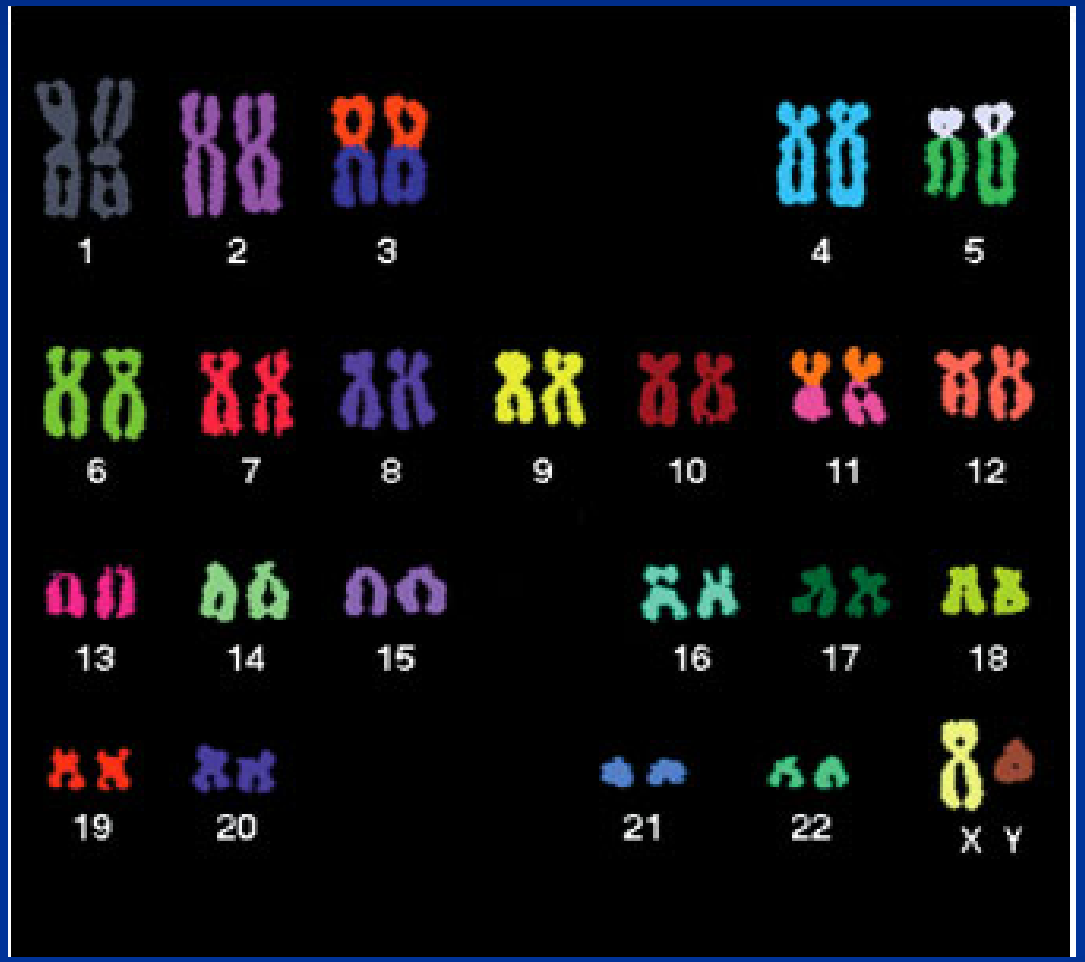


Fig. 19.4

Tumor-cell karyotypes often show increased chromosomal rearrangements

Normal cells



Cancer cells

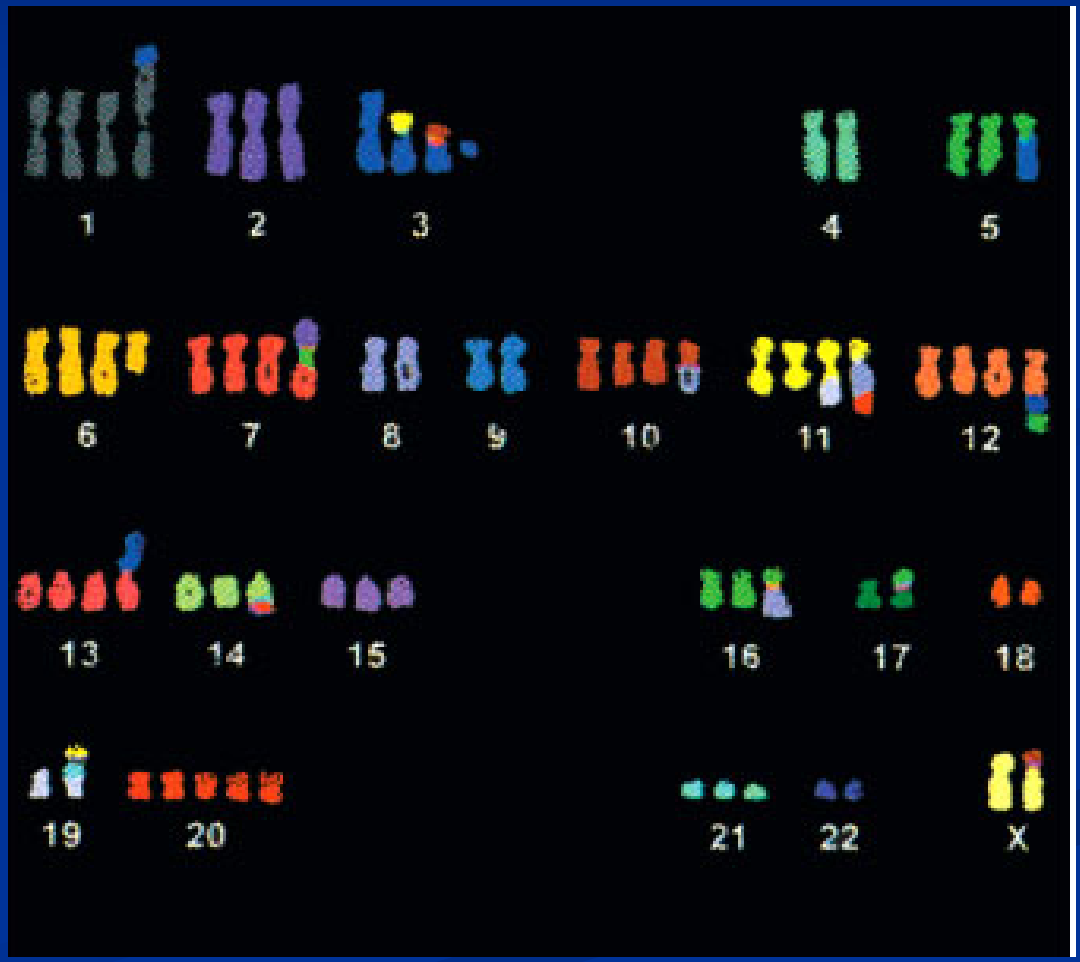
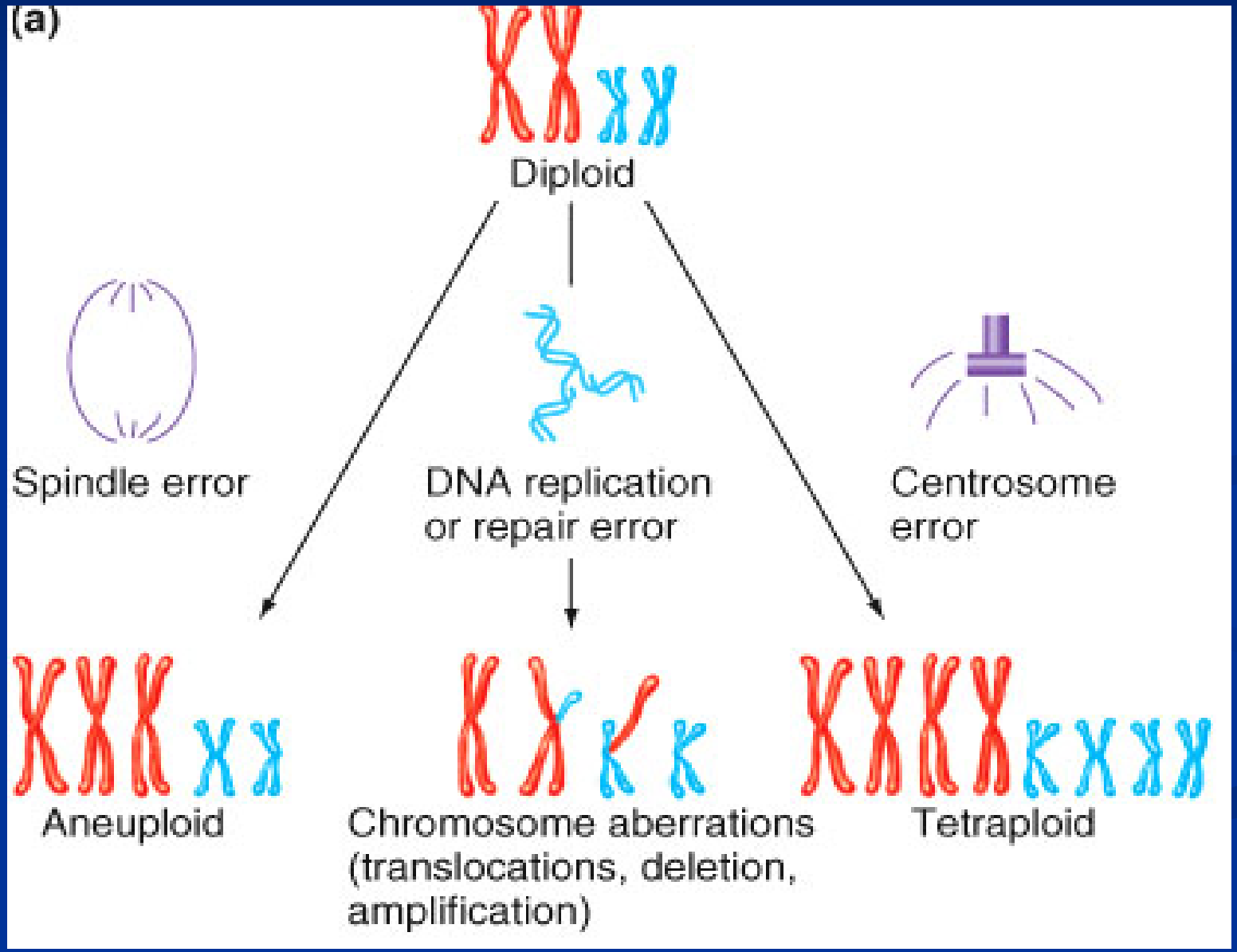


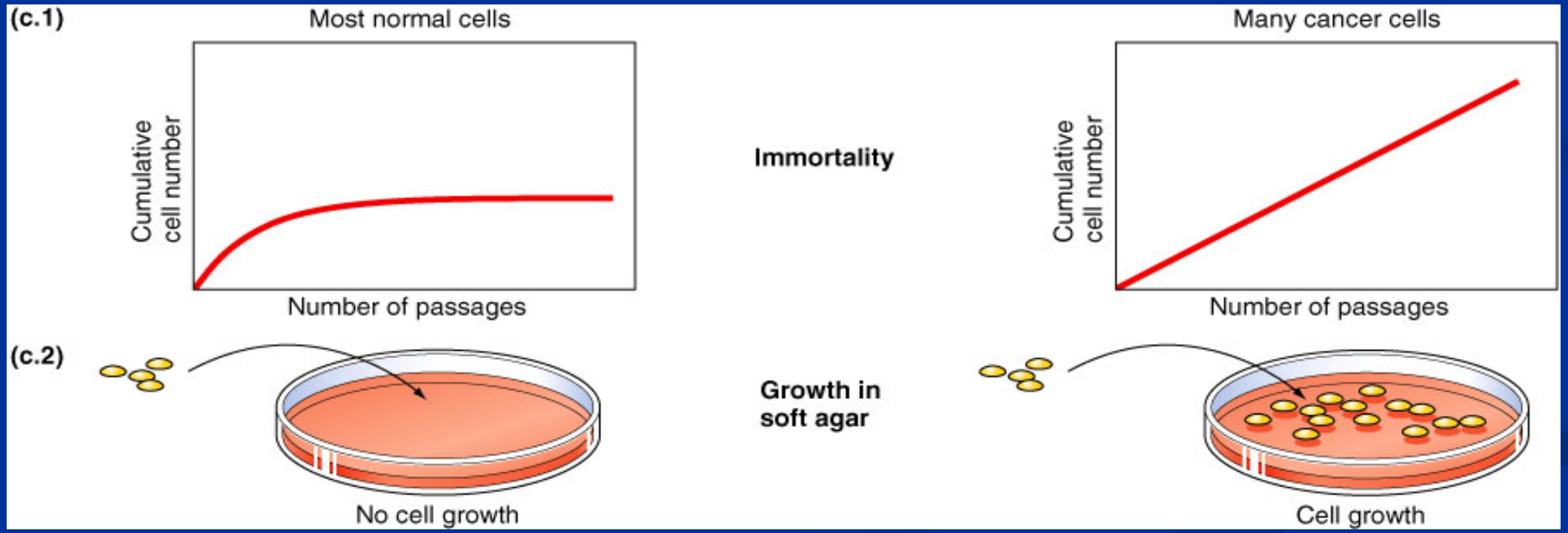
Fig. 19.4

Three classes of error lead to genomic instability in tumor cells



3. Changes that produce a potential for immortality

- Loss of limitations on the number of cell divisions.
- Ability to grow in culture – normal cells do not grow well in culture.
- Restoration of telomerase activity.



4. Changes that enable tumor to get more nutrients and invade distant tissues

- Some tumors get more nutrients by secreting substances that cause blood vessels to grow toward them.
  - **Angiogenesis** – A physiological process that new blood vessels form from pre-existing vessels.
- Ability to **metastasize**.
- Evasion of **immune surveillance**.

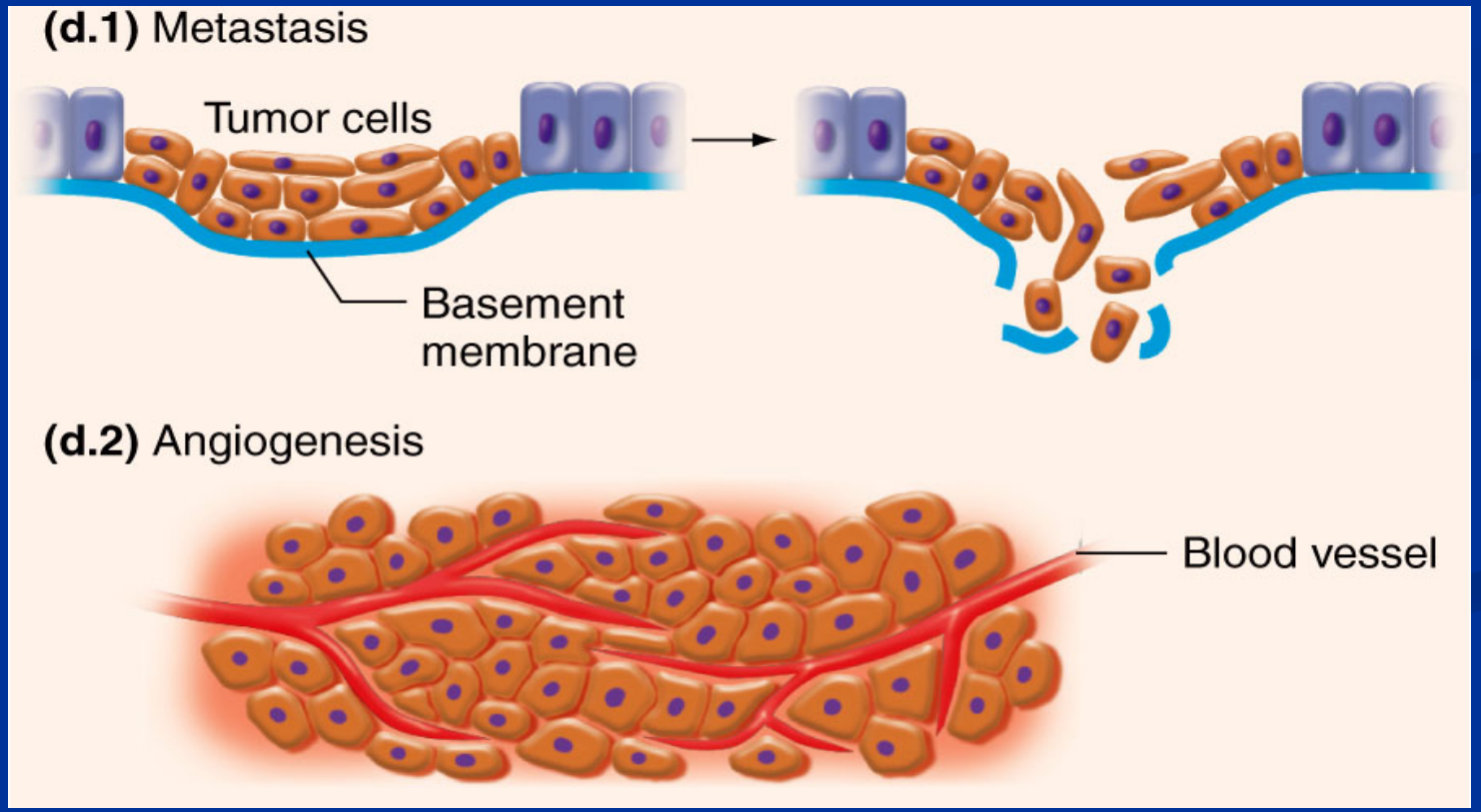


Fig. 19.5

19.2 The genetic basis of cancers

Cancer presumably arises by successive mutations in a clone of proliferating cells.

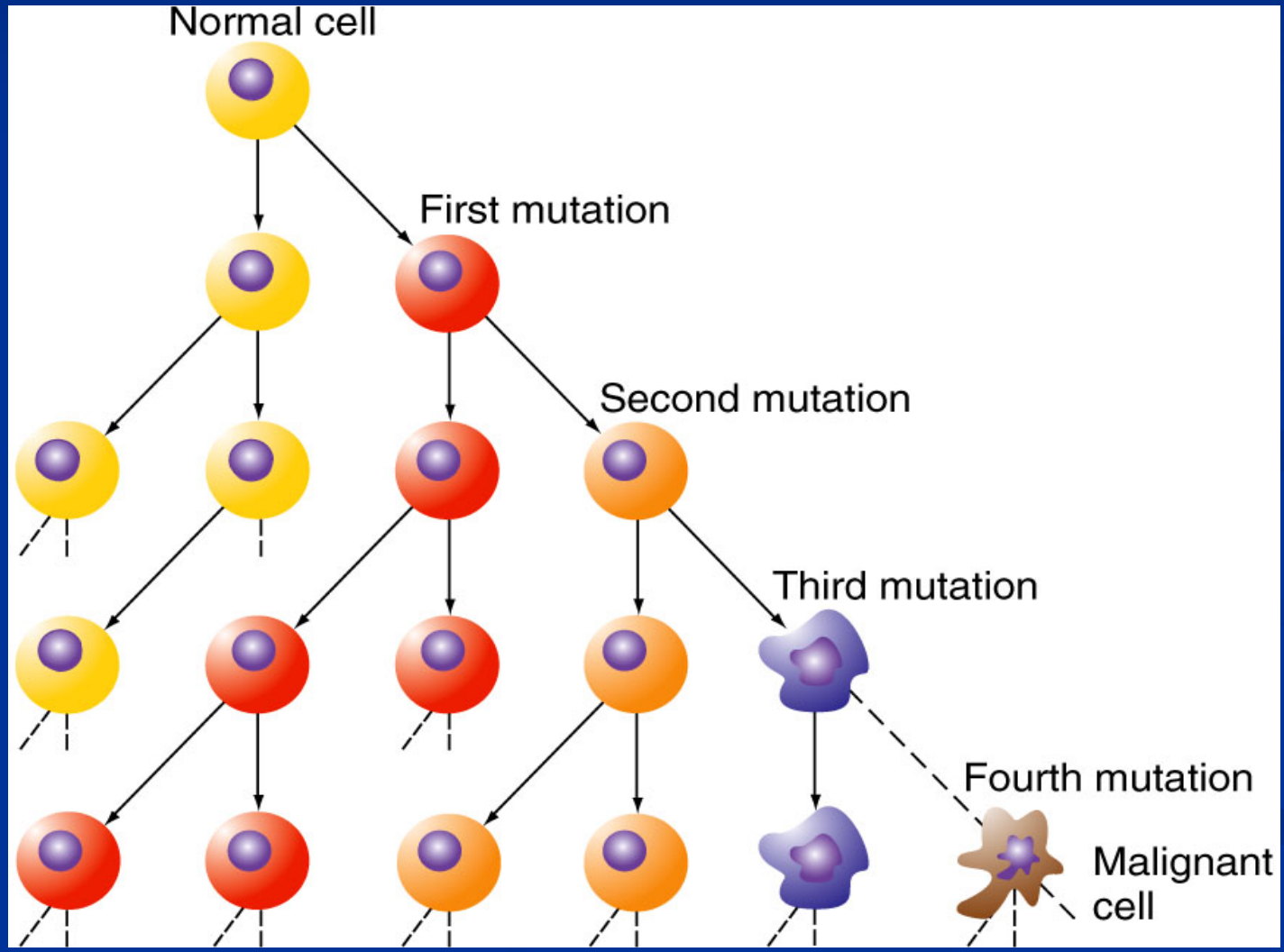
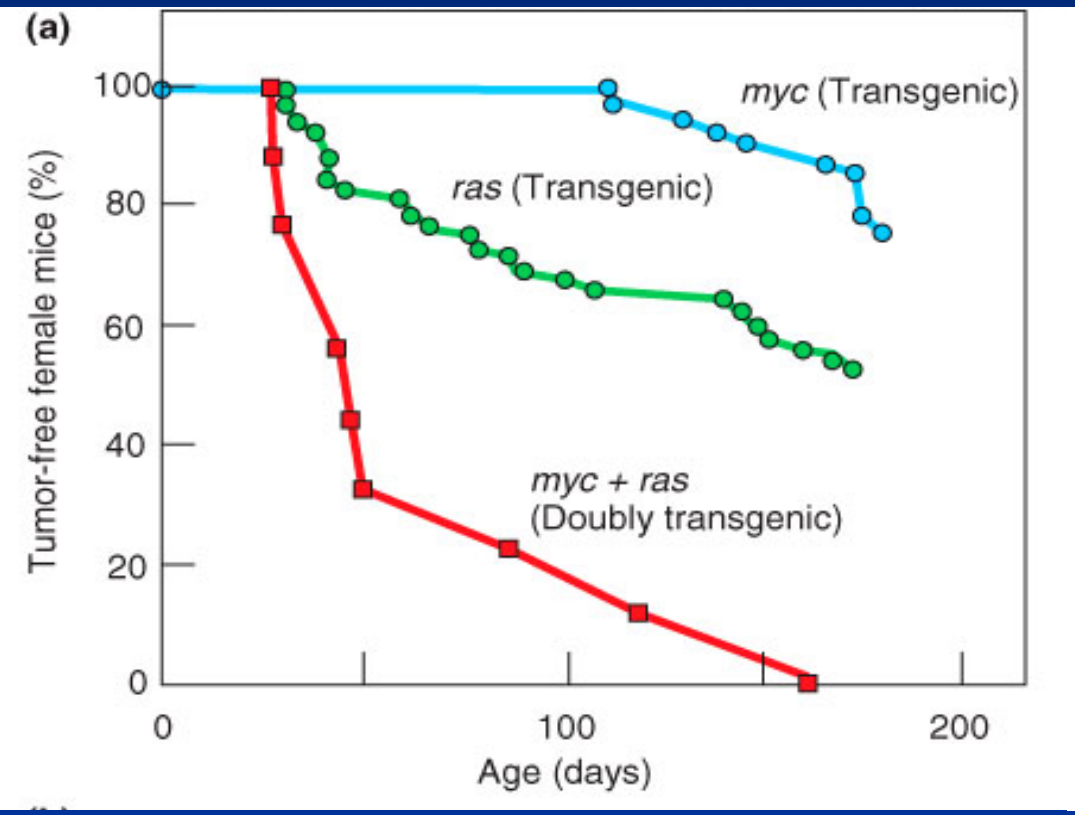
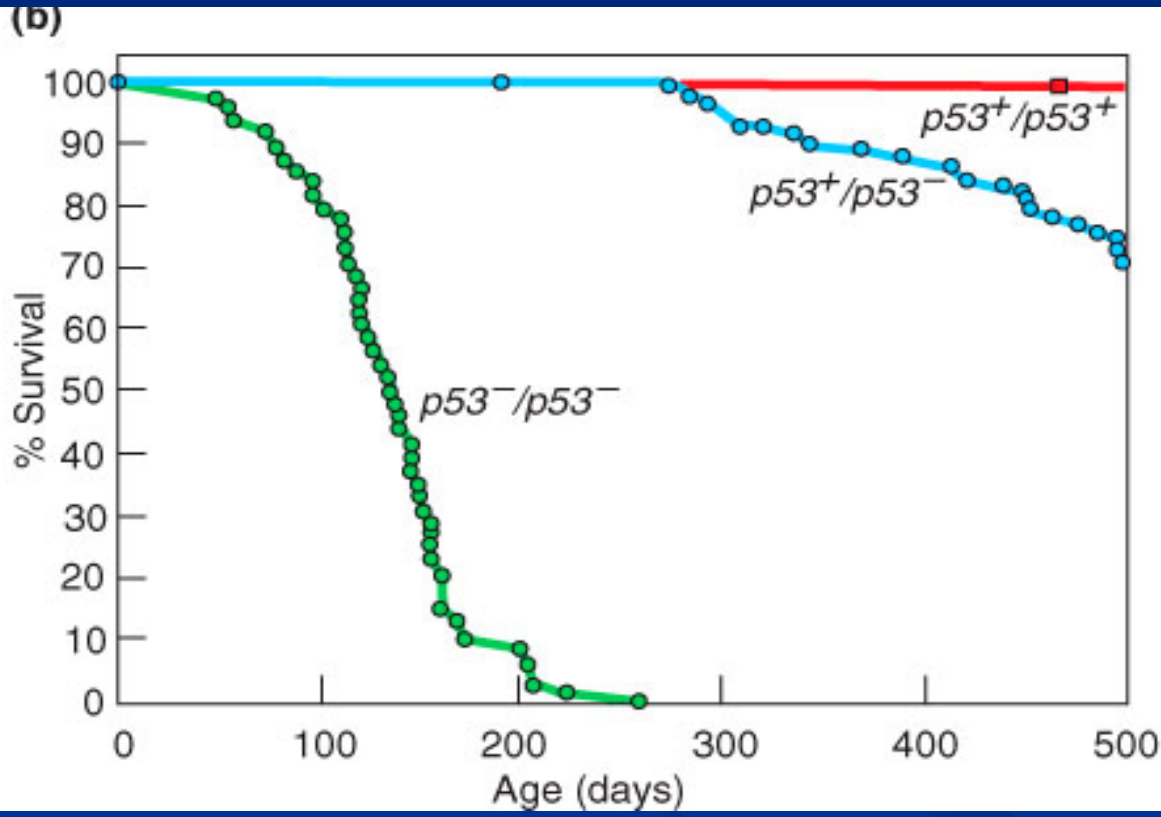


Fig. 19.6

It takes several mutations in different genes to produce a cancer





p53 **is not essential for normal cell function, but it plays a role in preventing tumor formation.**

Cancers are clonal descendents of one cell

Glucose-6-phosphate dehydrogenase (G6PD)

Beutler E *et al.* (1962) The normal human female is a mosaic of X-chromosome activity: studies using the gene for G6PD-deficiency as a marker. *P.N.A.S.*

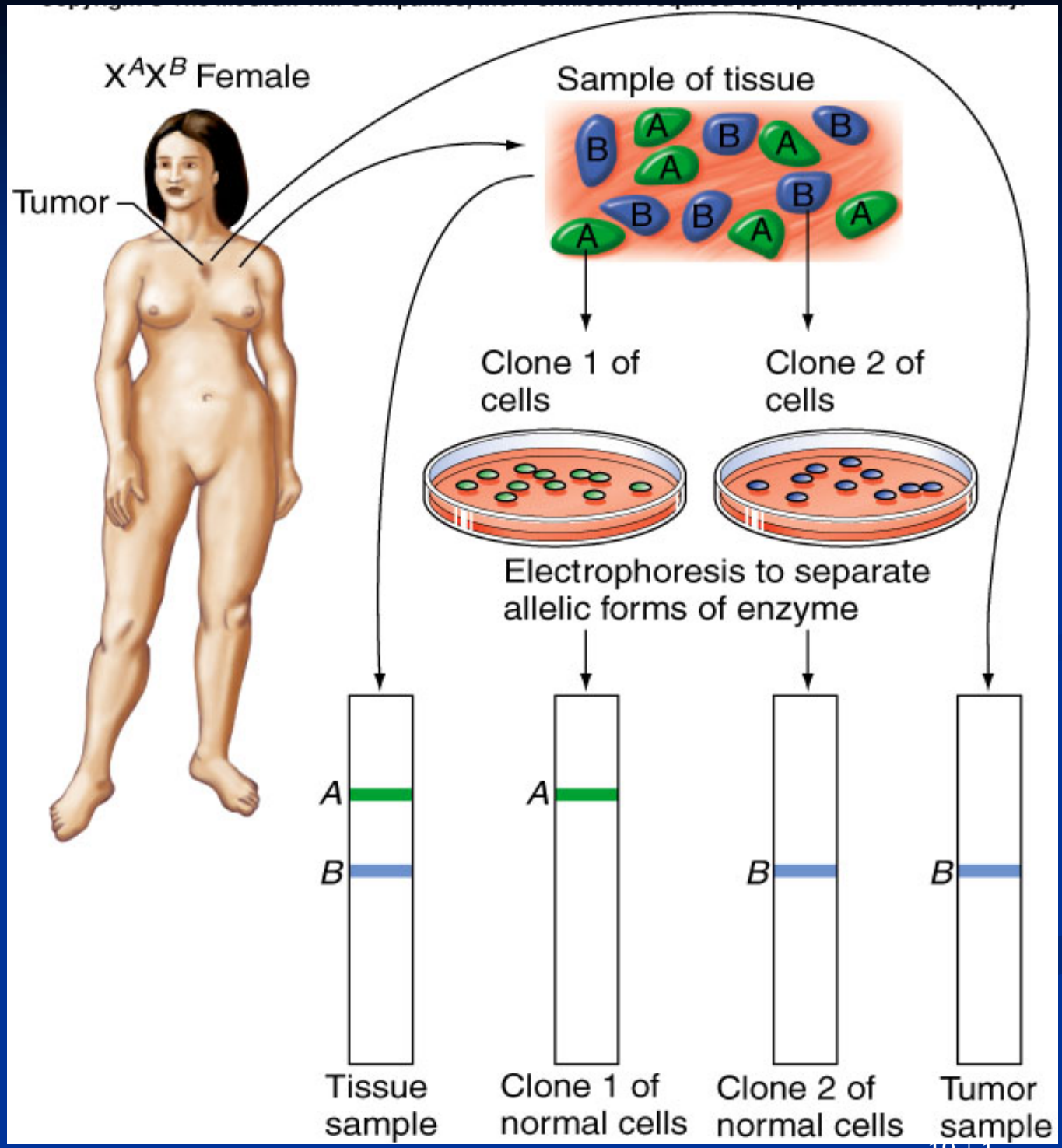
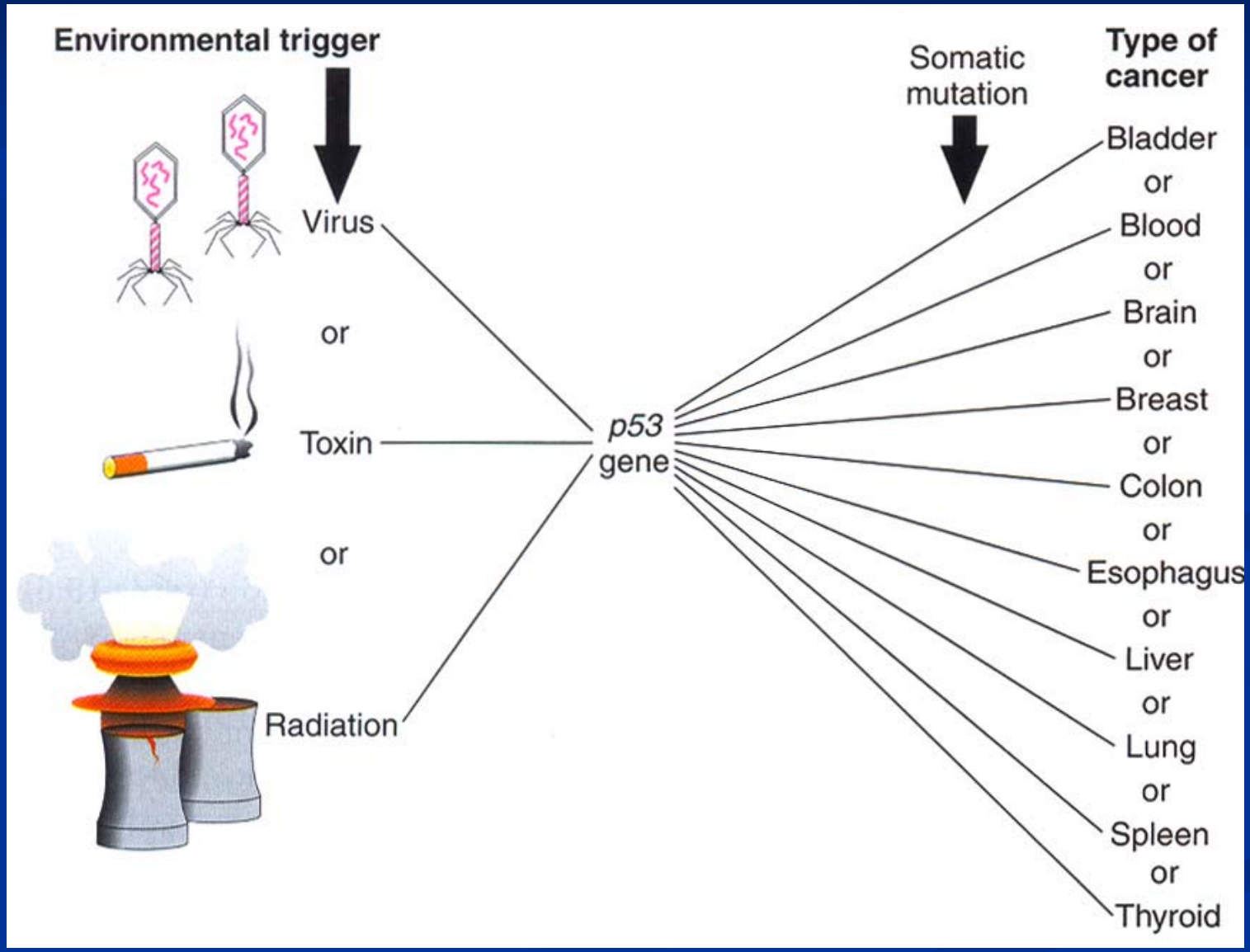


Fig. 19.7

Environmental mutagens increase the likelihood of cancer



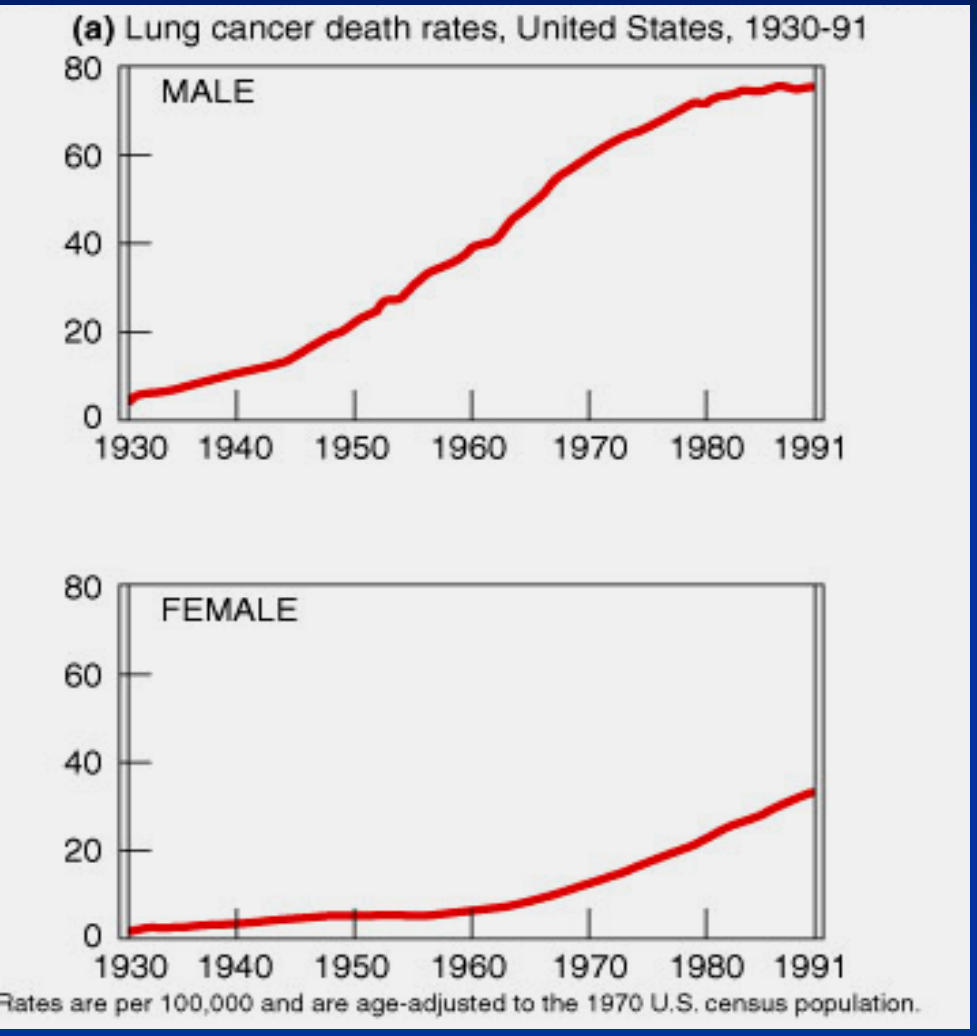
- If one sib or twin gets cancer, the other usually does not.
- Populations that migrate – profile of cancer becomes more like people indigenous to new location.
- Numerous environmental agents increase cancer development.

TABLE 19.2 The Incidence of Some Common Cancers Varies Between Countries

Site of Origin of Cancer	High-Incidence Population		Low-Incidence Population	
	Location	*Incidence**	*Location*	*Incidence**
Lung	USA (New Orleans, blacks)	110	India (Chennai)	5.8
Breast	Hawaii (Hawaiians)	94	Israel (non-Jews)	14.0
Prostate	USA (Atlanta, blacks)	91	China (Tianjin)	1.3
Cervix	Brazil (Recife)	83	Israel (non-Jews)	3.0
Stomach	Japan (Nagasaki)	82	Kuwait (Kuwaitis)	3.7
Liver	China (Shanghai)	34	Canada (Nova Scotia)	0.7
Colon	USA (Connecticut, whites)	34	India (Chennai)	1.8
Melanoma	Australia (Queensland)	31	Japan (Osaka)	0.2
Nasopharynx	Hong Kong	30	UK (southwestern)	0.3
Esophagus	France (Calvados)	30	Romania (urban Cluj)	1.1
Bladder	Switzerland (Basel)	28	India (Nagpur)	1.7
Ovary	New Zealand (Polynesian Islanders)	26	Kuwait (Kuwaitis)	3.3
Pancreas	USA (Los Angeles, Koreans)	16	India (Pune)	1.5
Lip	Canada (Newfoundland)	15	Japan (Osaka)	0.1

*Incidence indicates number of new cases per year per 100,000 population, adjusted for a standardized population age distribution (so as to eliminate effects due merely to differences of population age distribution). Figures for cancers of breast, cervix, and ovary are for women; other figures are for men. Adapted from V. T. DeVita, S. Hellman, and S. A. Rosenberg (eds.), *Cancer: Principles and Practice of Oncology*, 4th ed. Philadelphia: Lippincott, 1993; based on data from C. Muir et al., *Cancer Incidence in Five Continents*, Vol. 5. Lyon: International Agency for Research on

Cancer develops over time



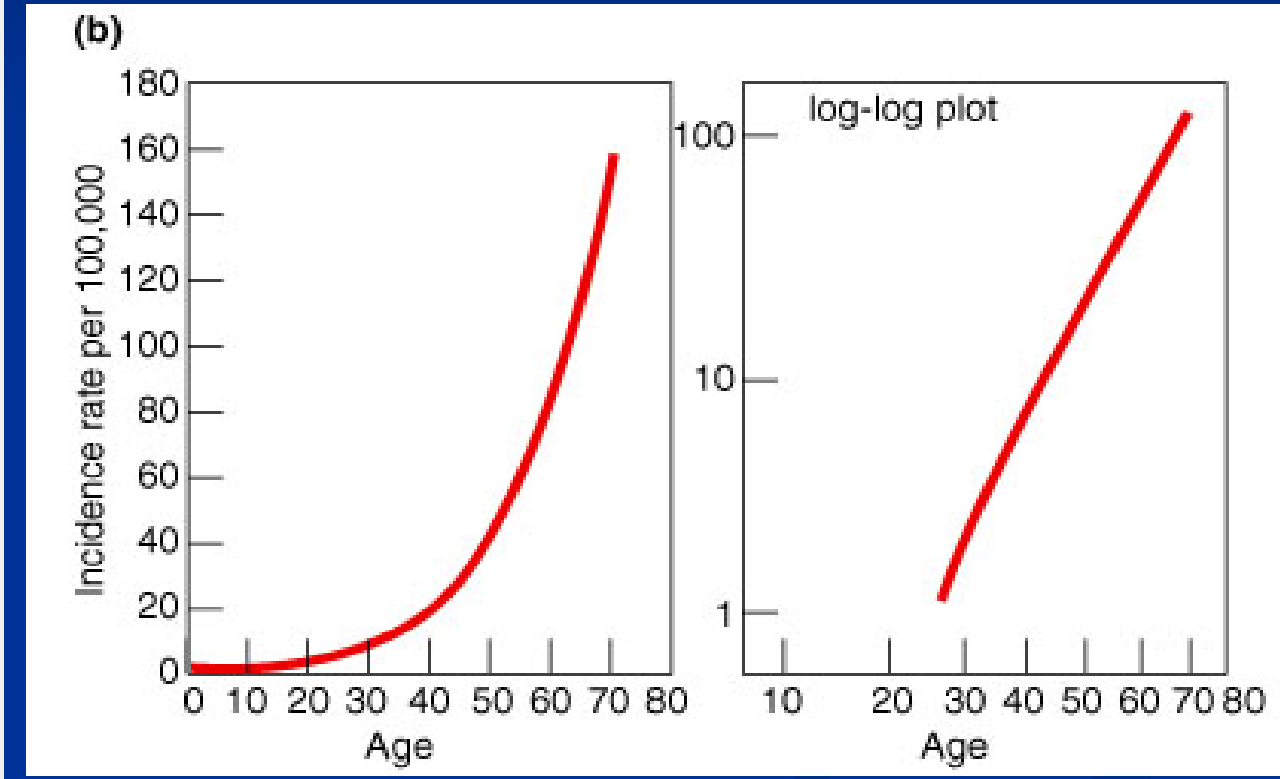
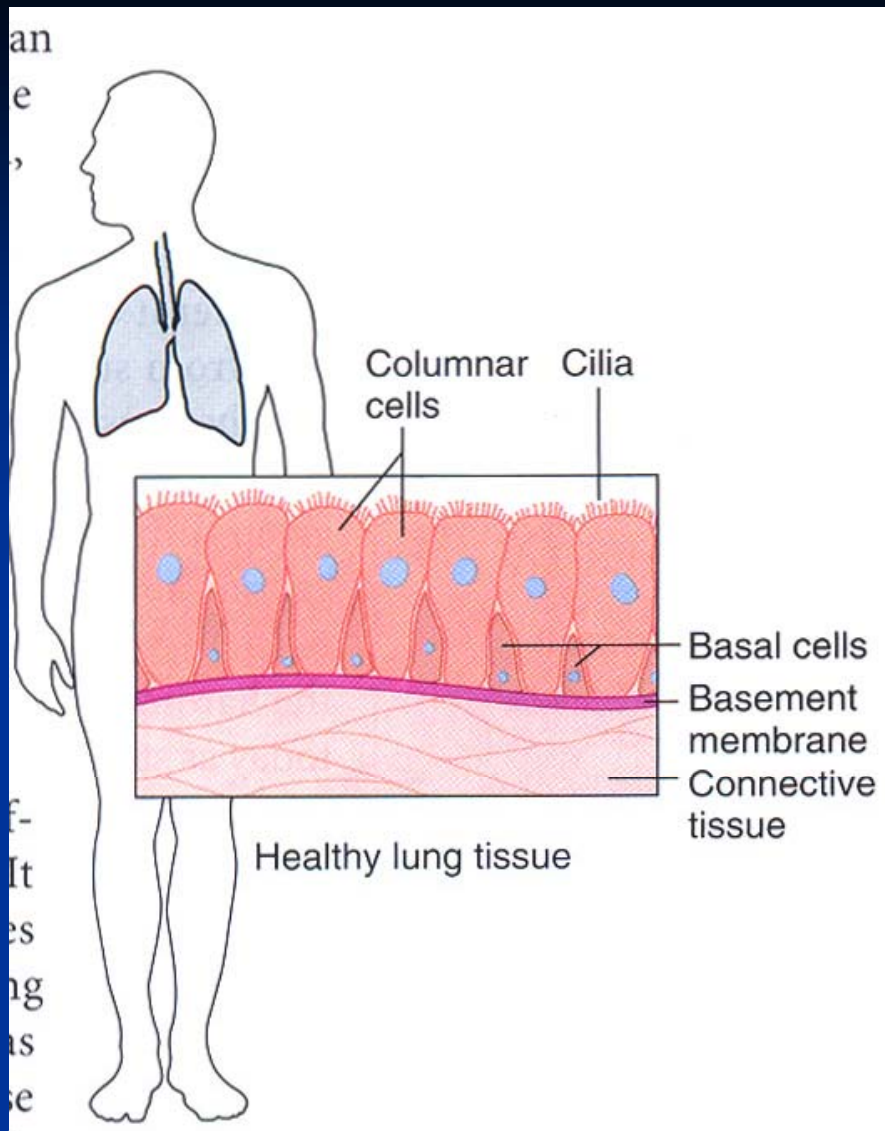
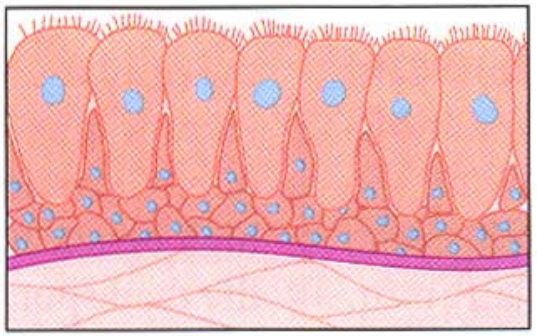
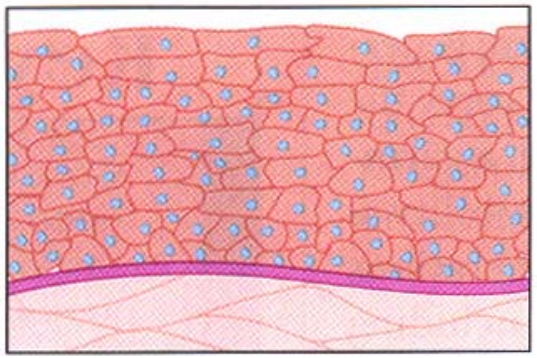


Fig. 19.8, 19.9

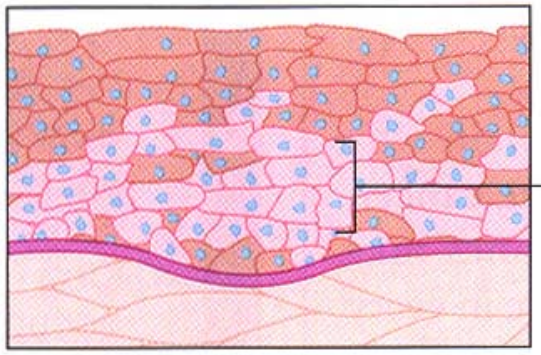




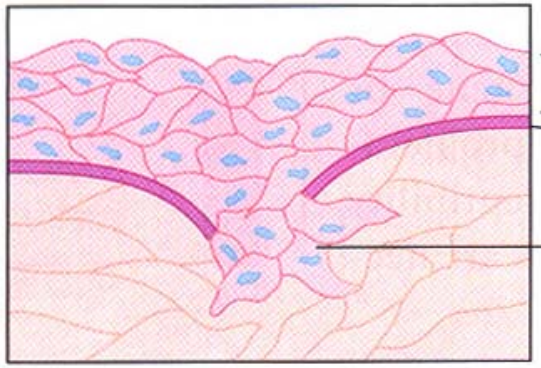
Basal cells proliferate
(1 year after smoking starts)



Cilia and columnar cells destroyed.
Squamous or "flattened" cells
(5 years after smoking starts)



Cancer cells with atypical nuclei
(8 years after smoking starts)



Cancer cells with atypical nuclei
Basement membrane

Early cancerous invasion
(20–22 years after smoking starts; first symptoms)

Lung cancer takes many years to develop and spread

Some cancers run in families

Individuals who inherit one copy of the *RB*⁻ allele are prone to cancer of the retina

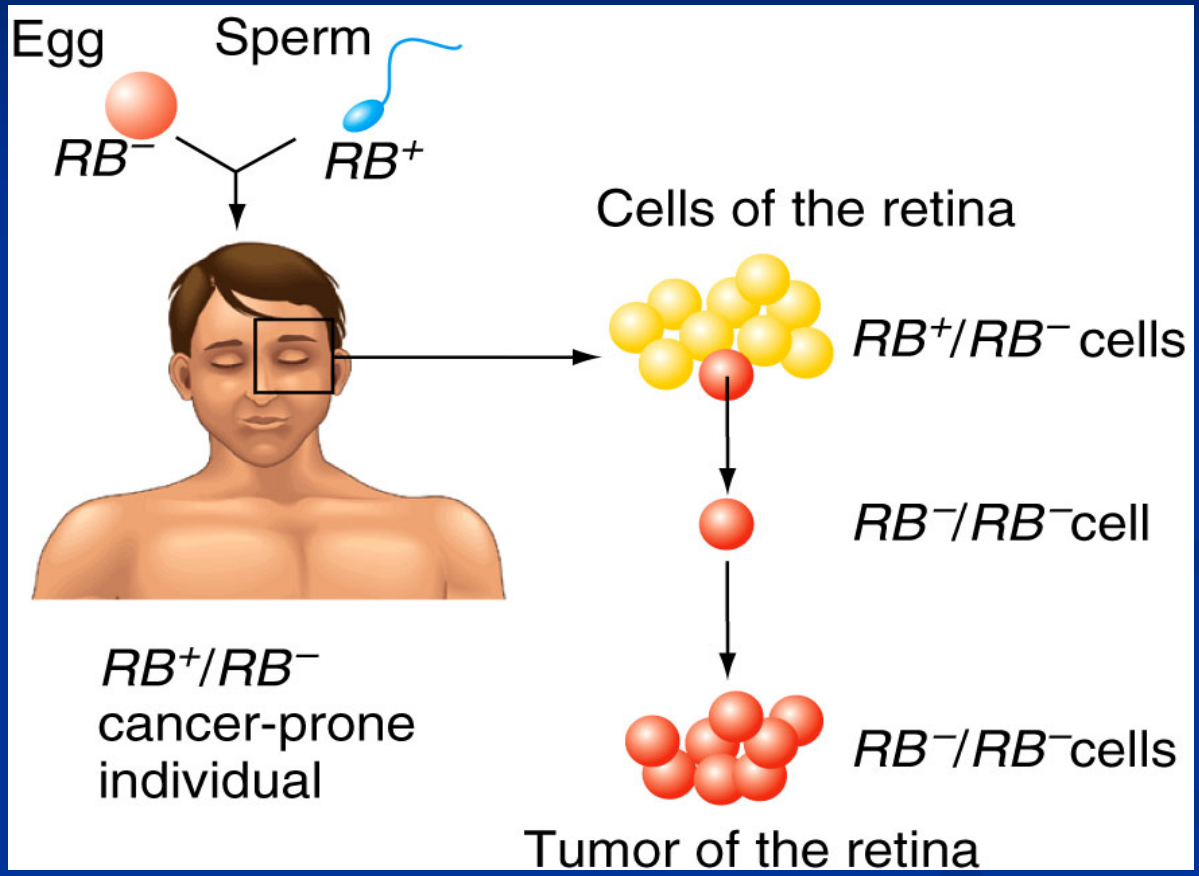


Fig. 19.23

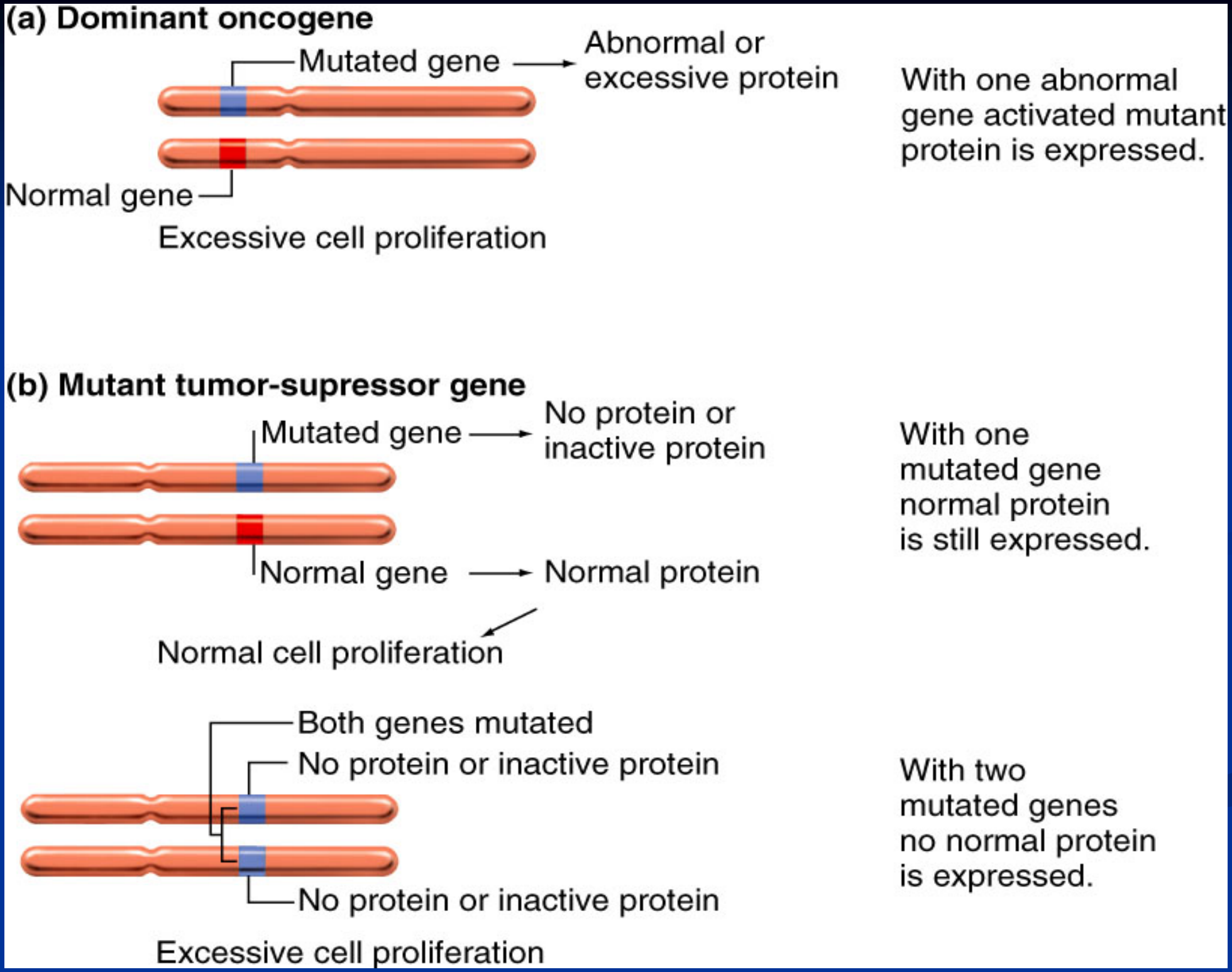
Cancer vs genetic diseases

Cancer is caused by mutations in genes that normally regulate cell growth and division.

- **Cancer differs in two ways from genetic diseases caused by the inheritance of one or two copies of a single defective gene.**
  1. **Most mutations that lead to cancer occur in the somatic cells of one tissue.**
  2. **Multiple mutations in an array of genes must accumulate over time in a clonal descendents of a single cell before the cancer phenotype appears.**

19.4 How mutations cause cancer phenotypes

- **Oncogene**: Mutant allele of a normal gene that acts dominantly in cancer formation.
  - **Protooncogene**: The normal gene that becomes oncogene upon mutation.
- **Mutant tumor-suppressor gene**: Mutant allele of a normal gene that acts recessively in cancer formation.
  - **Tumor-suppressor gene**: The normal gene of mutant tumor-suppressor gene.


(a) Dominant oncogene
Mutated gene
Abnormal or excessive protein
Normal gene
Excessive cell proliferation
With one abnormal gene activated mutant protein is expressed.
(b) Mutant tumor-supressor gene
Mutated gene
No protein or inactive protein
Normal gene
Normal protein
Normal cell proliferation
With one mutated gene normal protein is still expressed.
Both genes mutated
No protein or inactive protein
No protein or inactive protein
Excessive cell proliferation
With two mutated genes no normal protein is expressed.

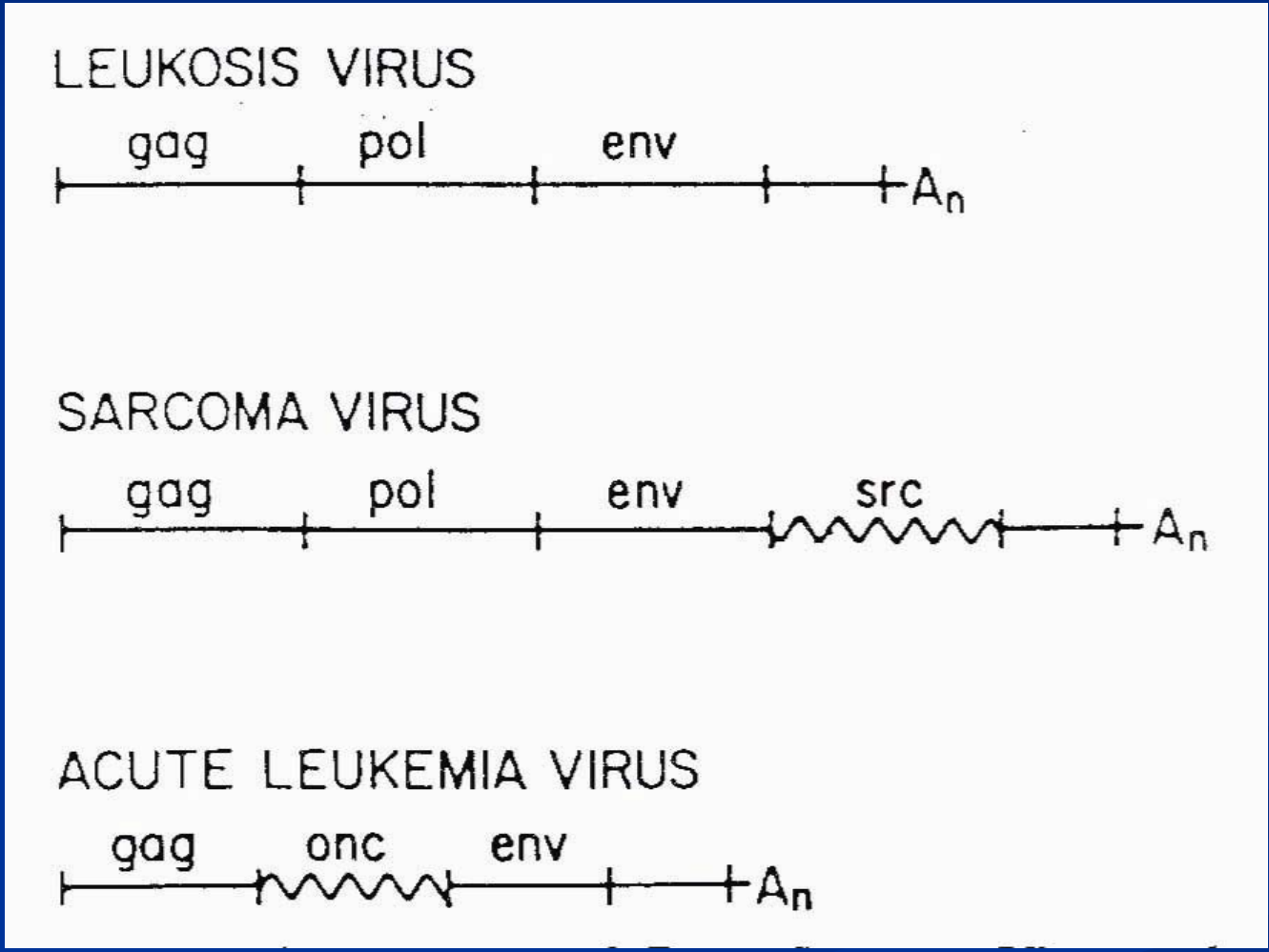
Oncogenes	Cancer Location/Type	Mechanism
myc	Blood, breast, lung, brain, stomach	Alters transcription factor
PDGF	Brain	Alters growth factors or growth factor receptors
RET	Thyroid	Alters growth factors or growth factor receptors
erb-B	Brain, breast	Alters growth factors or growth factor receptors
Her-2/neu	Breast, ovary, salivary glands	Alters growth factors or growth factor receptors
ras	Blood, lung, colon, ovary, pancreas	Affects signal transduction
bcl-2	Blood	Releases brake on apoptosis
PRAD1	Breast, head, and neck	Disrupts cell cycle protein (cyclin)
abl	White blood cells	Translocation alters proto-oncogene and stimulates cell division

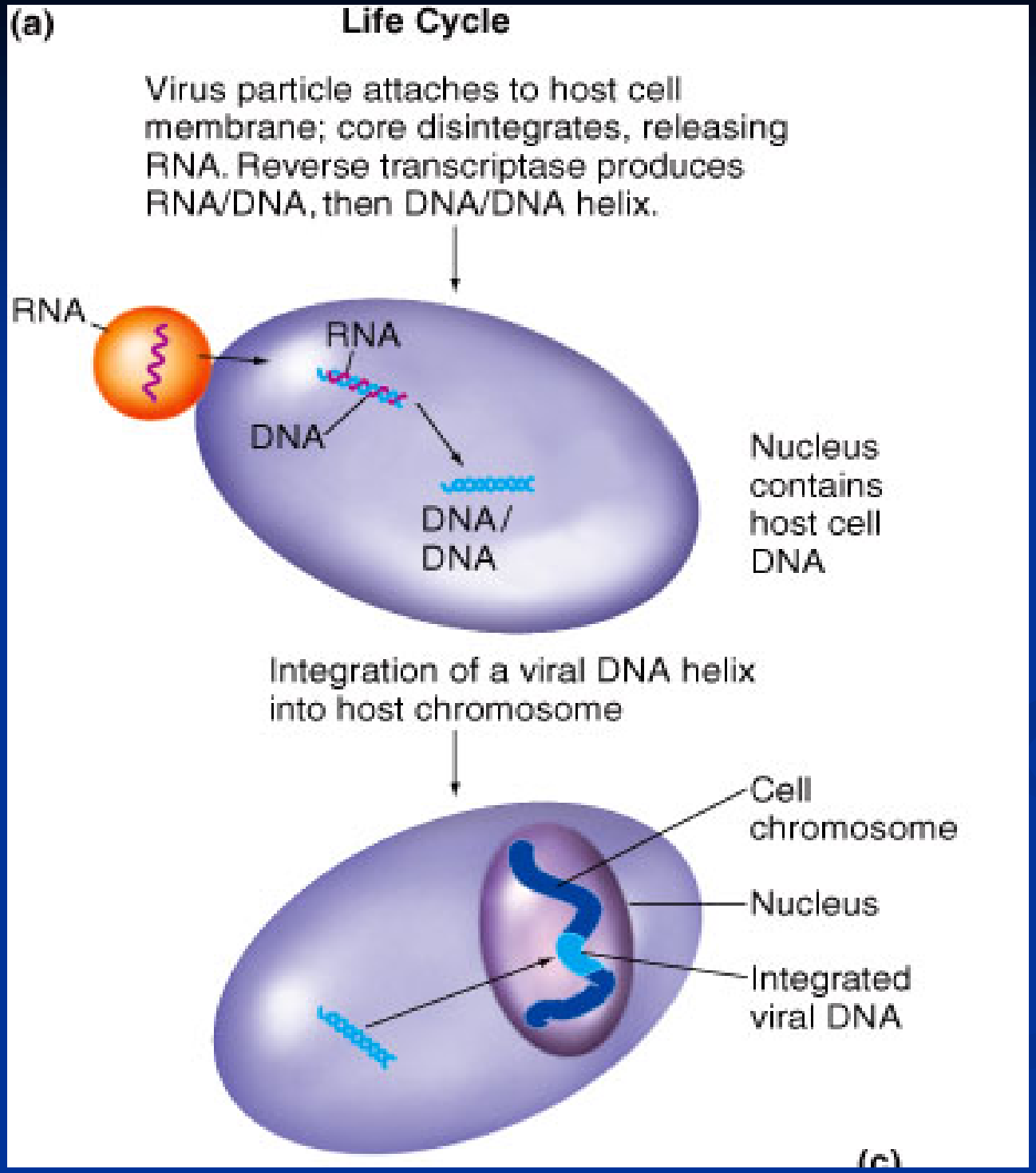
Tumor Suppressors

MTS1	Many sites	Releases brake on cell cycle
RB	Eye, bone, breast, lung, bladder	Releases brake on cell cycle
WT1	Kidney	Releases brake on cell cycle
p53	Many sites	Disrupts p53 protein, which normally determines whether DNA is repaired or cell dies
DPC4	Pancreas	Affects signal transduction
NF1	Peripheral nerves	Disrupts inhibition of normal *ras*, which stimulates cell division
APC	Colon, stomach	Makes nearby DNA more susceptible to replication errors
BRCA1, BRCA2	Breast, ovary, prostate	Faulty repair of double-stranded DNA breaks
hMSH2, hMLH1, hPMS1, hPMS2	Colon, uterus, ovary	Disrupts DNA mismatch repair
Lkb1	Peutz-Jeghers syndrome (many sites)	After birth, fails to block expression of vascular endothelial growth factor, normally active in embryo

Two methods to isolate oncogenes

1. **Analysis of tumor-causing retroviruses**




(a)
Life Cycle
Virus particle attaches to host cell membrane; core disintegrates, releasing RNA. Reverse transcriptase produces RNA/DNA, then DNA/DNA helix.
RNA
RNA
DNA
DNA/
DNA
Nucleus contains host cell DNA
Integration of a viral DNA helix into host chromosome
Cell chromosome
Nucleus
Integrated viral DNA
(c)

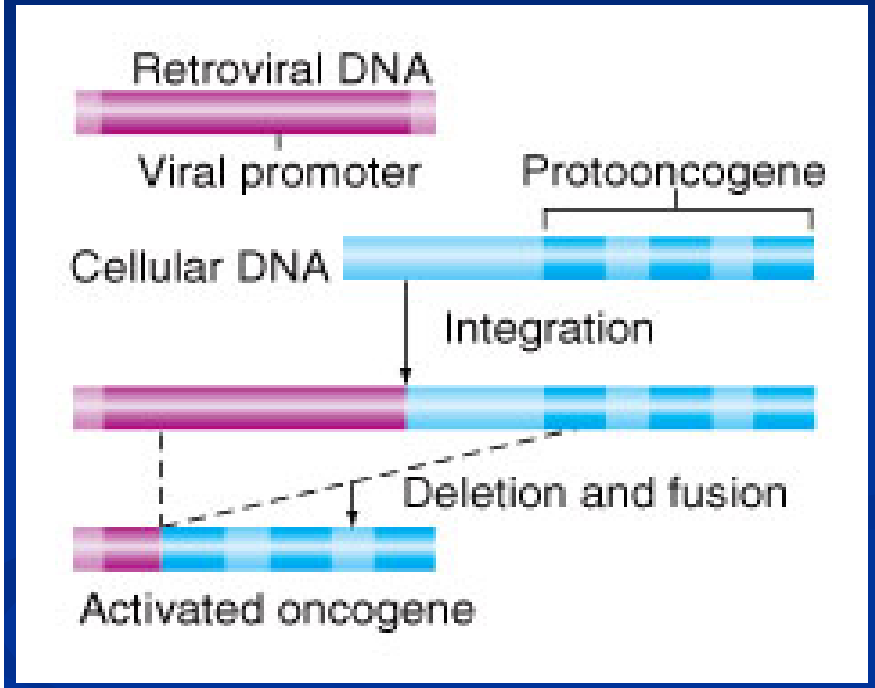
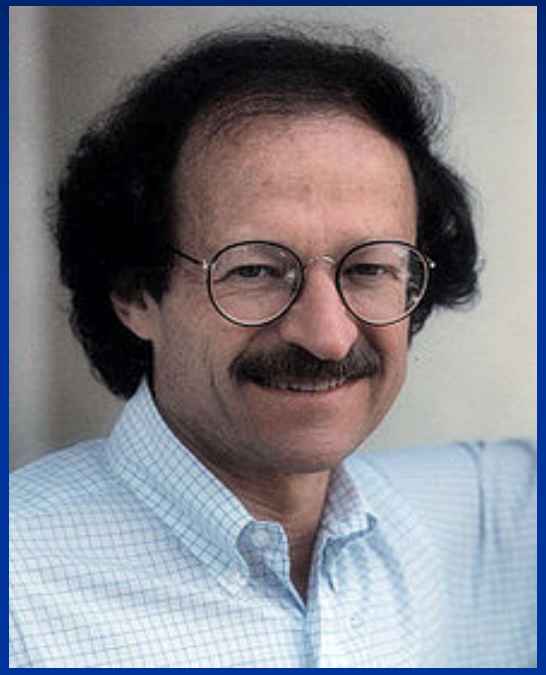
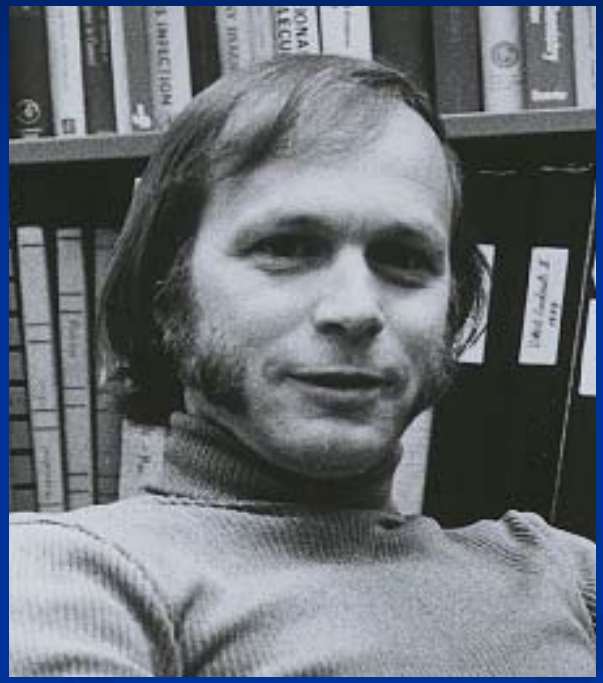

Retroviral DNA
Viral promoter
Protooncogene
Cellular DNA
Integration
Deletion and fusion
Activated oncogene

Fig. 19.20a

The 1989 Nobel Prize in Physiology or Medicine



Harold E. Varmus
UCSF



J. Michael Bishop
UCSF

For their discovery of the cellular origin of retroviral oncogenes.

TABLE 19.3 Retroviruses and Their Associated Oncogenes*

Virus	Species	Tumor	Oncogene
Rous sarcoma	Chicken	Sarcoma	*src*
Harvey murine sarcoma	Rat	Sarcoma and erthyroleukemia	*H-ras*
Kristen murine sarcoma	Rat	Sarcoma and erthyroleukemia	*K-ras*
Moloney murine sarcoma	Mouse	Sarcoma	*mos*
FBJ murine osteosarcoma	Mouse	Chondrosarcoma	*fos*
Simian sarcoma	Monkey	Sarcoma	*sis*
Feline sarcoma	Cat	Sarcoma	*sis*
Avian sarcoma	Chicken	Fibrosarcoma	*jun*
Avian myelocytomatosis	Chicken	Carcinoma, sarcoma, and myleocytoma	*myc*
Ableson leukemia	Mouse	B cell lymphoma	*abl*

*Retroviruses identified as causative agents of tumors in animals contain oncogenes that were derived from a cellular gene. Adapted from Lewin, *Genetics*, 1e, Oxford University Press, Inc. by permission.

2. **Exposure of noncancerous cells to tumor DNA in culture.**
   - **Use human tumor DNA to transform normal mouse cells.**
   - **Isolate human DNA from transformants.**

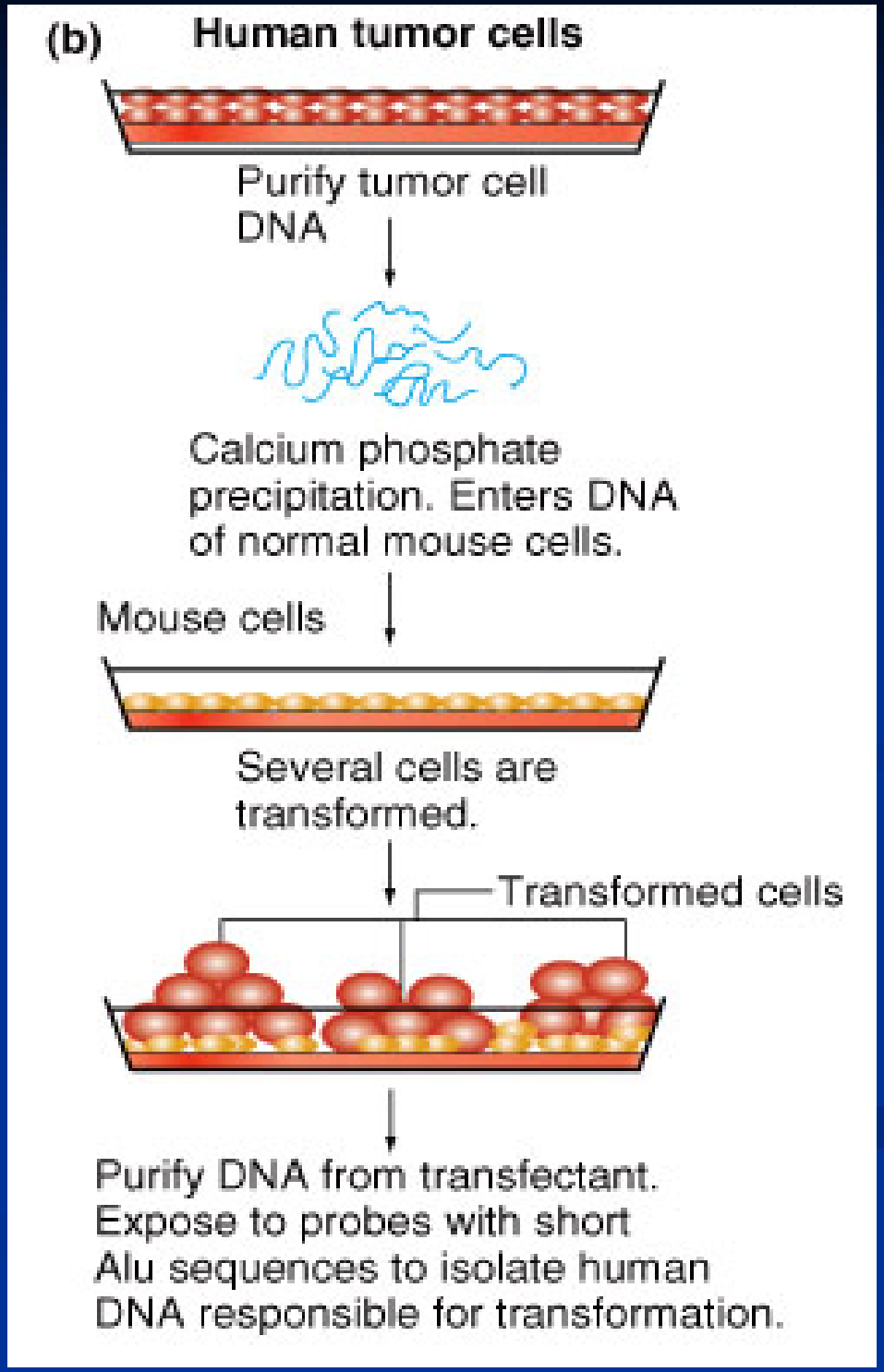


Fig. 19.21

Tumor-suppressor gene mutations release a brake on cell division and decrease accuracy of cell reproduction

TABLE 19.5 Mutant Alleles of These Tumor-Suppressor Genes Decrease the Accuracy of Cell Reproduction*

Gene	Normal Function of Gene (if known), or Disease Syndrome Resulting from Mutation	Function of Normal Protein Product
p53	Controls G_1-to-S checkpoint	Transcription factor
RB	Controls G_1-to-S transition	Inhibits a transcription factor
ATM	Controls G_1-to-S phase, and G_2-to-M checkpoint	DNA-dependent protein kinase
BS	Recombinational repair of DNA damage	DNA/RNA ligase
XP	Excision of DNA damage	Several enzymes
hMSH2, hmLH1	Correction of base-pair matches	Several enzymes
FA	Fanconi anemia	Unknown
BRCA1	Repair of DNA breaks	Unknown
BRCA2	Repair of DNA breaks	Unknown

*Many tumor-suppressor genes have been associated with a specific function in the cell cycle necessary for accuracy of cell division.

Several cancers caused by mutant tumor-suppressor genes are inherited in a dominant fashion

- ~ 75% of RB^+/RB^- individuals develop retinoblastoma.
- ~ 66% of $BRCA^+/BRCA^-$ women develop breast cancer at the age of 55.

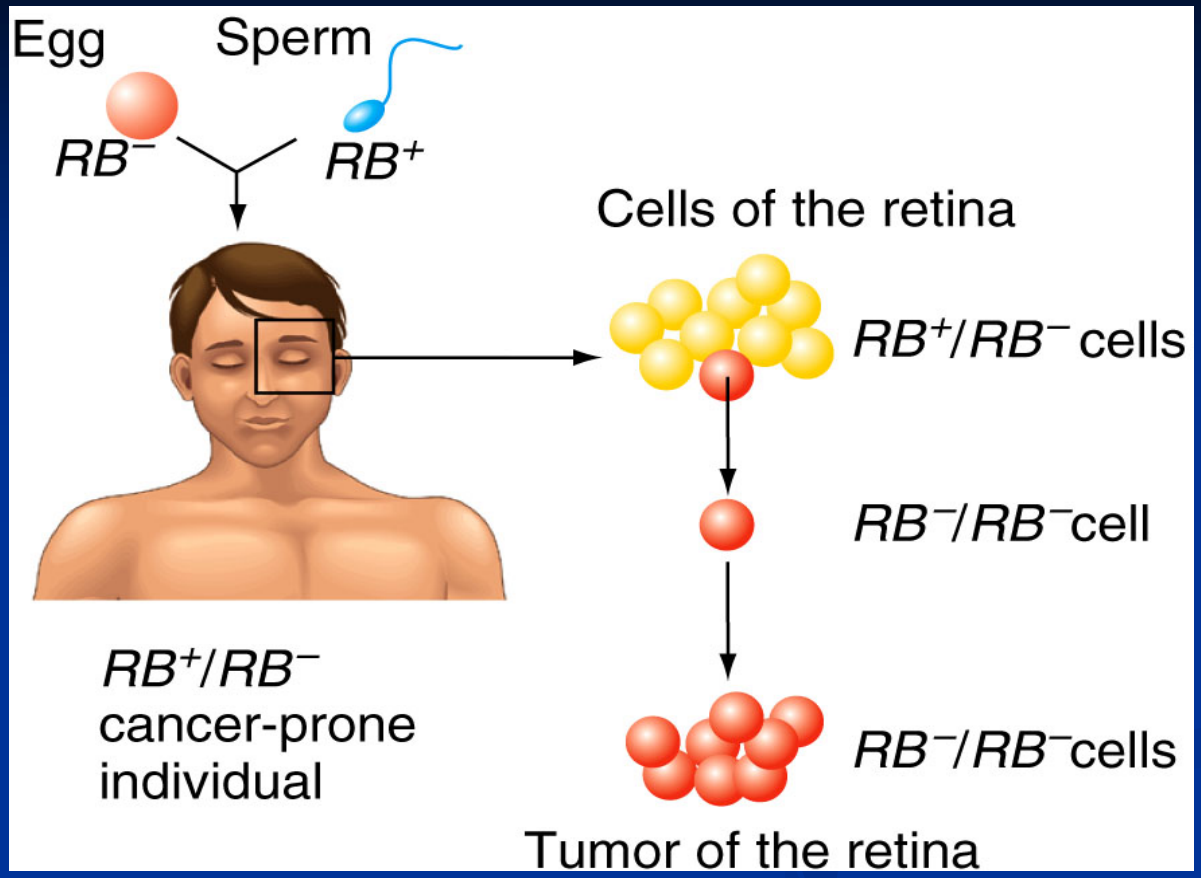


Fig. 19.23, 19.24

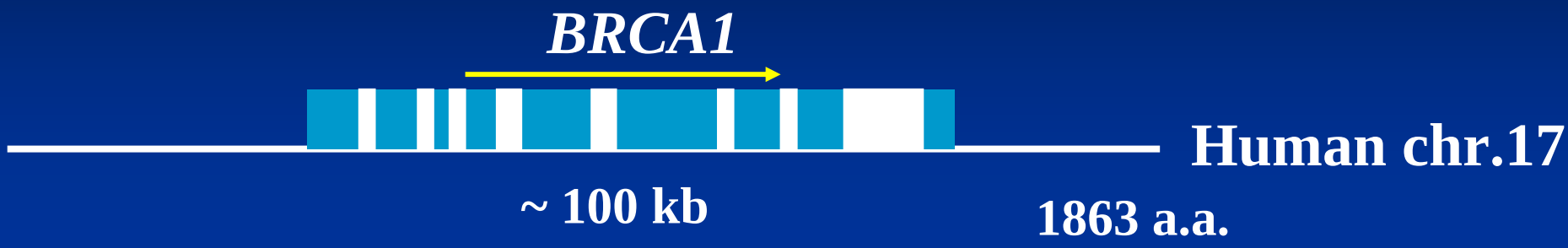
Summary on cancer development

- Several mutations in different genes are required for cancer formation.
  - Mutations in DNA synthesis and DNA damage repair.
  - Mutations that prevent apoptosis.
  - Mutations that help to stimulate blood vessel formation.
- Dominant mutations in **protooncogenes** may overactivate expression of proteins that promote cell proliferation.
- Recessive mutations in **tumor-suppressor genes** may release the brakes that keep cells from proliferating.

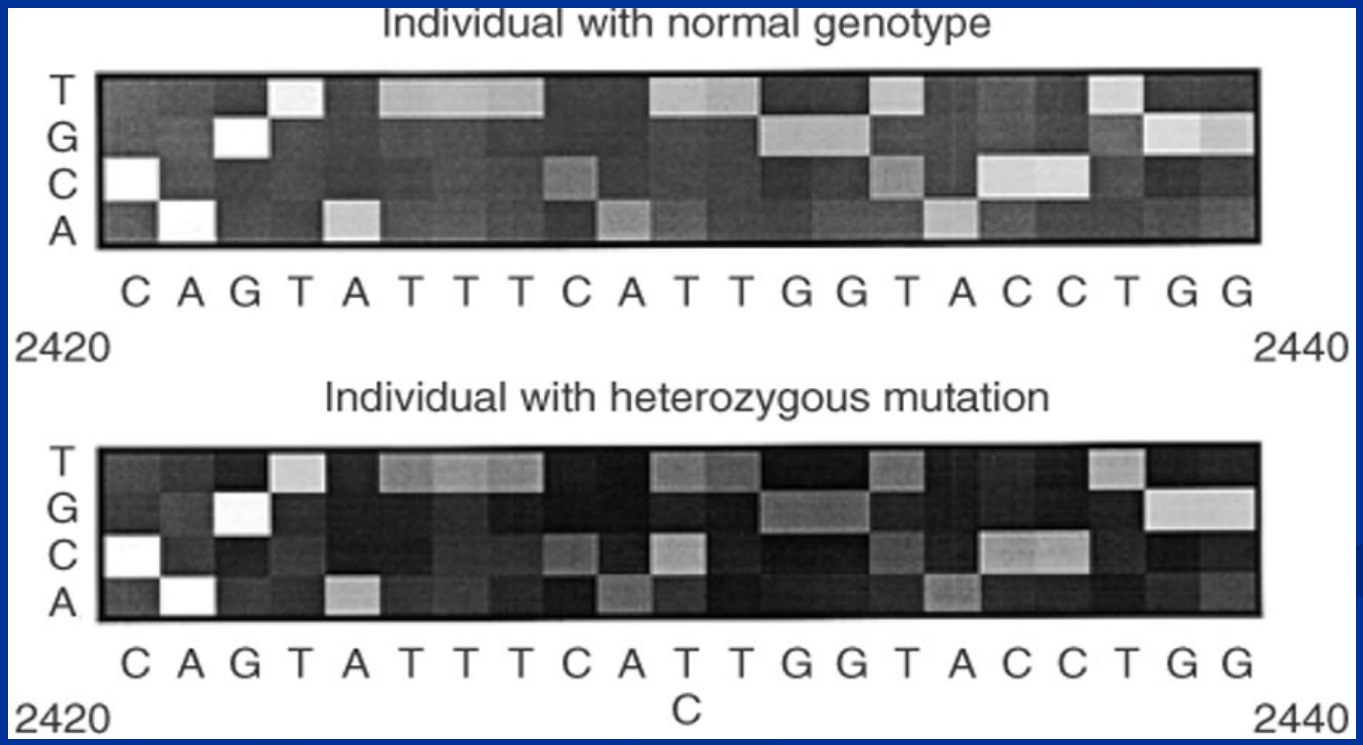
19.5 Personalized cancer treatment

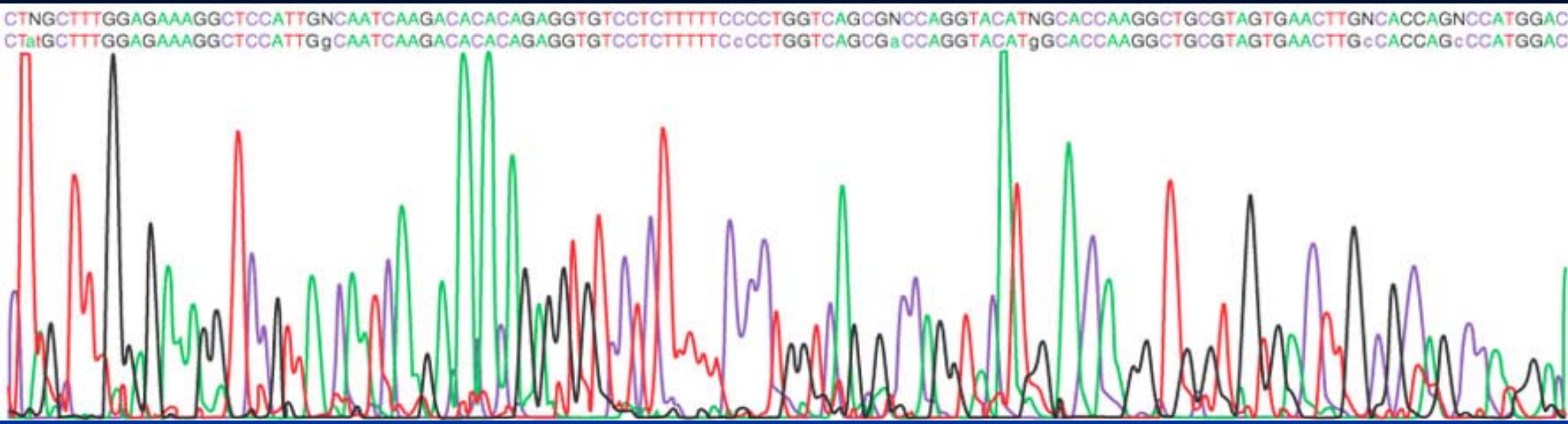
- Cancers affecting the same tissue may have different origins and effects. Cancers in different patients often have unique properties.
  - Mutations in a variety of different genes that regulate cell division can help produce cancer.
- Early diagnosis is the key.
- Surgery to remove cancer and chemotherapy to kill cancer cells.

Detection of cancer-causing *BRCA1* mutations with DNA microarrays or DNA sequencing



- 5500 bp *BRCA1* coding region requires 22000 ASOs.
- Each column contains an ASO differing only at the nucleotide position under analysis.



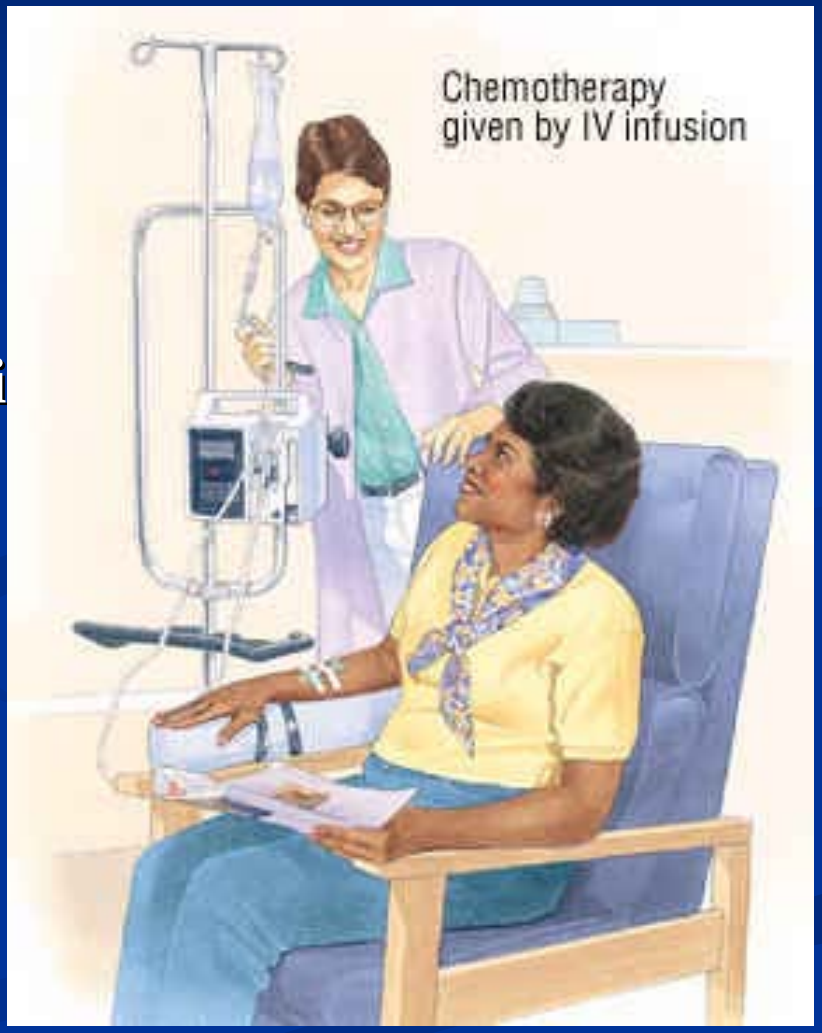


- **Prices for diagnosis of cancer-causing *BRCA1* and *BRCA2* mutations are high.**
  - **Protected by patents from Myriad Genetics.**

Proactive treatment against cancer

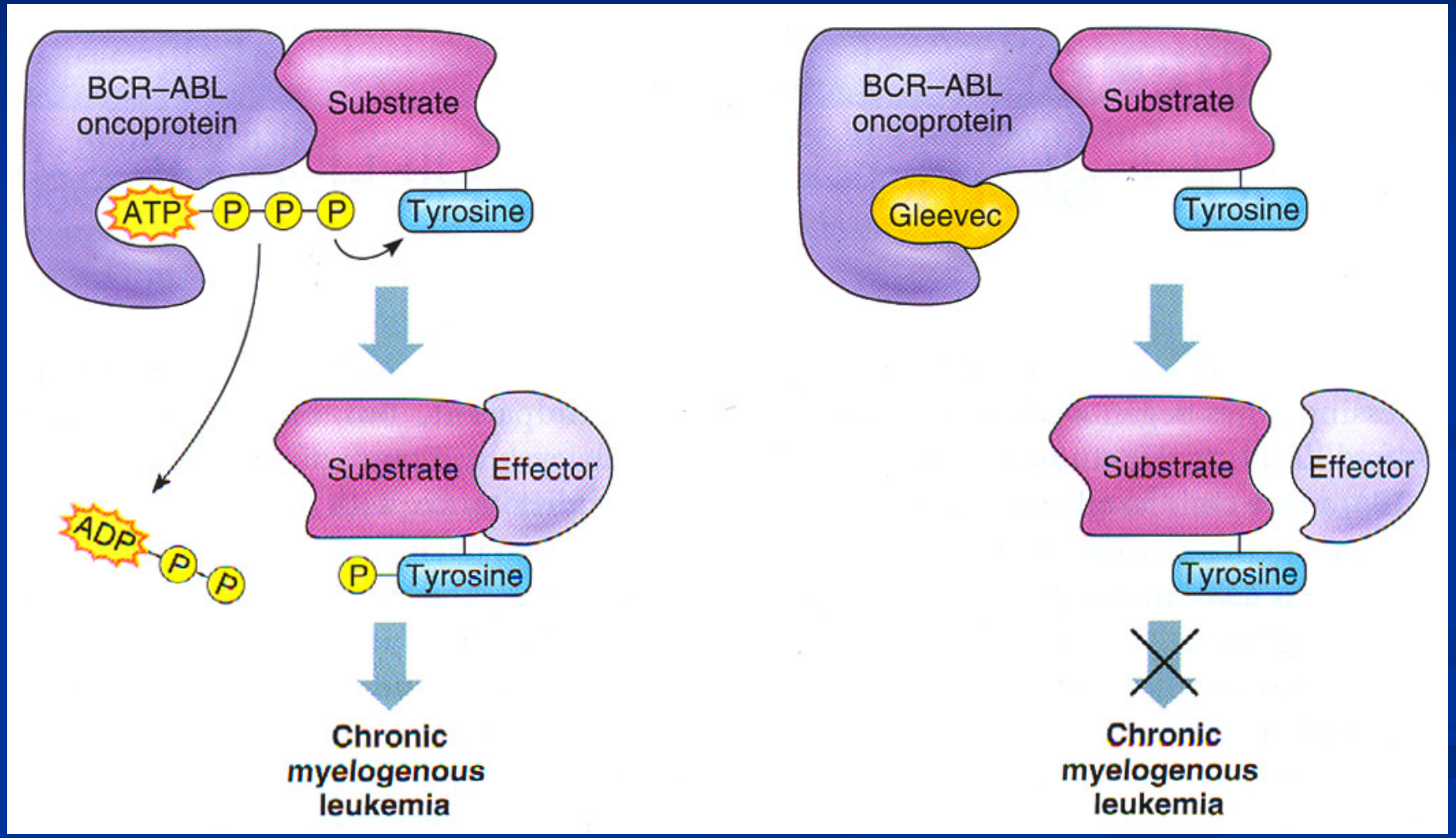
1. Surgery to remove cancer and chemotherapy to kill cancer cells.

- Angelina Jolie underwent breast tissue-removing surgery to prevent breast cancer in 2013.
  - Her mother died of cancer at 56.
  - She carried cancer-causing mutations i *BRCA1*.



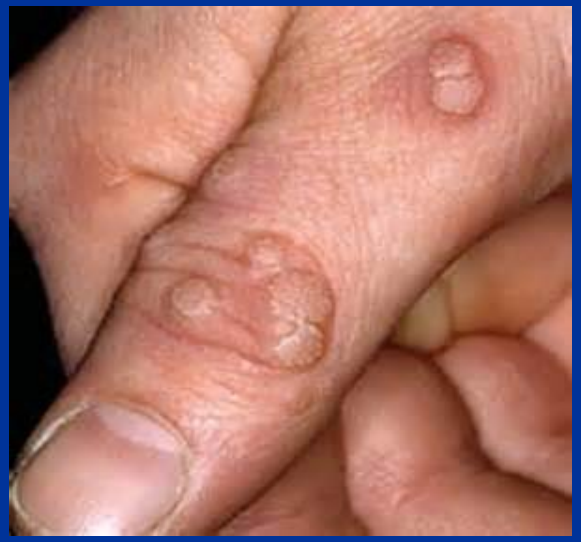
Gleevec treats chronic myelogenous leukemia.

(格列卫，瑞士诺华Novartis制药公司)



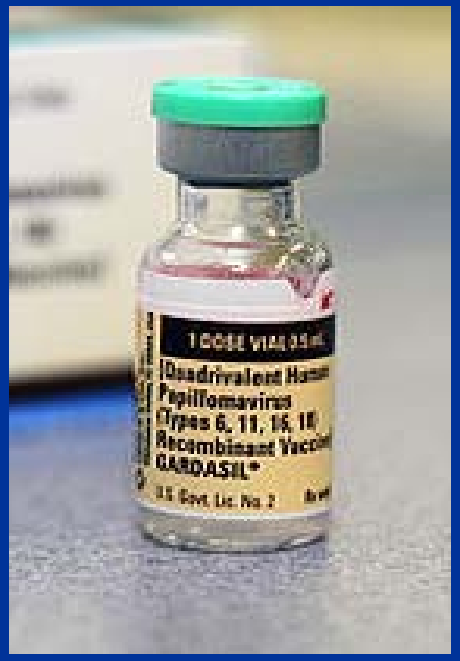
2. Vaccination against cancer caused by viral infection

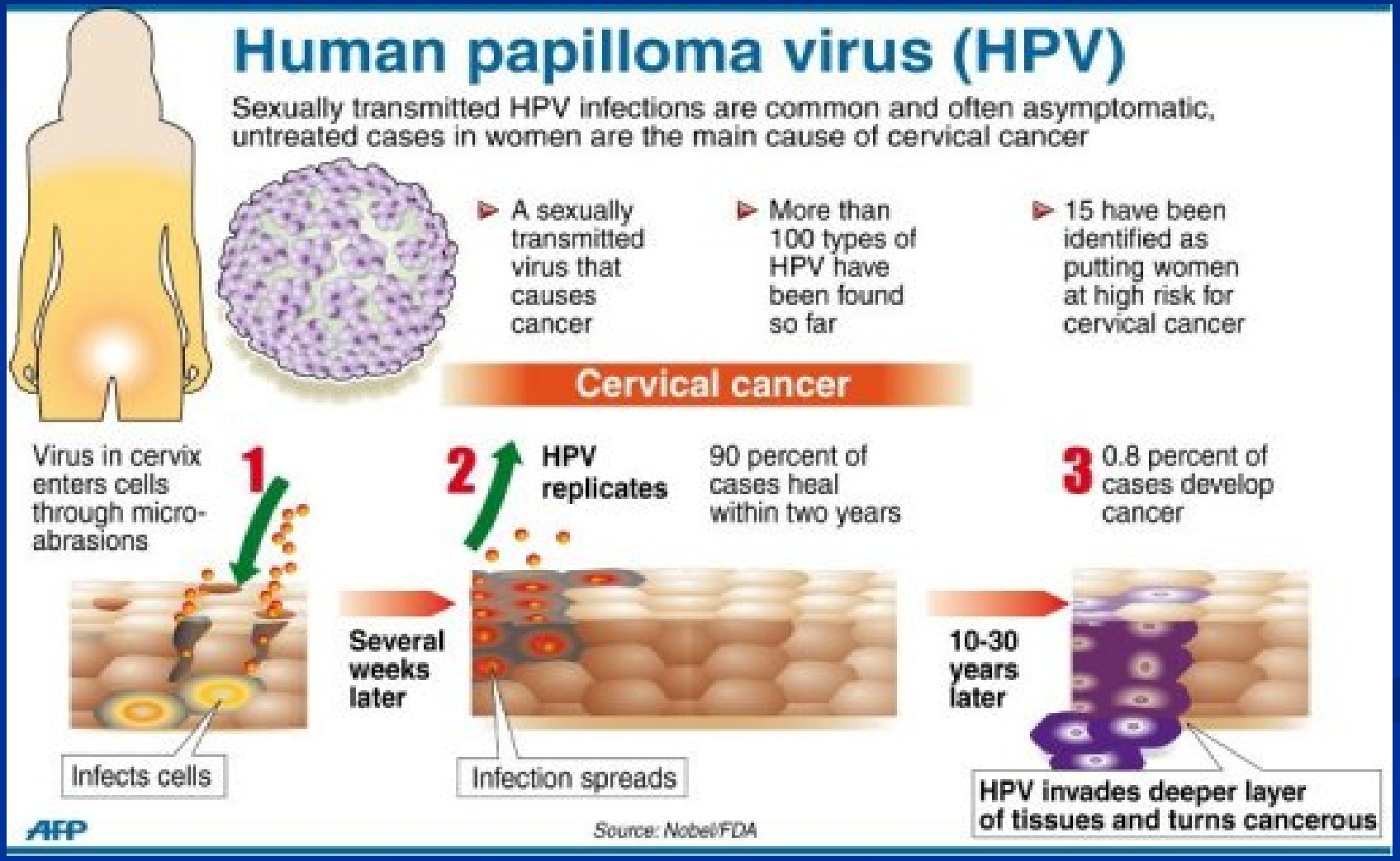
Human papillomavirus (HPV, 人乳头瘤病毒)



Disease	HPV type
Common warts	2, 7, 22
Plantar warts	1, 2, 4, 63
Flat warts	3, 10, 8
Anogenital warts	6, 11, 42, 44 and others[13]
Anal dysplasia (lesions)	6, 16, 18, 31, 53, 58[14]
Genital cancers	• Highest risk:[13] 16, 18, 31, 45 • Other high-risk:[13][15] 33, 35, 39, 51, 52, 56, 58, 59 • Probably high-risk:[15] 26, 53, 66, 68, 73, 82
Epidermodysplasia verruciformis	more than 15 types
Focal epithelial hyperplasia (oral)	13, 32
Oral papillomas	6, 7, 11, 16, 32
Oropharyngeal cancer	16
Verrucous cyst	60
Laryngeal papillomatosis	6, 11

- **Gardasil, a subunit vaccine against human papillomavirus (HPV) that cause ~70% of cervical cancers. Developed by Merck and was approved by FDA in 2005.**





3. Oncolytic virotherapy (病毒溶瘤疗法)

Oncolytic viruses (溶瘤病毒): Viruses that can kill cancer.

- **Natural viruses that can infect and kill tumor cells.**
  - **Rabies virus (狂犬病毒), parvovirus (细小病毒).**

- **Engineered viruses that can specifically kill tumor cells.**
  - **1991, Herpes simplex virus-1 (HSV-1, I型单纯疱疹病毒) killed human glioma.**
  - **Adenovirus (腺病毒)**
  - **Newcastle disease virus (NDV, 新城疫病毒), reovirus (呼肠孤病毒), influenza A virus (甲型流感病毒) and measles virus (麻疹病毒).**

Martuza RL *et al*. (1991) Experimental therapy of human glioma by means of a genetically engineered virus mutant. *Science* 252: 854–856