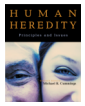
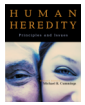
Chapter 12
Genes and Cancer



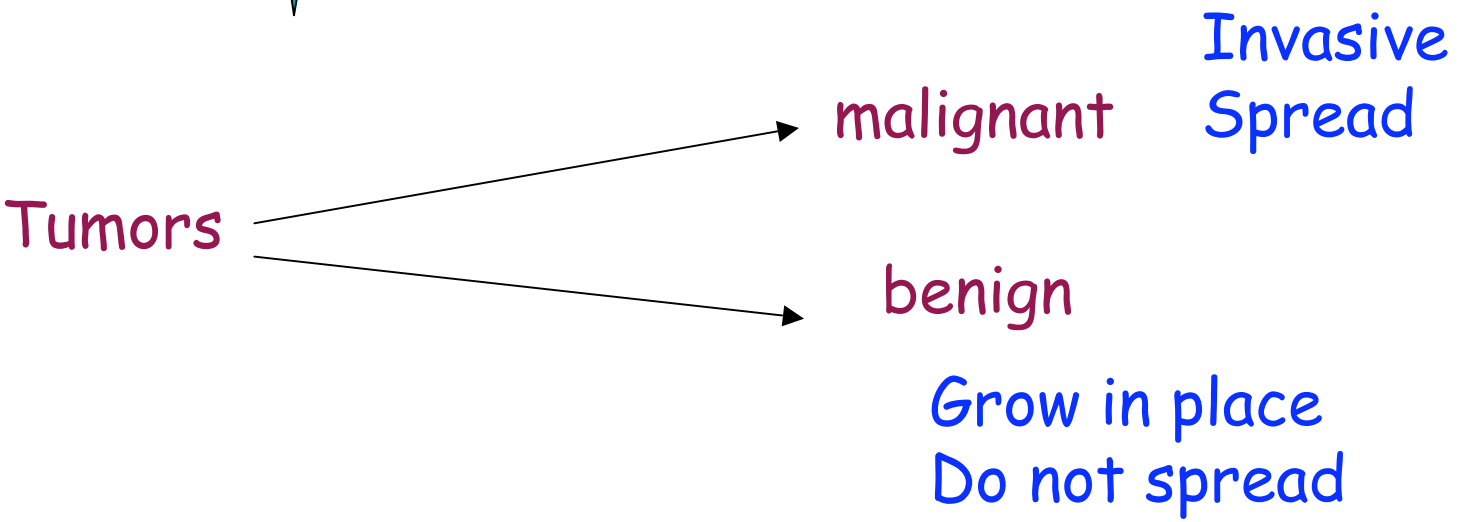
Cancer

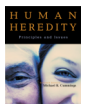
- Produced by the environment and the genotype
- Can affect many different cells and tissues in the body
- Results from unregulated cell proliferation
- May be able to metastasize or spread to other sites



Properties of cancer cells:

- Uncontrolled proliferation
- Ability to metastasize
- Are clonal





Copyright © The McGraw-Hill Companies, Inc. Permission required for reproduction or display.

Table 18.2

Characteristics of Cancer Cells

Oilier, less adherent

Loss of cell cycle control

Heritable

Transplantable

Dedifferentiated

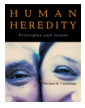
Lack contact inhibition

Induce local blood vessel formation (angiogenesis)

Invasive

Increased mutation rate

Can spread (metastasize)



n Learning

Metastasis of Cancer Cells

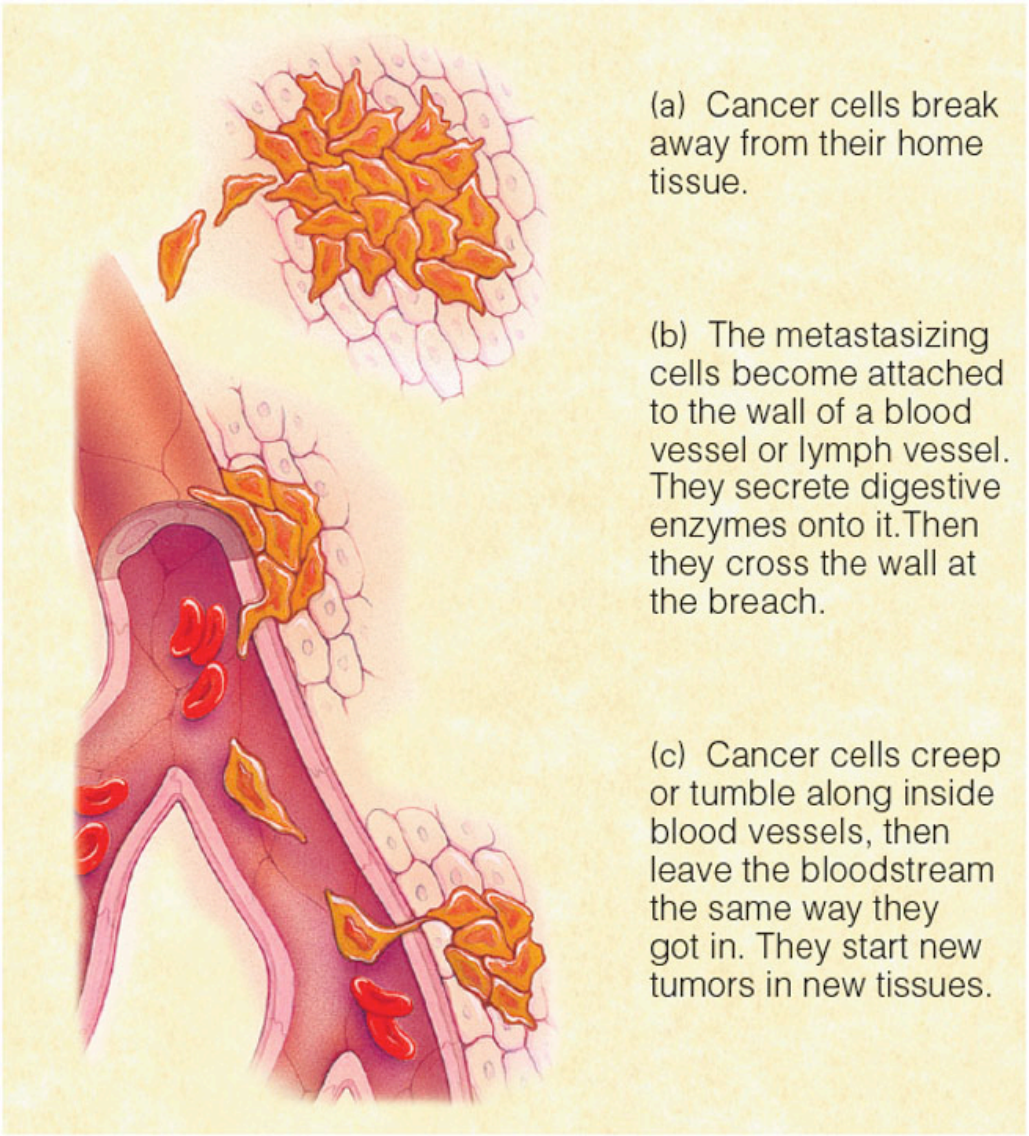
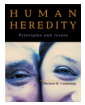


Fig. 12.2



Unregulated Cell Cycle

- Cancer cells show uncontrolled cell division
- They have abnormal shapes
- Bypass checkpoints in the cell cycle

Fig. 12.4

The Cell Cycle

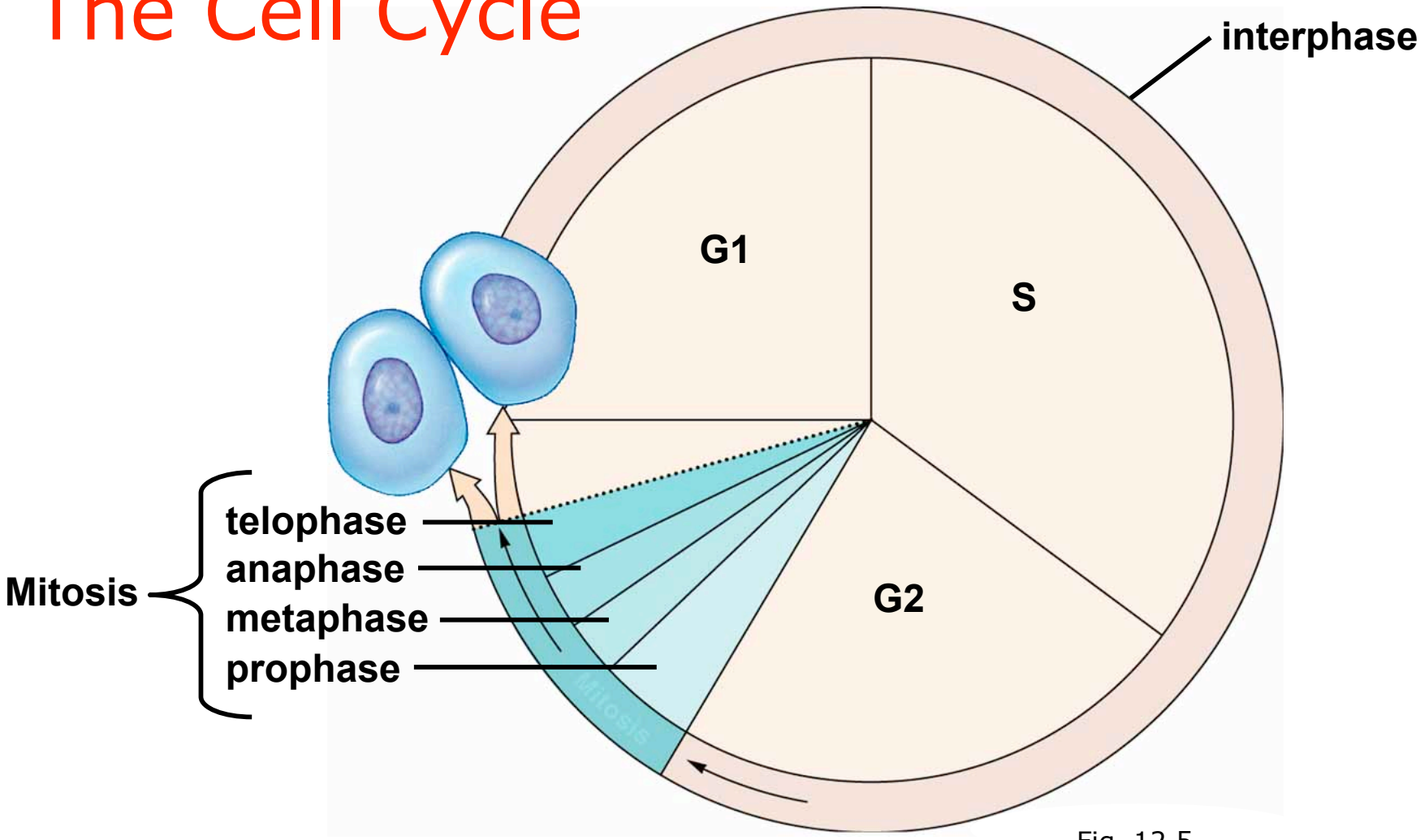
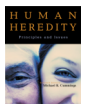


Fig. 12.5

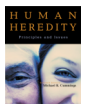
Checkpoint Genes

- Tumor suppressor genes
  - Suppress cell division
  - Act at either G1/S or G2/M control points
- Proto-oncogenes
  - Promote cell division if mutant
- Oncogenes
  - Mutant forms of proto-oncogenes induce or continue uncontrolled cell division

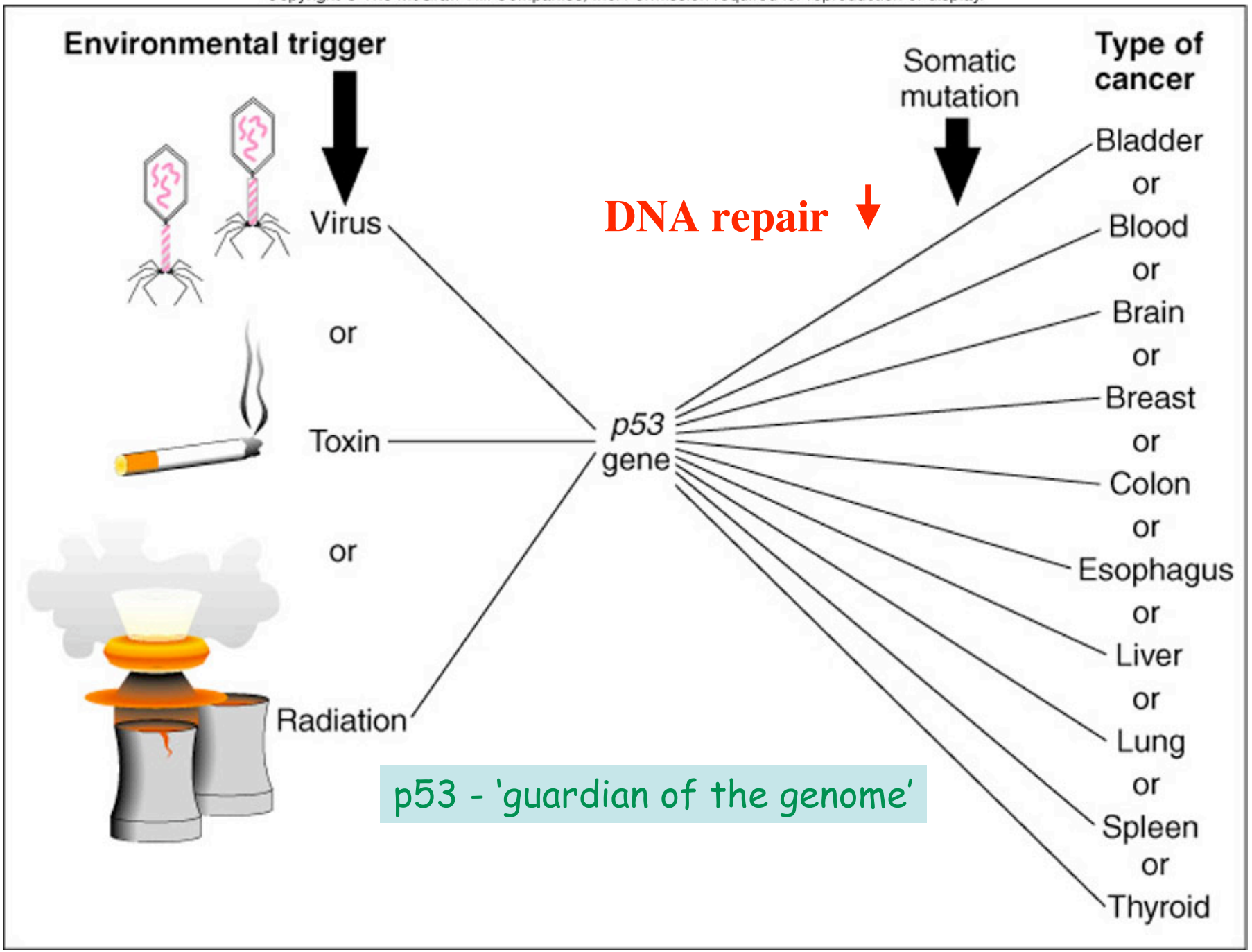


Cancer Is Most Often a Sporadic Event

- Cancer can be an inherited susceptibility or a sporadic event
- Sporadic cases are the **most** common
- In some inherited cancers, individuals carrying the mutant allele causing a predisposition to cancer have a 100,000 fold increased risk



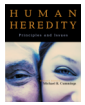
Copyright © The McGraw-Hill Companies, Inc. Permission required for reproduction or display.



Cancer Is a Genetic Disorder

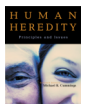
Evidence that cancer has a genetic origin

- >50 forms of cancer have some degree of inherited predisposition
- Most carcinogens are also mutagens
- Some viruses carry mutant genes (oncogenes) that promote and maintain the growth of a tumor
- Specific chromosomal changes are found in some cancers

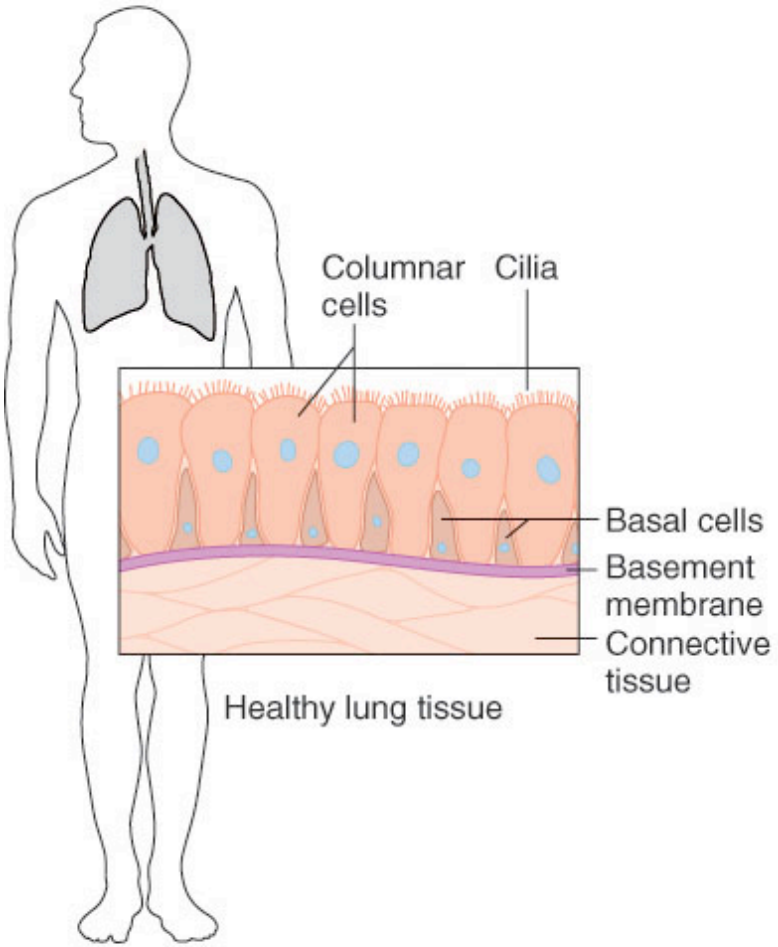


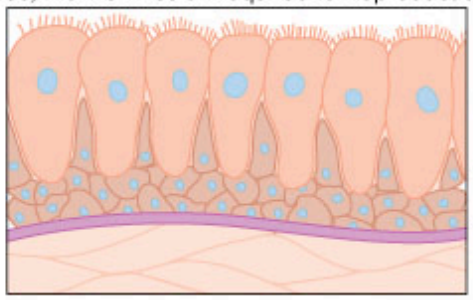
Cancer Begins with a Single Cell

- All cells in the tumor are descended from a single cell - CLONAL
- Most cancers develop after a cell accumulates multiple mutations over a long period of time
- Once formed, cancer cells divide continuously
- Mutations continue to accumulate and the cancer may become more aggressive

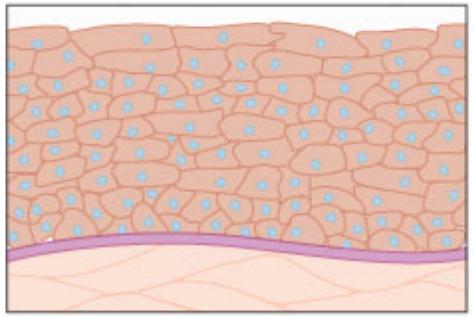


Copyright © The McGraw-Hill Companies, Inc. Permission required for reproduction or display.

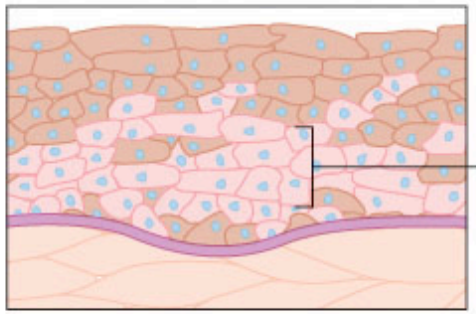




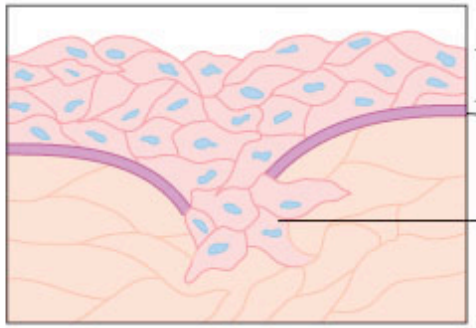
Basal cells proliferate
(1 year after smoking starts)



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



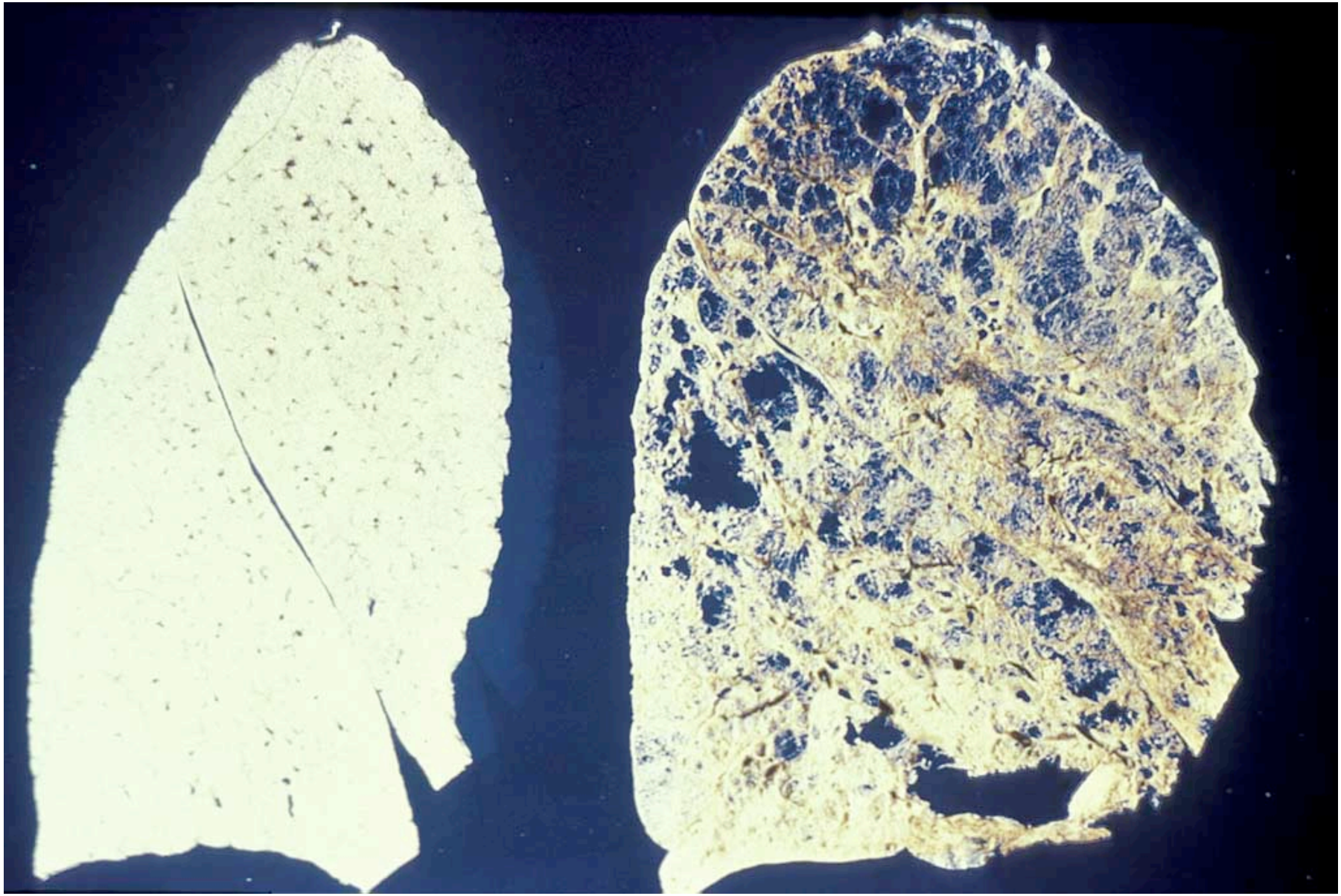
Cancer cells with atypical nuclei
(8 years after smoking starts)



Cancer cells with atypical nuclei
Basement membrane

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

Lung cancer takes a long time to spread



Credit: © O. Auerbach/Visuals Unlimited

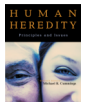
227358

Lung sections of non-smoker, left, and smoker, right.

Inherited Susceptibilities

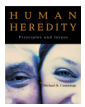
Table 12.1 Heritable Predispositions to Cancer

Disorder	Chromosome	OMIM Number
Early-onset familial breast cancer	17q	113705
Familial adenomatous polyposis	5q	175100
Hereditary nonpolyposis colorectal cancer	2p	120435
Li-Fraumeni syndrome	17p	151623
Multiple endocrine neoplasia type 1	11q	131100
Multiple endocrine neoplasia type 2	10	171400
Neurofibromatous type 1	17q	162200
Neurofibromatous type 2	22q	101000
Retinoblastoma	13	180200
Von Hippel-Lindau disease	3p	193300
Wilms tumor	11p	194070



Cancer Is Caused by Mutations

- May be caused by a single dominant mutation or a number of recessive mutations in a somatic cell
- This causes uncontrolled cell growth
- Age is the leading risk factor for many cancers because cancer causing mutations accumulate over time



Several Independent Mutations May Cause Cancer

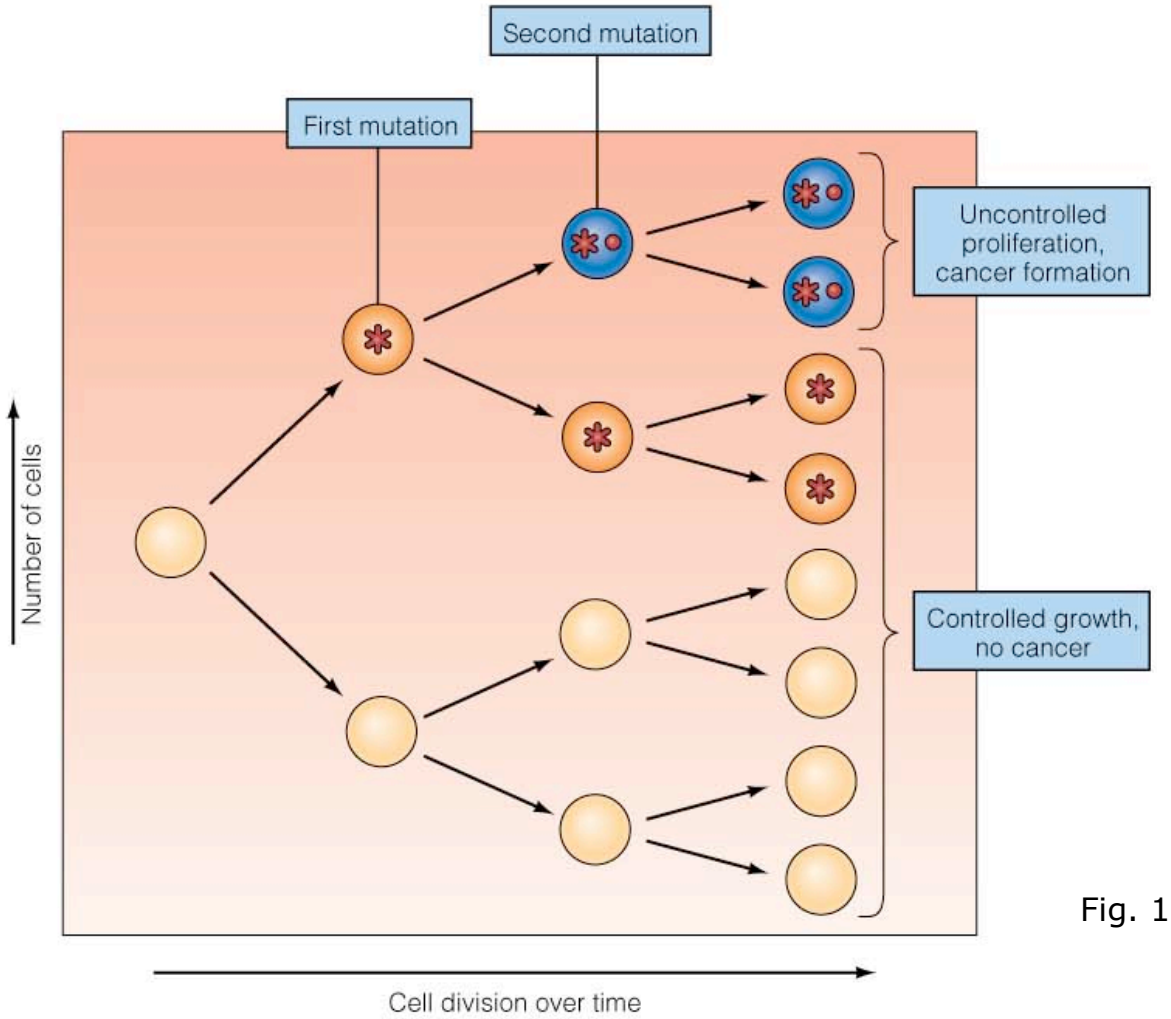
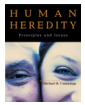


Fig. 12.3

Familial p53: Ly-Fraumeni Syndrome

One p53 mutant allele

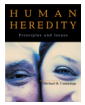
- Cancer Risk
- ~50% by age 30
- ~90% by age 70
- ~ 100% for Breast cancer



Retinoblastoma

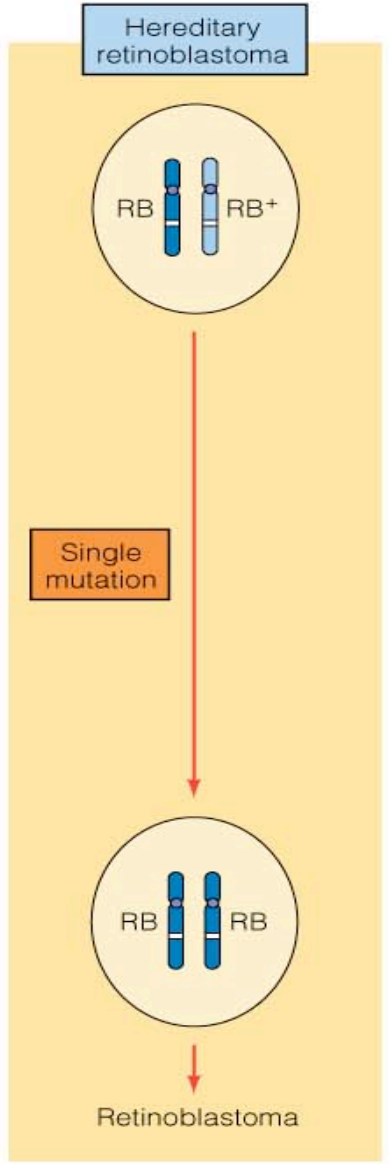
- Cancer of the retina
- Diagnosed between 1–3 years of age
- 40% of all cases are due to an autosomal dominant trait
- 60% are sporadic cases

Fig. 12.6

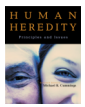


Hereditary Retinoblastoma

- Autosomal dominant
- Individuals with the allele, *RB* have a 90% chance of developing retinoblastoma
- Usually in both eyes
- High risk for other cancers especially osteosarcoma and fibrosarcoma



(a) Fig. 12.7



Sporadic Form of Retinoblastoma

- Mutations occur in both copies of the *RB1* gene at 13q14
- Tumors form generally in only one eye
- No increased risk of other cancers

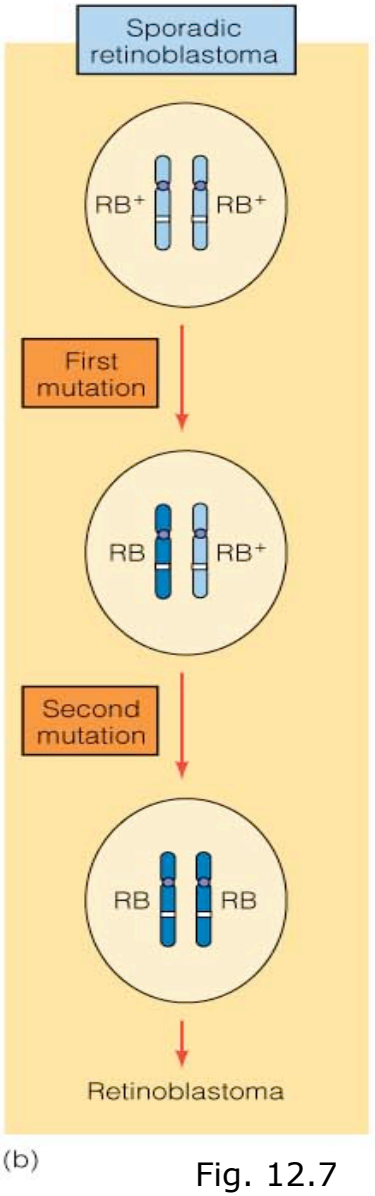
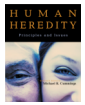


Fig. 12.7

Knudson Two-Step Model

- Disease develops when two mutant copies of *RB1* are present in the cell
- With inherited retinoblastoma, a child inherits one mutant allele and if the normal copy becomes mutated, the child develops retinoblastoma
- In the sporadic form, both copies must become mutated to develop the disease, generally only in one eye and later in childhood



RB1 gene

- Located at 13q14 and encodes for protein pRB
- pRB regulates the cell cycle
  - It is present in most cells
  - Activated pRB prevents the cell from moving from G1 to S
- If both copies of the *RB1* gene are deleted or mutated, the cell divides in an uncontrolled manner

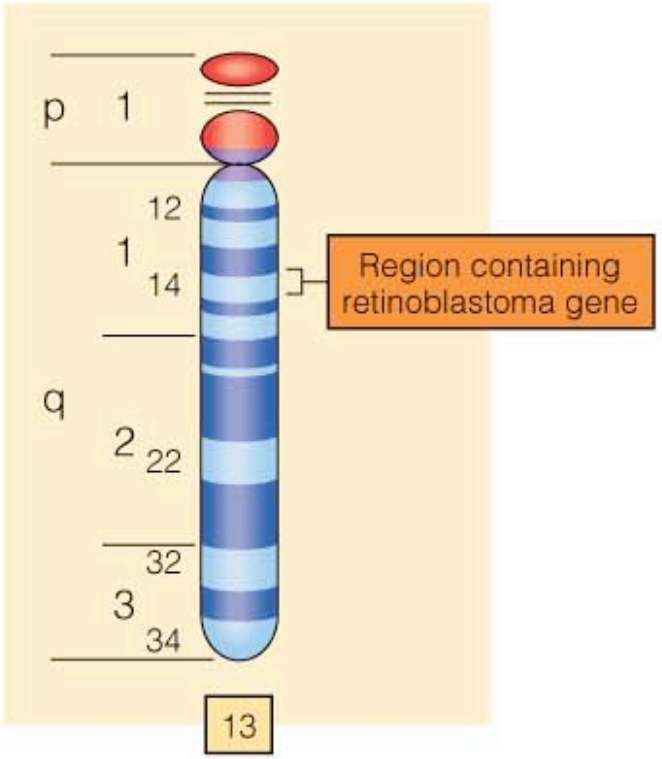


Fig. 12.8

The Cell Cycle

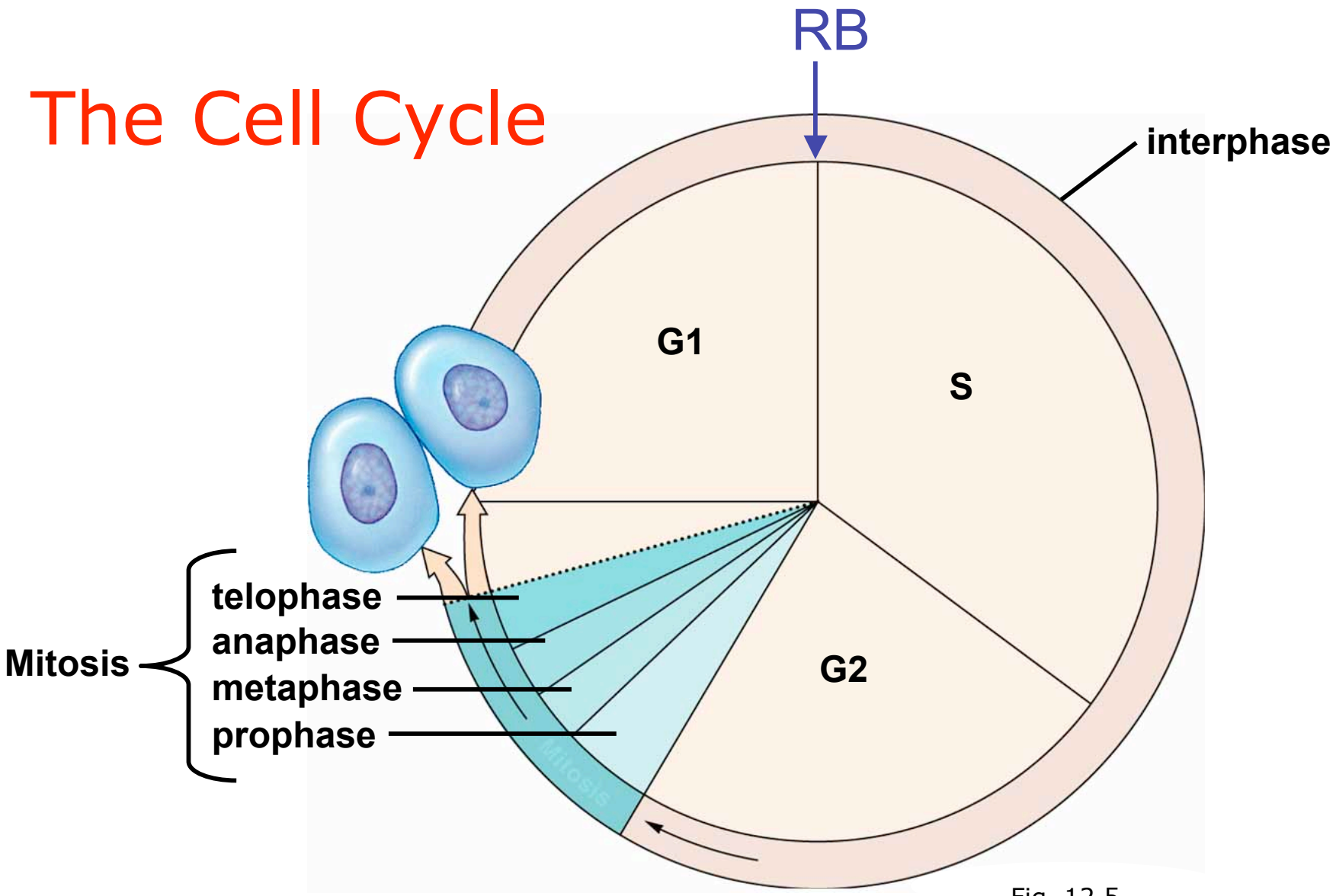
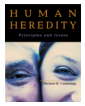
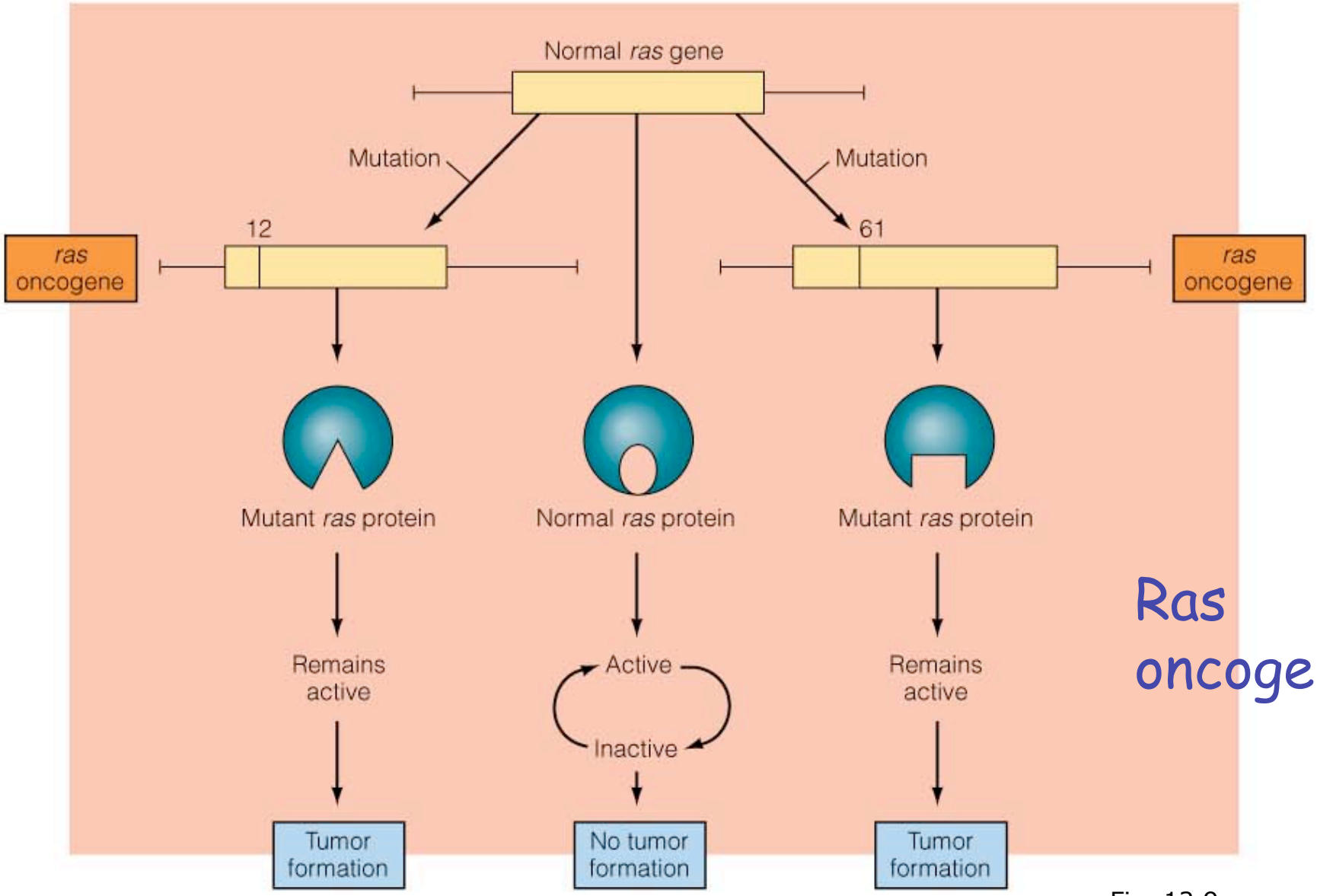


Fig. 12.5

Proto-Oncogenes to Oncogenes

- Proto-oncogenes turn cell division on or off
- Mutant forms permanently switch on cell division and are called oncogenes
- Many different types of mutations have been identified
- Example: *ras* proto-oncogene receives and transfers signal needed for cell division



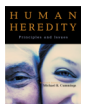


Ras oncogene

Fig. 12.9

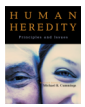
Breast Cancer

- Most common form of cancer in US women, but also occurs in men
- 40,000 deaths/year
- Most cases are sporadic, but approximately 5% are the result of a mutation in the *BRCA1* gene
- About 1/200 women inherit the allele; of these, approximately 90% will develop breast cancer



BRCA1 Gene

- Mary-Claire King's research began in the 1970s
- In 1990, using recombinant DNA technology found linkage with a DNA marker
- Marker is also linked to ovarian cancer
- The autosomal dominant *BRCA1* gene was identified in 1994



BRCA1 and *BRCA2*

- *BRCA1* maps to chromosome 17
- Another autosomal dominant gene, *BRCA2* maps to chromosome 13
- Together *BRCA1* and *BRCA2* account for 10–15% of genetic breast cancers
- Allele frequencies of these genes vary among populations
- Frequency of mutations high in Ashkenazi Jewish population

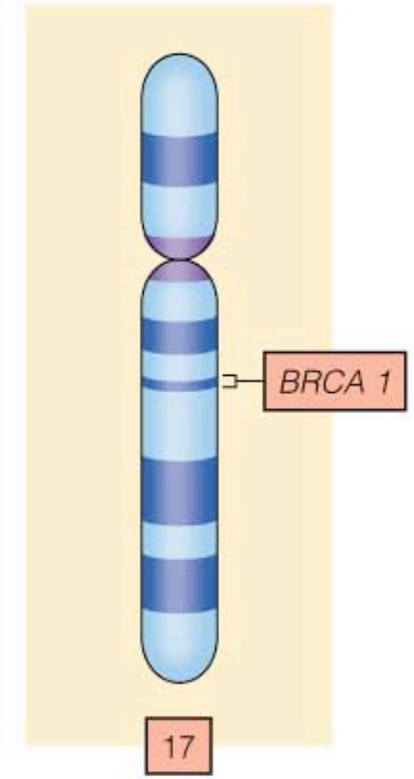
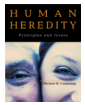


Fig. 12.10

Some (depressing) facts about BRCA1 and BRCA2

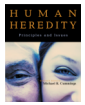
- Women with BRCA1 gene mutations have an 50% chance of developing breast cancer (compared to 13% in normal), and 16% chance of ovarian cancer by age 70 (compared to 1.6% in normal).
- Also increased risk of prostate cancers in men.
  In men, estimated 1/6 men with a mutation will develop prostate cancer.
- Note that just having the mutation does not automatically mean that breast cancer will develop, and *vice versa*.
- 73% of Ashkenazi Jews with family history of breast/ovarian cancer carry one of these mutations.
- Different families have different mutations in BRCA1/2.
- 1% of the general Jewish population has mutations in BRCA1 and BRCA2.
  In general population, frequency is 0.1-0.6%.

Source: Genome.gov



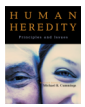
BRCA1 and *BRCA2* Are DNA Repair Genes

- Expression is highest at the G1/S boundary and S phase of the cell cycle
- BRCA proteins are activated when DNA is damaged
- Involved with repair of double stranded breaks in the DNA
- Regarded as tumor suppressor genes



Colon Cancer

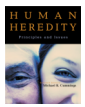
- Common form of cancer, approximately 84% are sporadic forms
- Multiple mutations are required to initiate formation of cancer cell
- Two forms of genetic predisposition
  - Familial adenomatous polypoisis (FAP) accounts for 1% of all cases
  - Hereditary nonpolyposis colon cancer (HNPCC) accounts for 15% of all cases



Colon and Rectal Cancer

Table 12.2 Colon and Rectal Cancer in the United States

Estimated new cases, 2004	
Colon	106,370
Rectum	40,570
Total	146,940
Mortality (estimated deaths, 2004)	
Colon and rectum	56,730
	(16% of cancer deaths)
5-year survival rate (early detection)	
Colon	90%
Rectum	85%



Familial Adenomatous Polyposis

- Autosomal dominant trait
- Mutation in the APC gene
- Frequency in general population 3/1,000
- Results in development of polyps and benign growths in the colon
- Polyps often become malignant

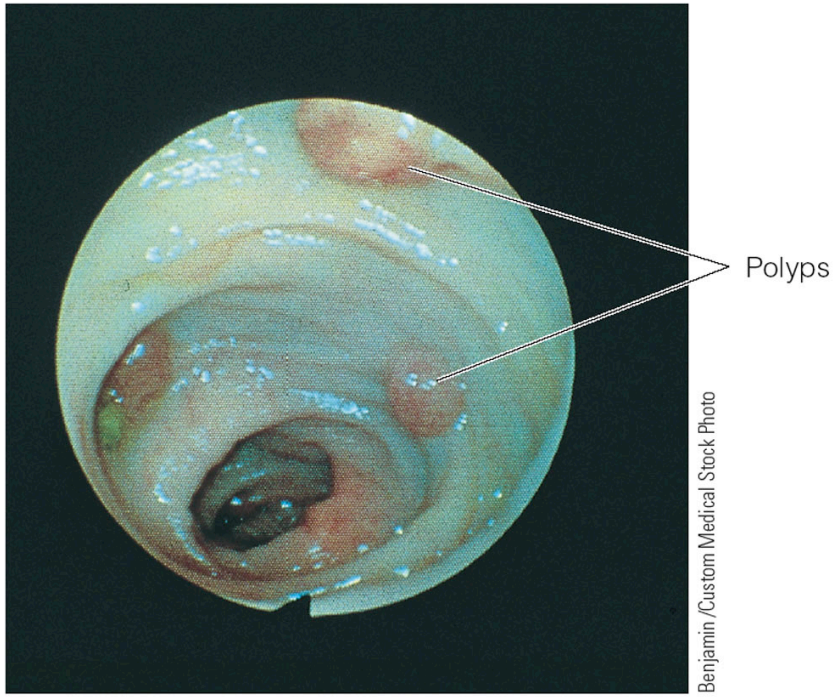
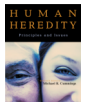


Fig. 12.11



Multistep model for Colon Cancer

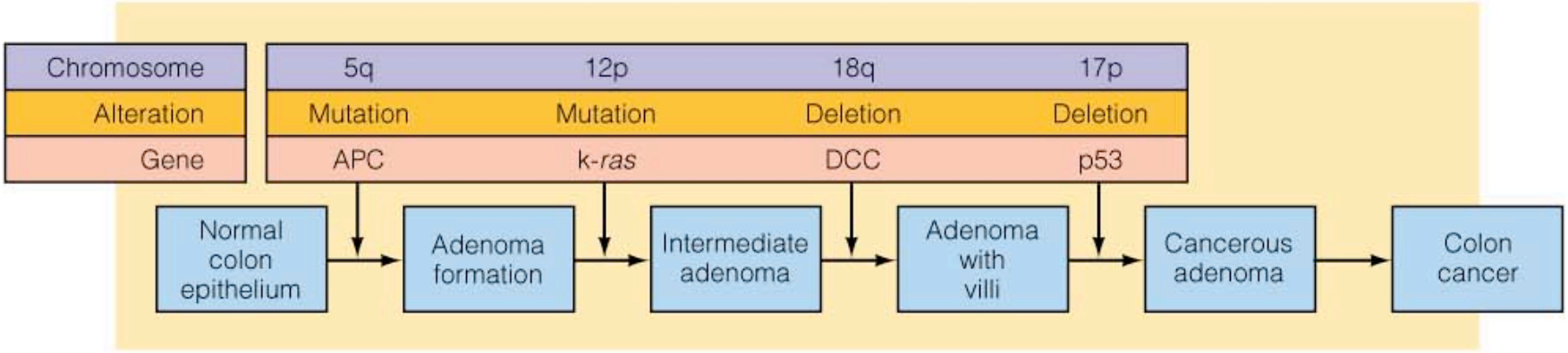
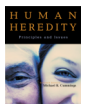


Fig. 12.12

Hereditary Nonpolyposis Colon Cancer

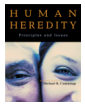
- Two forms
  - *HPNCC1* (2p16)
  - *HPNCC2* (3p23-21.3)
- Genes function to repair errors during DNA replication
- Mutations destabilize the genome, generating numerous mutations in DNA sequences known as microsatellites
- HNPCC tumors may carry more than 100,000 mutations
- Increased risk for many types of cancer



Mutations and Cancer

Table 12.3 Number of Mutations Associated with Specific Forms of Cancer

Cancer	Chromosomal Sites of Mutations	Minimal Number of Mutations Required
Retinoblastoma	13q14	2
Wilms tumor	11p13	2
Colon cancer	5q, 12p, 17p, 18q	5 to 7
Small-cell lung cancer	3p, 11p, 13q, 17p	10 to 15



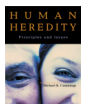
Two Types of Genes Involved in Cancer

Gatekeeper genes

- Regulate cell growth and passage through cell cycle
  - Example tumor suppressor genes and some oncogenes

Caretaker genes

- Help maintain the integrity of the genome
  - Example DNA repair genes



Chromosome Instability and Cancer Susceptibility

Table 12.4 Human Genetic Disorders Associated with Chromosome Instability and Cancer Susceptibility

Disorder	Inheritance	Chromosome Damage	Cancer Susceptibility	Hypersensitivity
Ataxia telangiectasia	Autosomal recessive	Translocations on 7, 14	Lymphoid, others	X-rays
Bloom syndrome	Autosomal recessive	Breaks, translocations	Lymphoid, others	Sunlight
Fanconi anemia	Autosomal recessive	Breaks, translocations	Leukemia	X-rays
Xeroderma pigmentosum	Autosomal recessive	Breaks	Skin	Sunlight

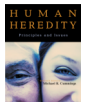
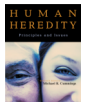


Table 12.5 Chromosomal Translocation Associated with Human Cancers

Chromosomal Translocation	Cancer
t(9;22)	Chronic myelogenous leukemia (Philadelphia chromosome)
t(15;17)	Acute promyelocytic leukemia
t(11;19)	Acute monocytic leukemia, acute myelomonocytic leukemia
t(1;9)	Pre-B-cell leukemia
t(8;14),t(8;22),t(2;8)	Burkitt's lymphoma, acute lymphocytic leukemia of the B-cell type
t(8;21)	Acute myelogenous leukemia, acute myeloblastic leukemia
t(11;14)	Chronic lymphocytic leukemia, diffuse lymphoma, multiple myeloma
t(4;18)	Follicular lymphoma
t(4;11)	Acute lymphocytic leukemia
t(11;14)(p13;q13)	Acute lymphocytic leukemia



Philadelphia Chromosome

- Abnormal chromosome produced by a translocation between long arms of chromosome 9 and chromosome 22
- Linked to chronic myelogenous leukemia (CML)

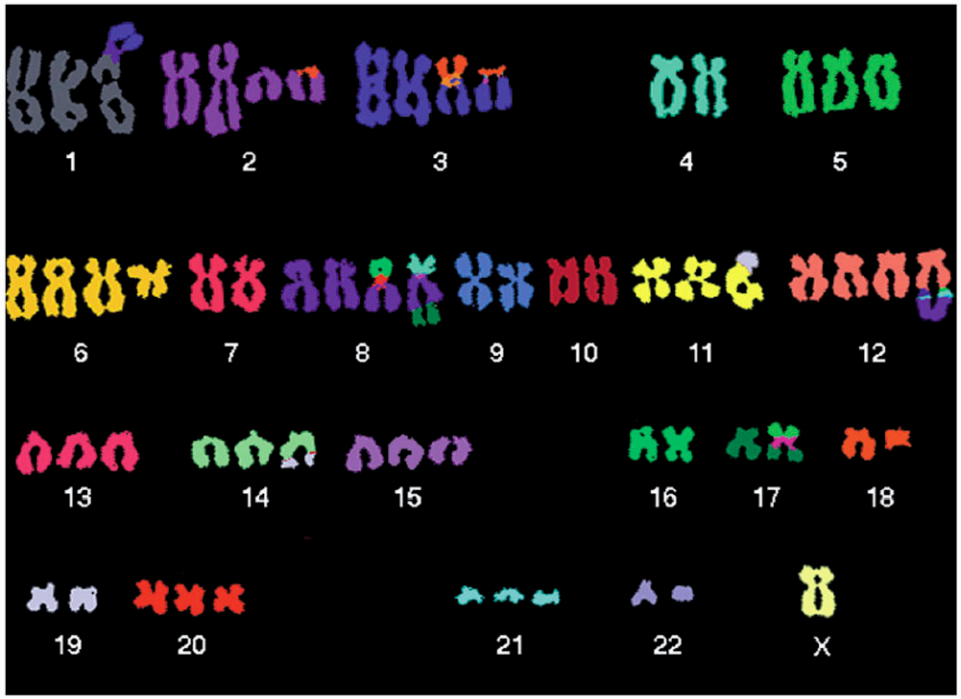
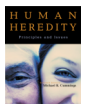
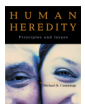


Fig. 12.13



Translocations

- Chromosomal breaks can convert proto-oncogenes to oncogenes
- In CML
  - The oncogene c-*abl* is on chromosome 9 at the breakpoint; the *bcr* gene is on chromosome 22 at the breakpoint
  - Translocation creates a hybrid gene
  - The hybrid protein acts a signal for cell division causing CML



Chronic Myelogenous Leukemia

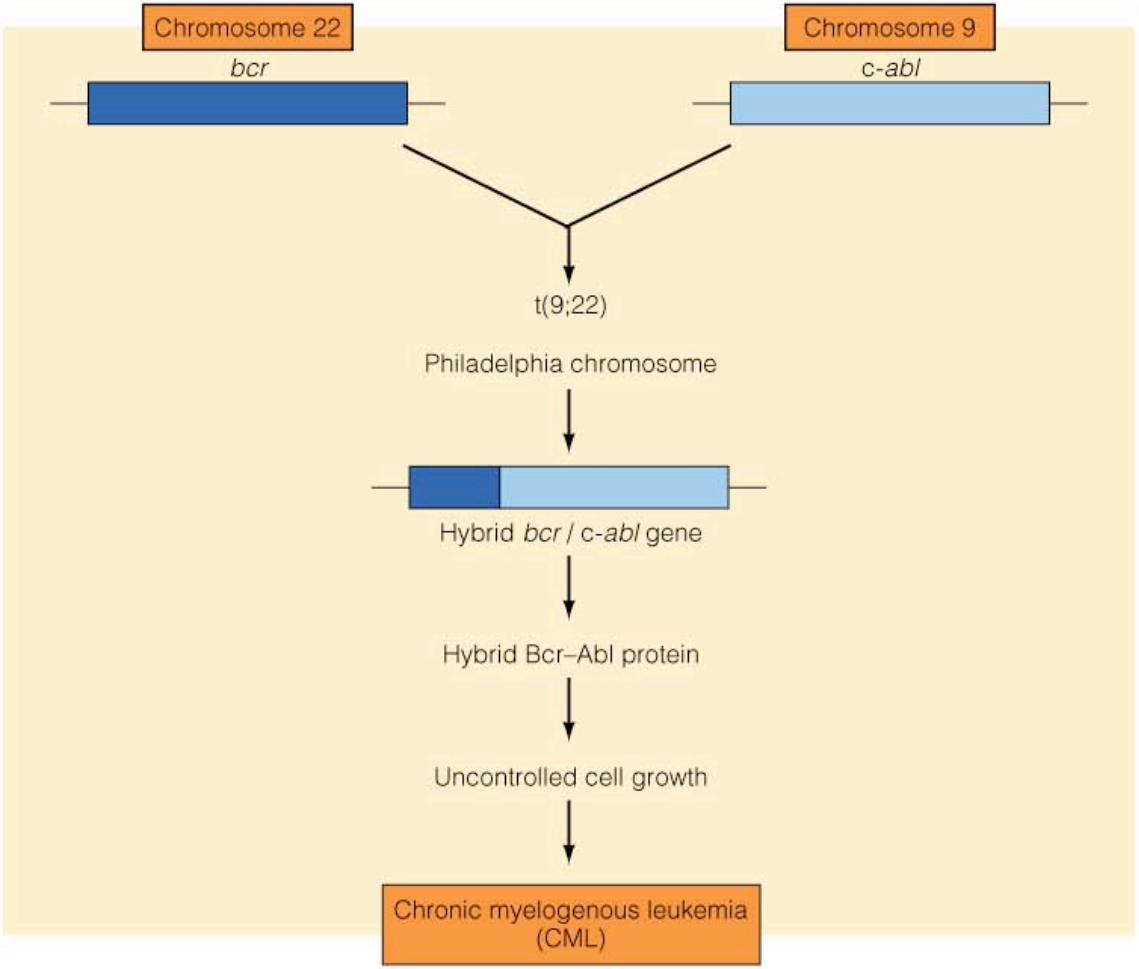
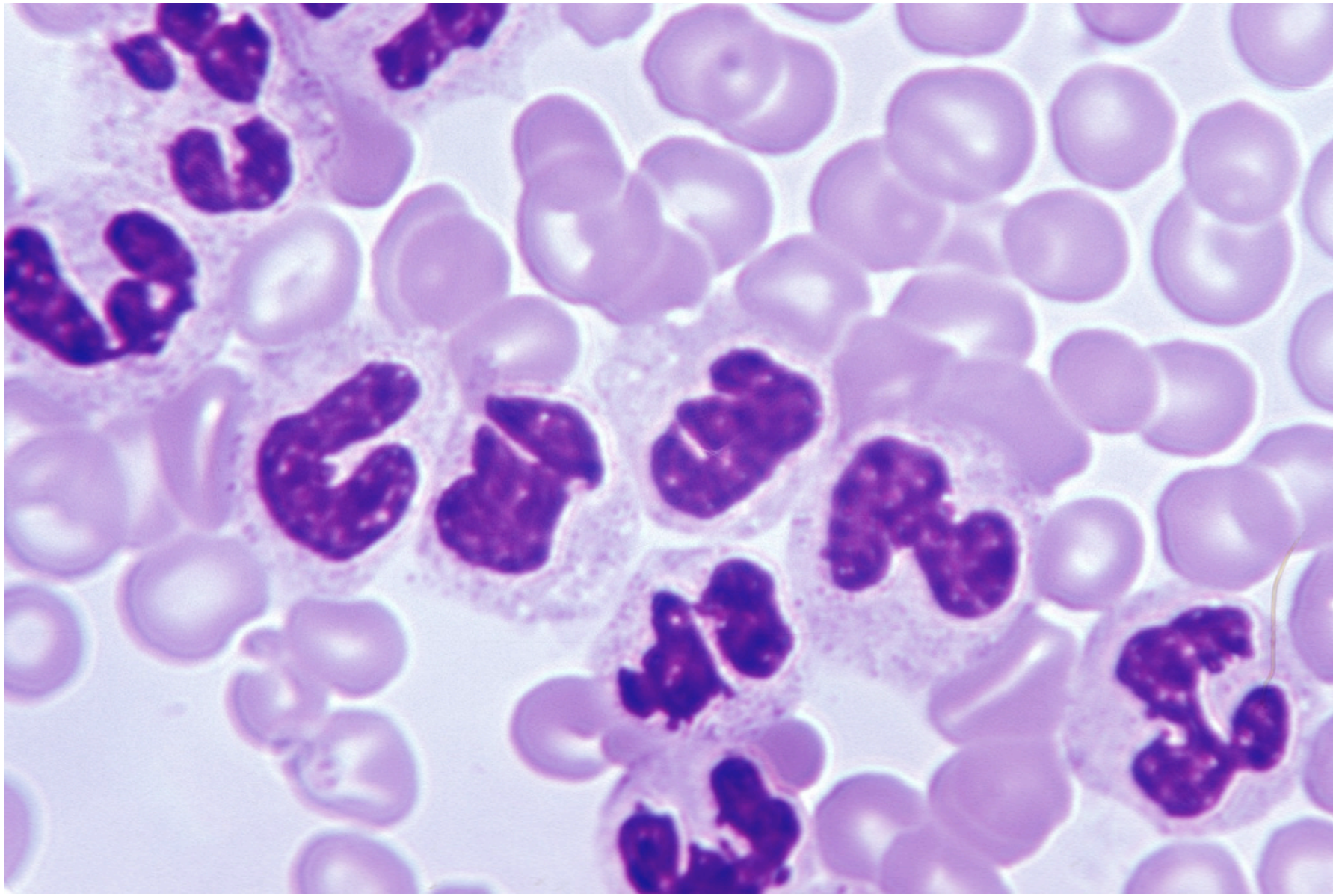


Fig. 12.15



Credit: © Biodisc/Visuals Unlimited

416235

Myelogenous leukemia in human blood. LM X600.

Cancer Drugs

- Traditional chemo- and radiation therapy, target all rapidly dividing cells and create serious side effects
- New drug, Gleevec, targets the specific hybrid protein
- 90% of patients with early stage CML go into remission

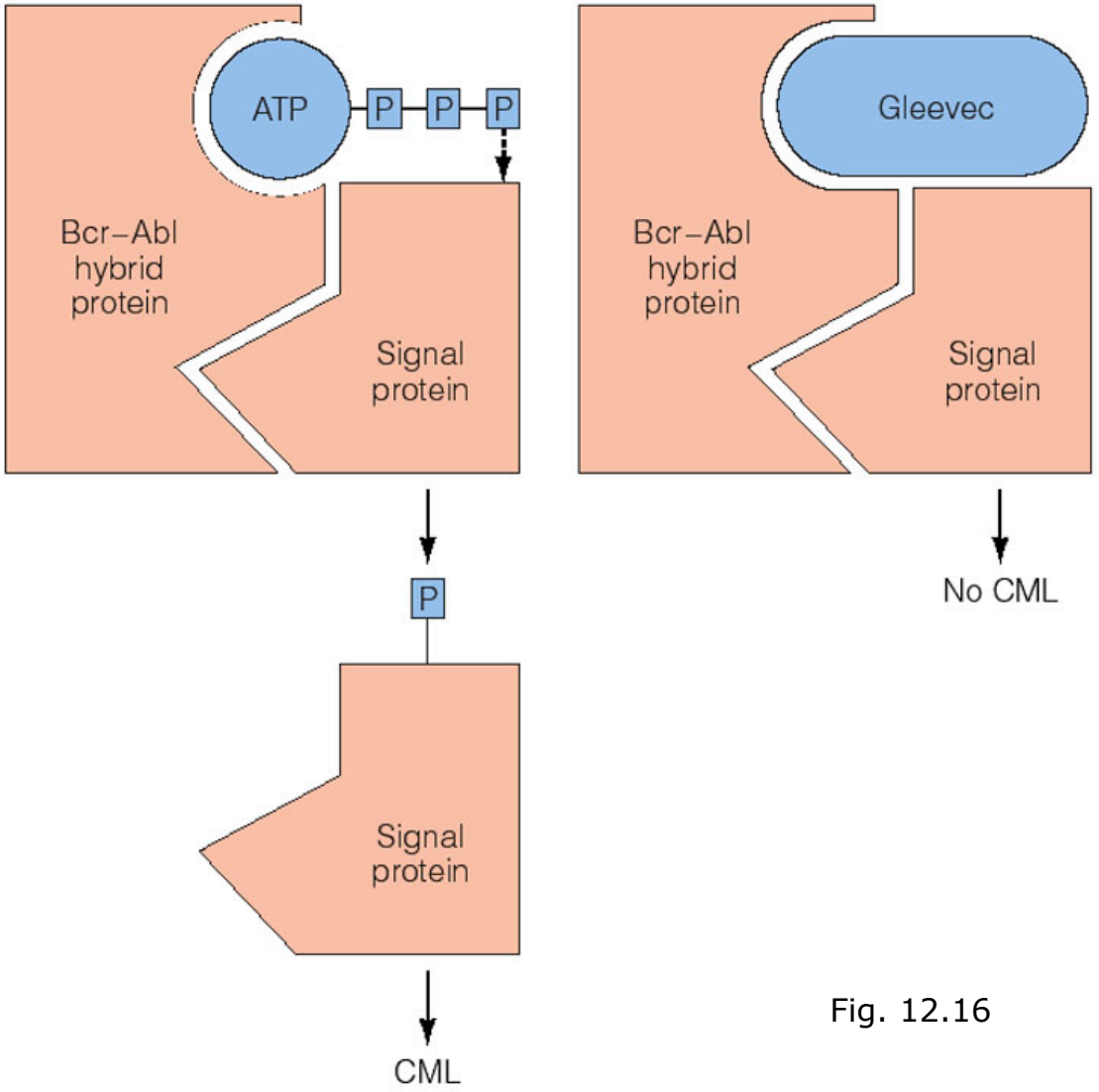
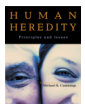


Fig. 12.16

Avastin - prevents angiogenesis
does not cure, just prolongs life a bit

Herceptin - works on HER2 overexpressing metastatic breast cancer
May reduce the risk of relapse by 50%



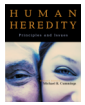
Cancer and the Environment

- Epidemiological studies can identify variation in cancer deaths between populations and help identify environmental factors

Table 12.6 Age-Adjusted Cancer Death Rates per 100,000 Population

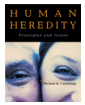
	All Sites	
Country	Male	Female
United States	165.3 (27)*	111.1 (18)
Australia	158.5 (28)	100.2 (20)
Austria	171.6 (20)	105.6 (16)
Denmark	178.7 (17)	138.1 (1)
Germany	177.3 (18)	108.2 (11)
Hungary	258.7 (1)	135.2 (2)
Japan	149.8 (32)	75.2 (43)
Latvia	206.1 (6)	98.7 (23)
Mauritius	85.4 (47)	63.8 (46)
Mexico	81.6 (48)	77.6 (41)
Poland	204.2 (8)	107.6 (13)
Romania	140.2 (36)	84.5 (38)
Slovenia	203.9 (9)	108.0 (12)
Switzerland	167.2 (24)	96.5 (26)
Trinidad, Tobago	120.0 (42)	91.4 (31)
United Kingdom	179.1 (16)	124.6 (5)

* Number in parentheses refers to rank order.

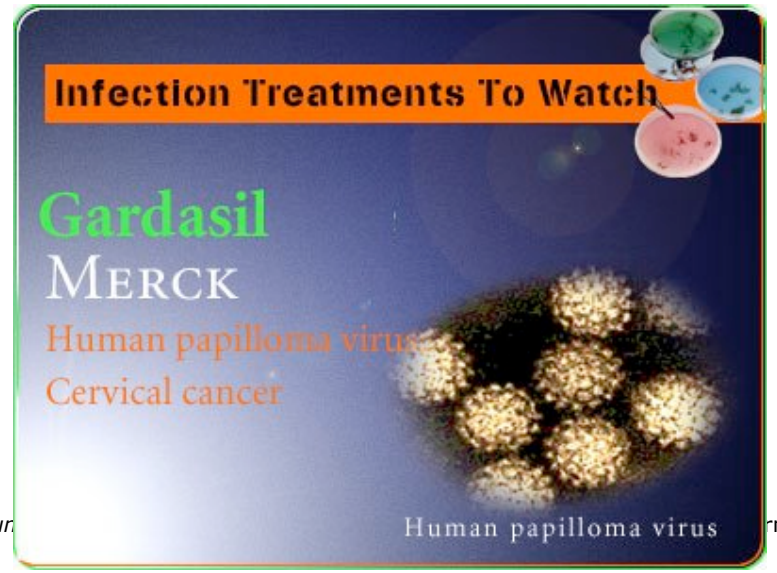


Human Genome and New Technologies

- Predict risk
- May help tailor diagnosis and treatment
- Development of specialized drugs
- Identify specific characteristics of cancer cells



Human papilloma virus infection can cause cervical cancer

Current recommendation: vaccinate using Gardasil - vaccine against HPV

Vaccine triggers antibody production against yeast-produced HPV proteins, protecting against future infection