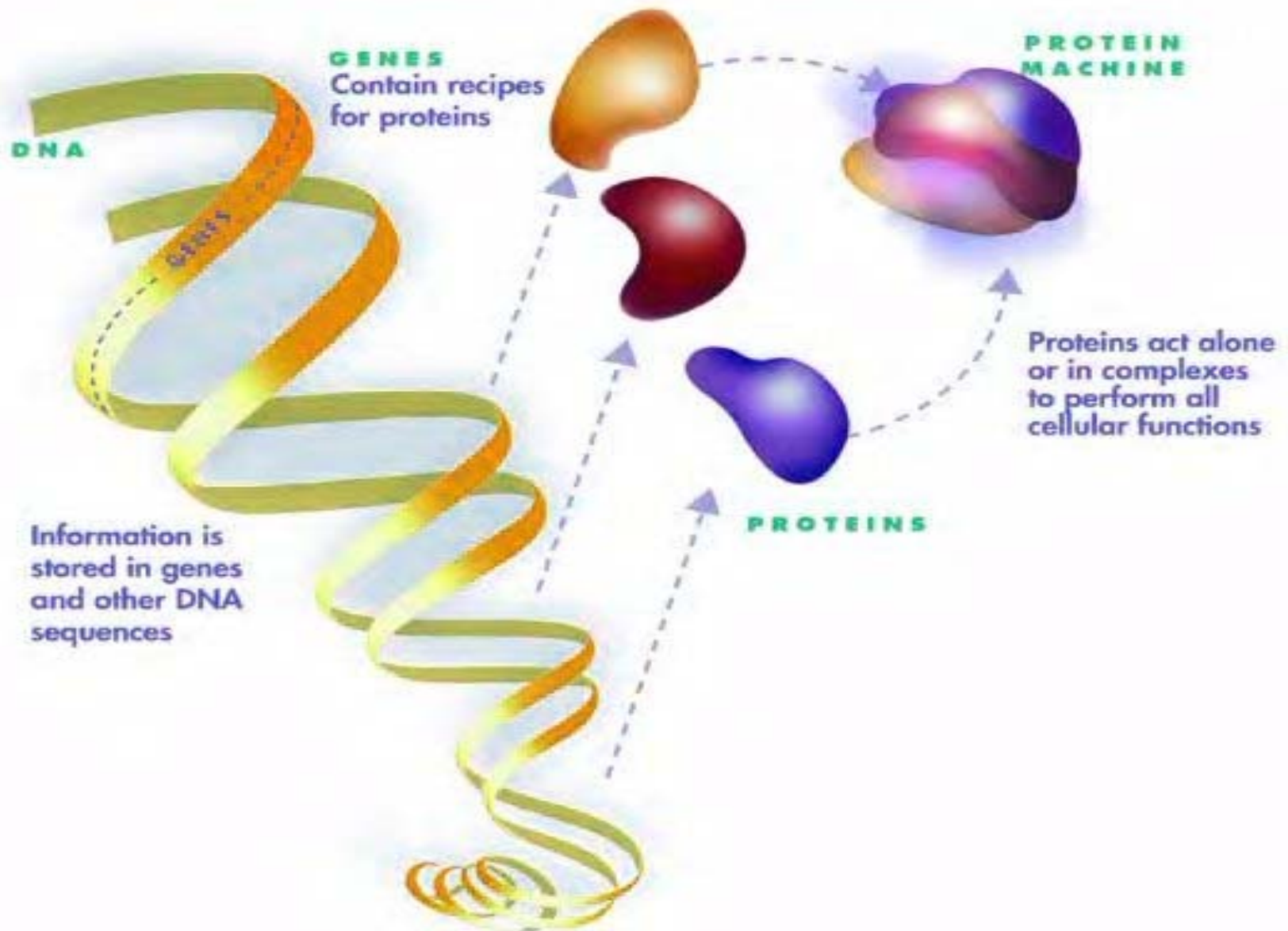
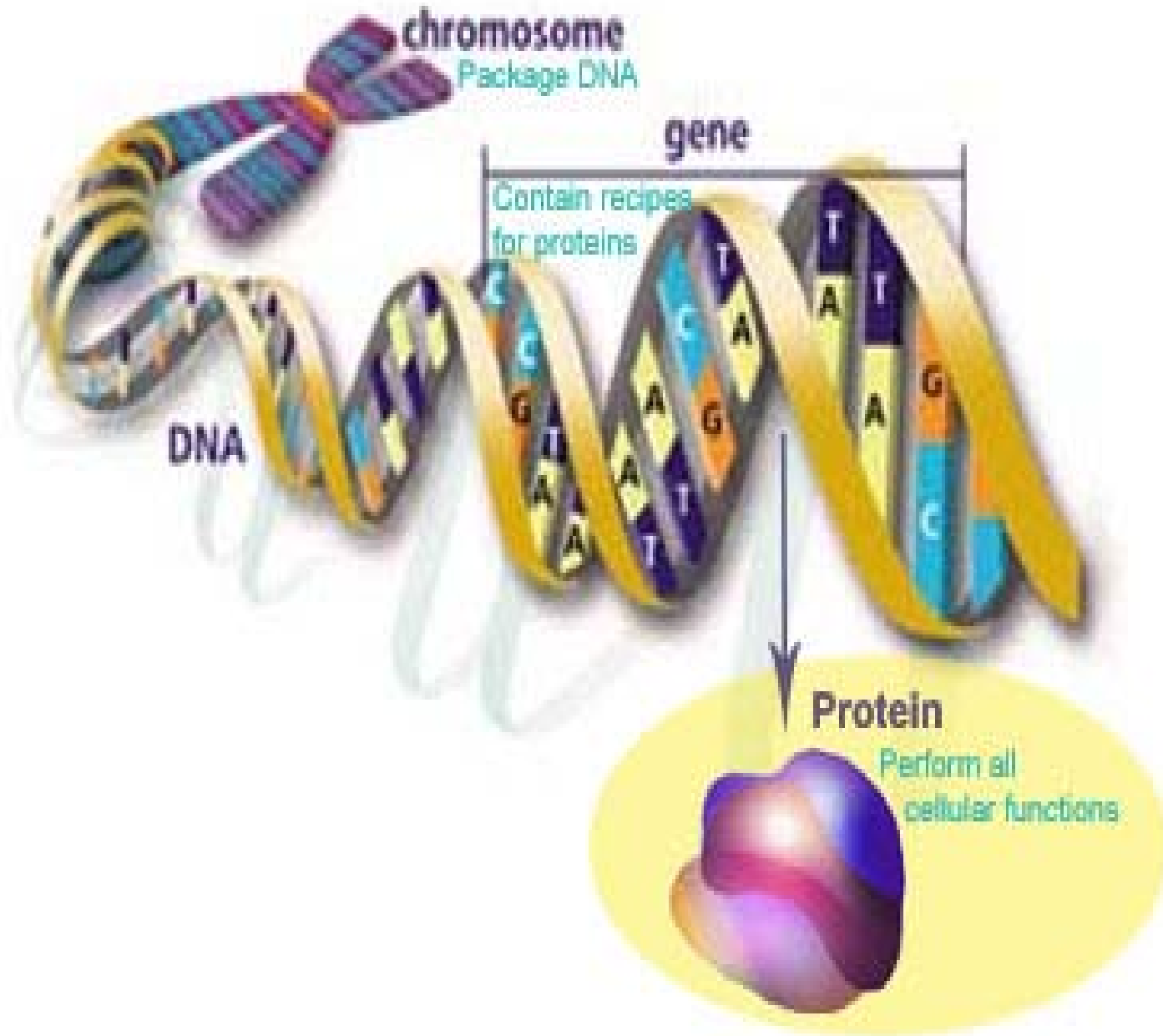
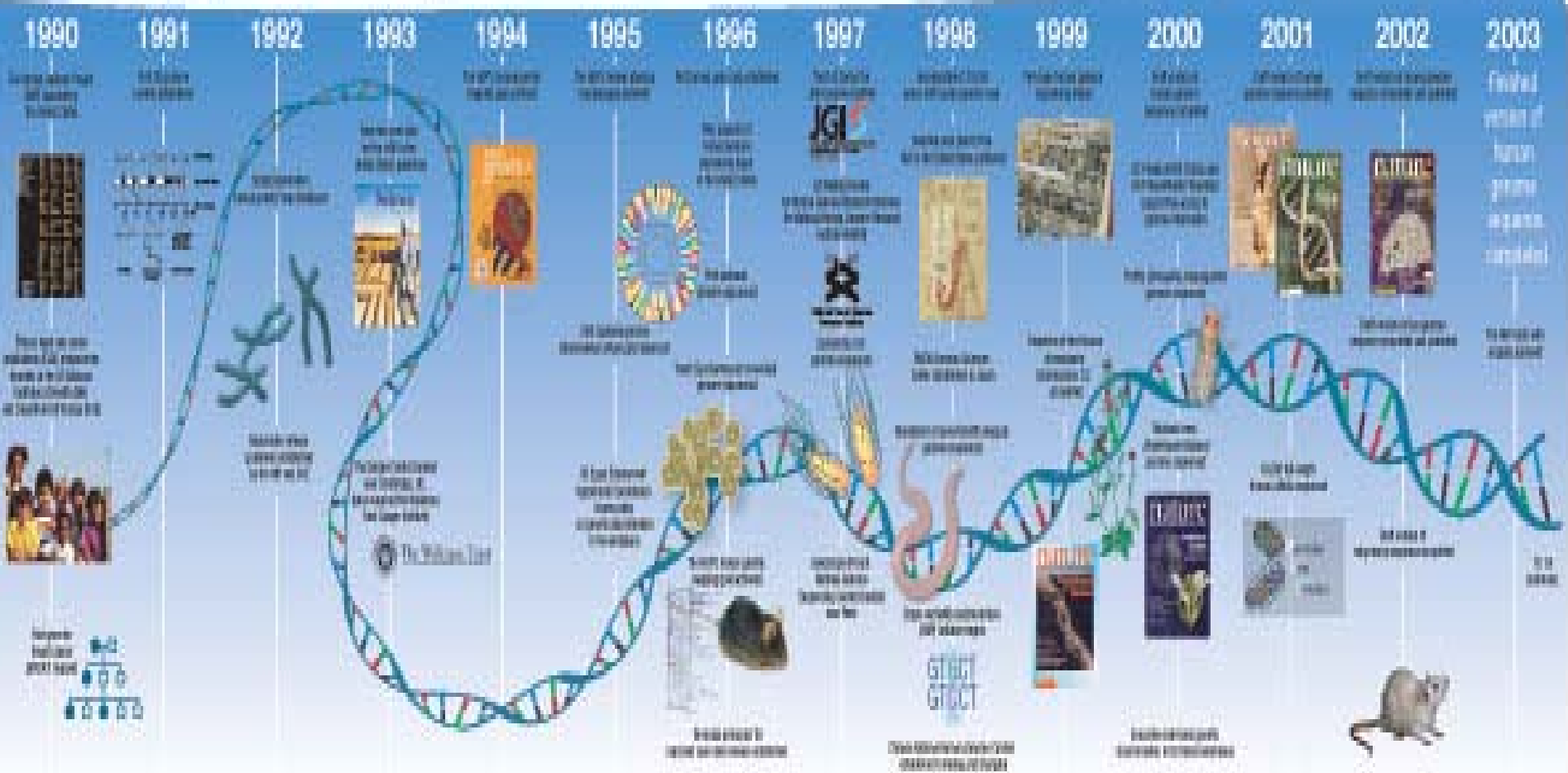
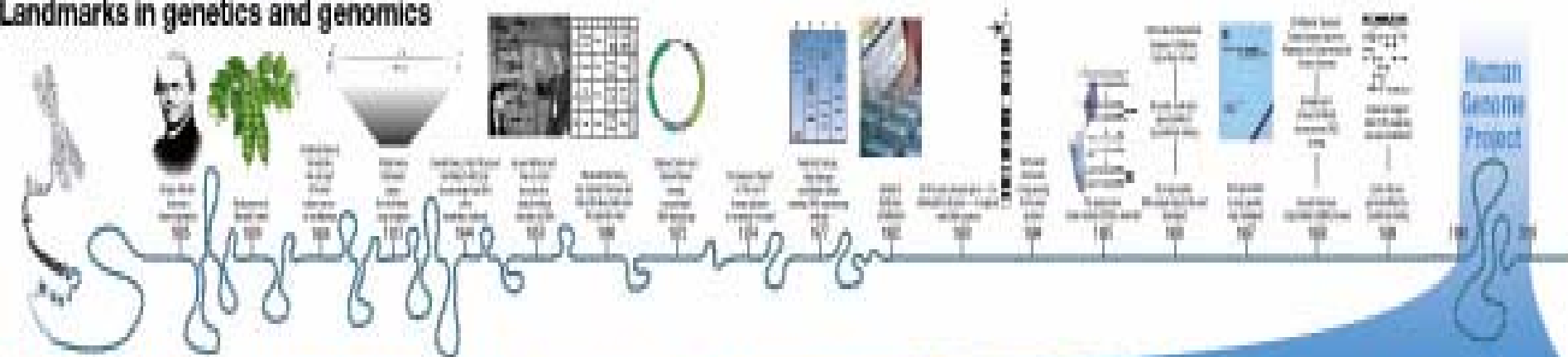


GENES, PROTEINS, AND MOLECULAR MACHINES



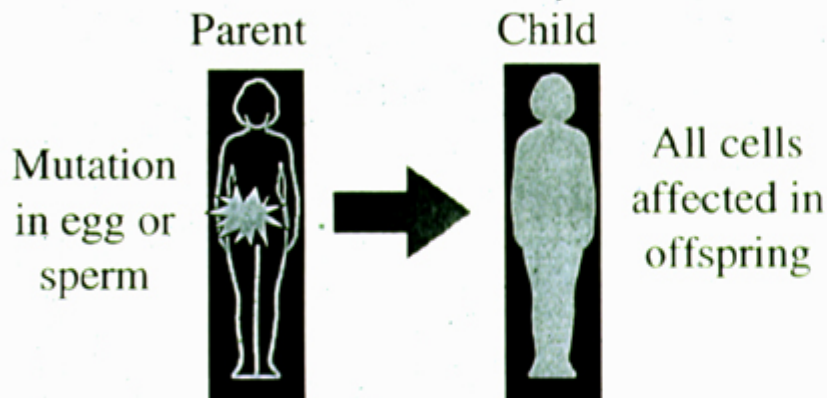


Landmarks in genetics and genomics



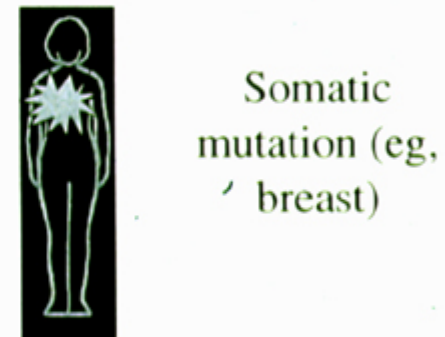
Cancer Arises From Gene Mutations

Germline mutations



- Present in egg or sperm
- Are heritable
- Cause cancer family syndromes

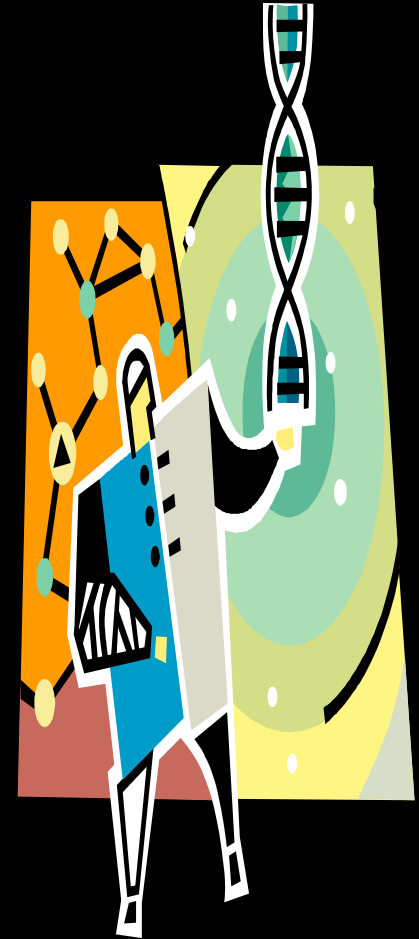
Somatic mutations



- Occur in nongermline tissues
- Are nonheritable

25,000 genes

- **Control the body's development, growth, maturation, body functions and aging.**
- **These processes depend on specific sequences of these chemical pairs**
- **Even a small change in the sequence can be enough to cause disease.**
 - **Disruption shown in movie clip in next slide**



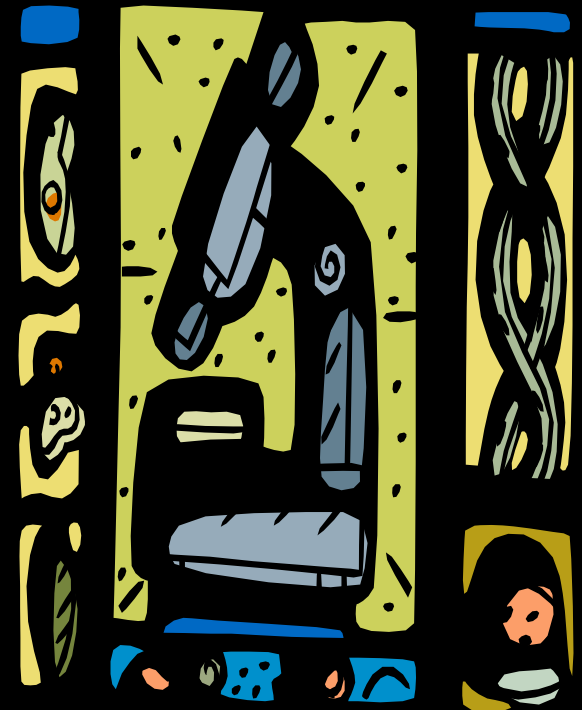
Turning genes off and on

- **during differentiation of cells some genes become permanently inactivated.**
 - **e.g., liver enzyme genes that go to neurons are not needed. Therefore, they are covered with proteins so that they cannot be “turned on”.**

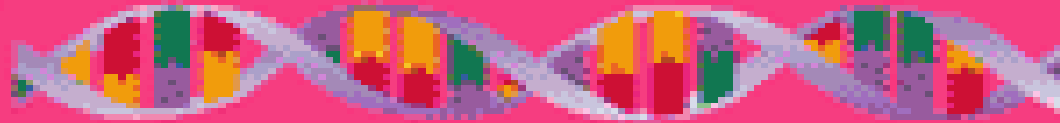


- **viruses have the ability to carry foreign genes into neurons**
 - **sometimes the genes become integrated into the DNA of the infected cell.**
 - **they soon direct the synthesis of new viral particles that can injure the cell and infect others.**
 - **(this ability is used in research but virus is inactivated)**

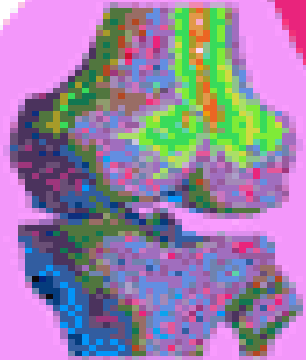
Virtually every disease has a genetic component



Genes

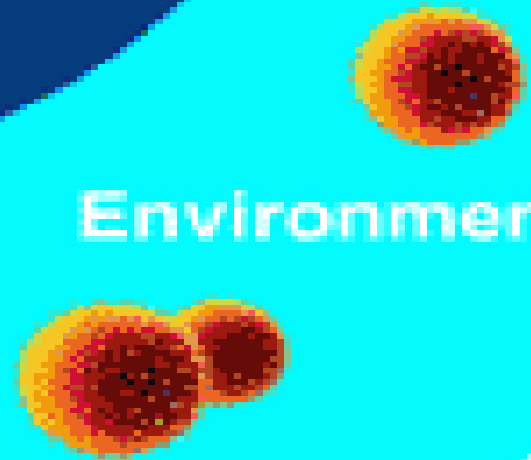


Osteoporosis/
Bone
Metabolism



**Bone
Metabolism
Regulation
SNPs**

Environment



Problematic thinking: “disease-gene”

- **All disease is a product of gene-environment interaction.**
 - **Genes specify protein structures -ONLY**
- **Only when genes come into contact with an environment is their advantage or disadvantage apparent: environment could be cellular or geographic.**
- **Lifestyle, (includes ageing, nutrition, infection, toxin exposure)**

What is the cause of cancer?

Cancer is caused by genetic dysregulation

Mutagens

chemicals
radiation

Viruses

Retroviruses

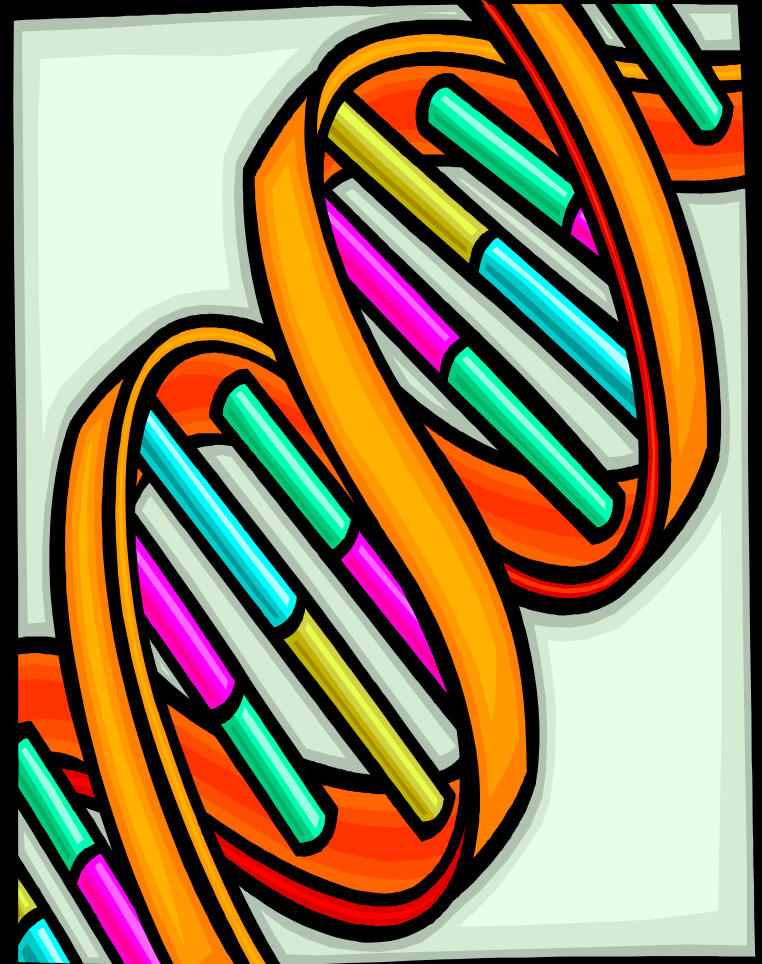
Anything that can
mutate genes

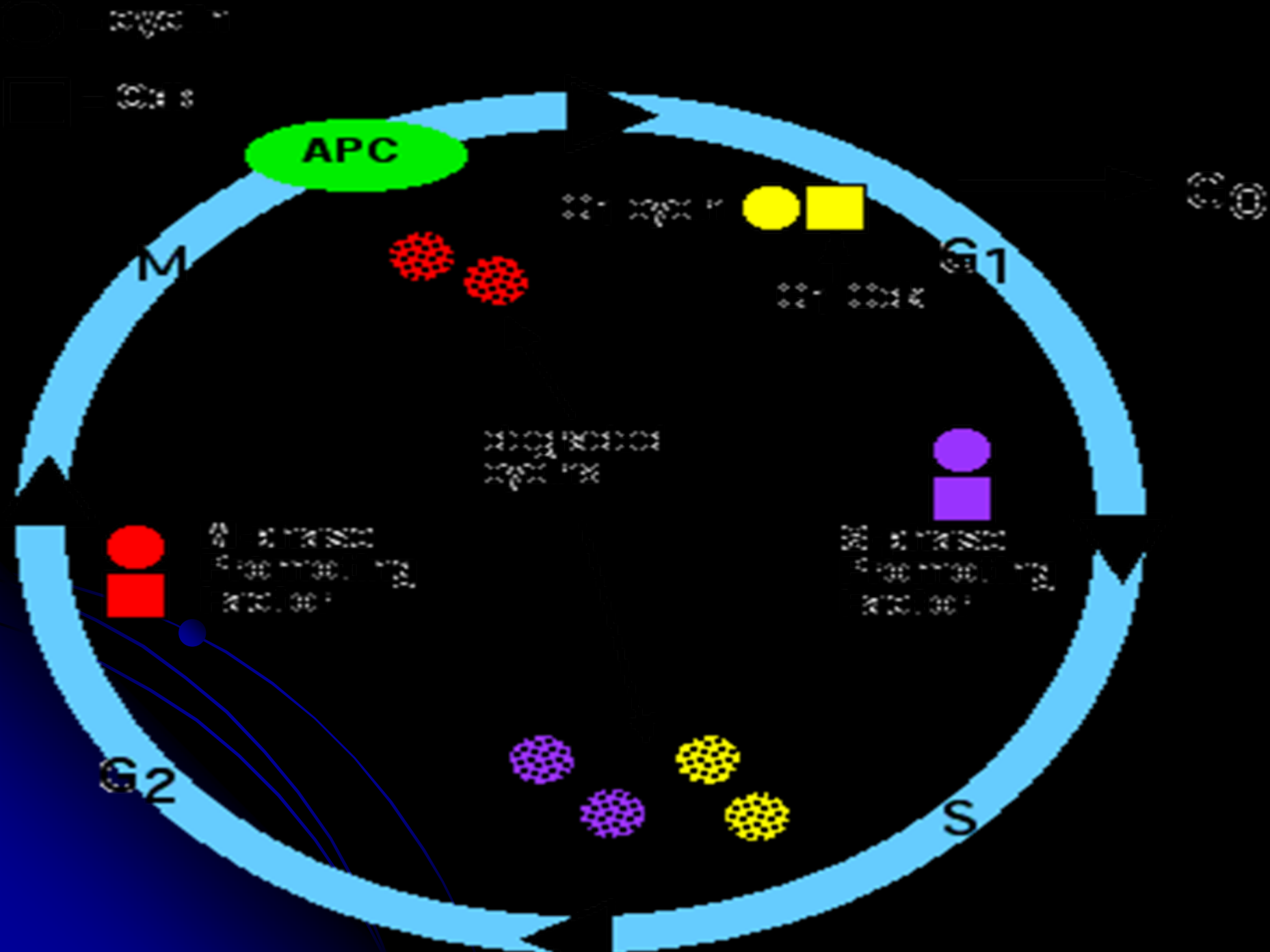
Anything that can
alter the function
of genes

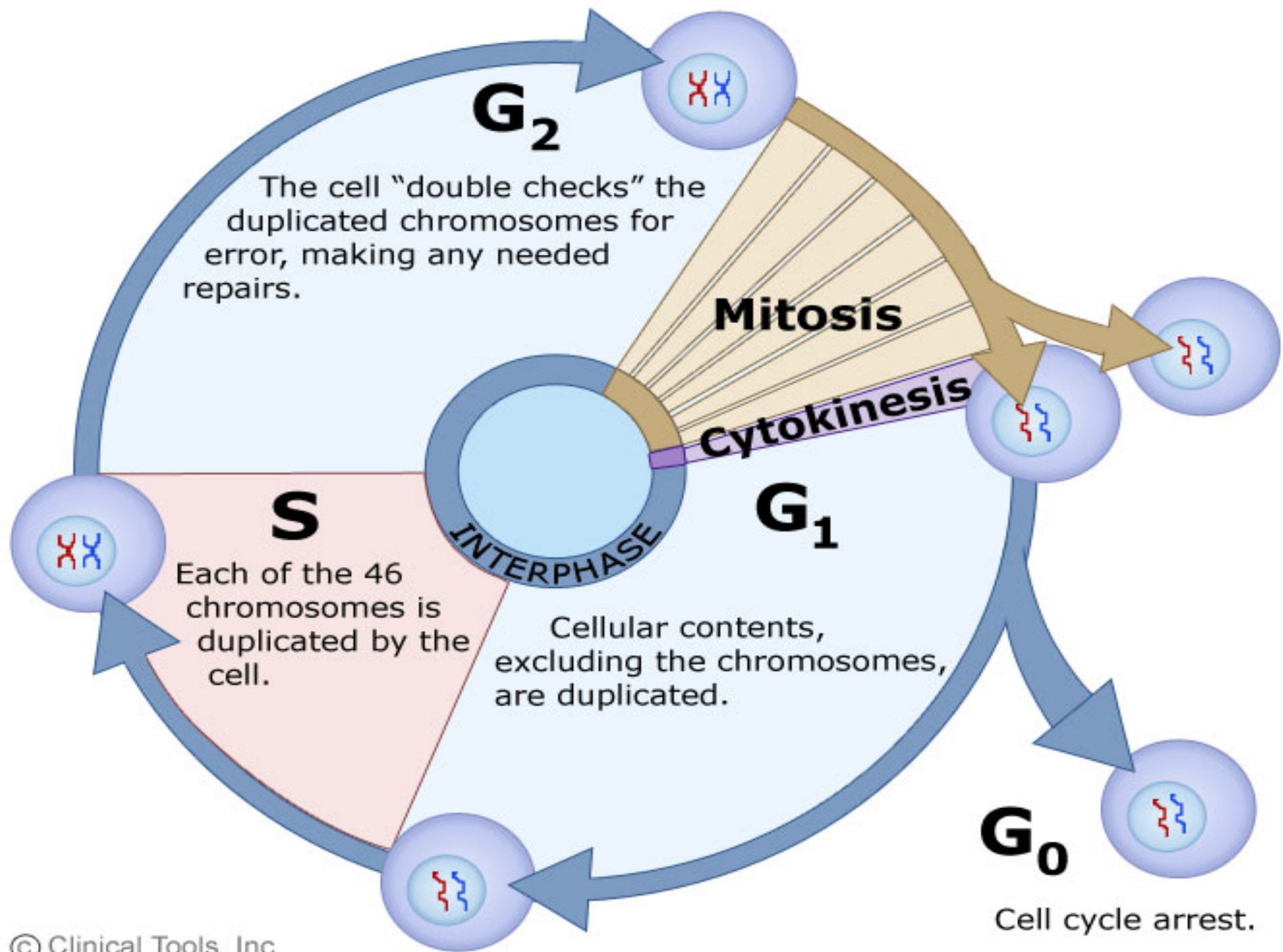
Don't forget random mutations

cancer

- **Over 100 diseases that we call cancer.**
- **What they have in common is that cancer is a disease of the DNA.**
- **it is the result of cumulative mutations that alter specific locations in a cell's DNA.**







Cell cycle

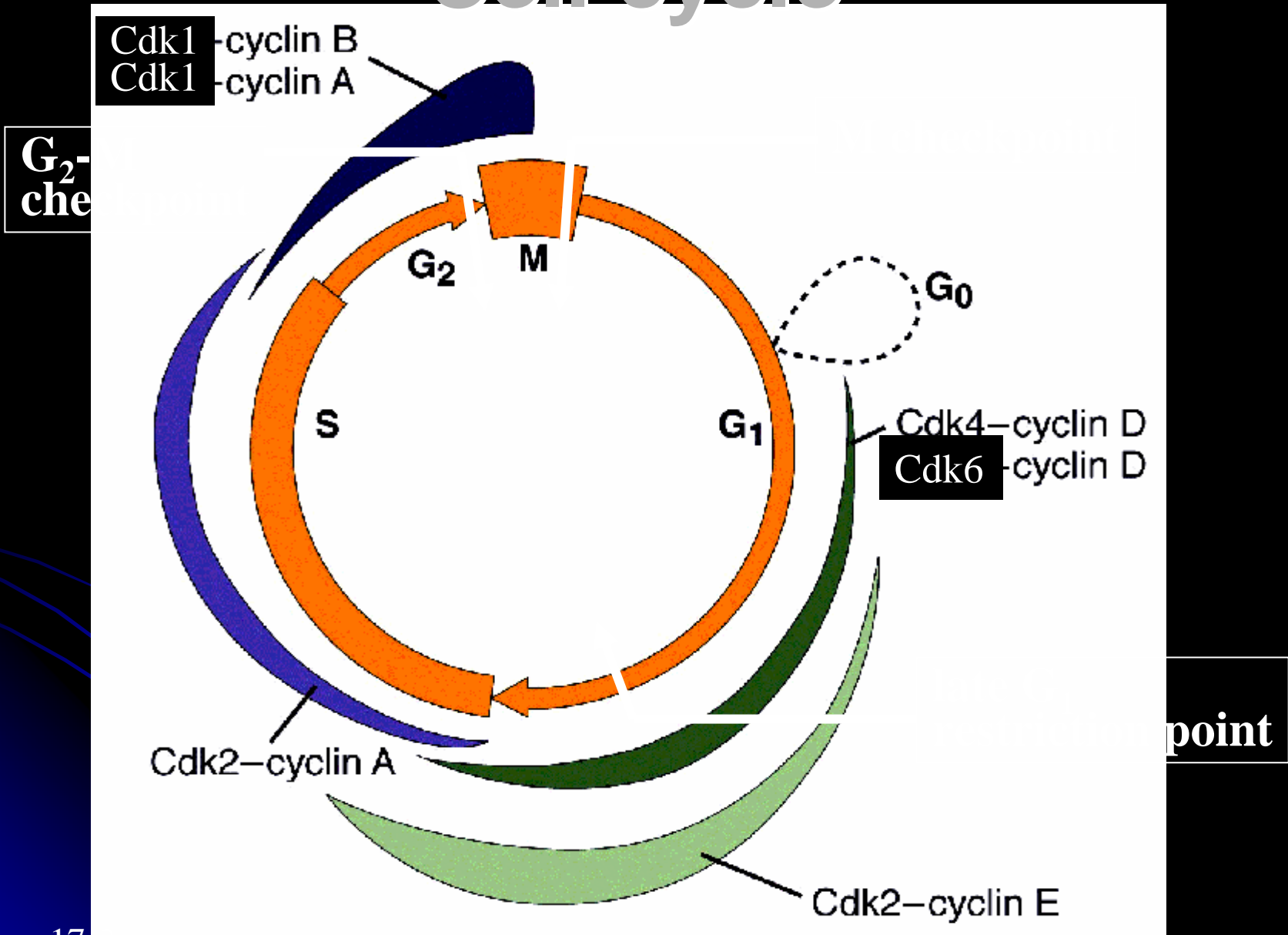
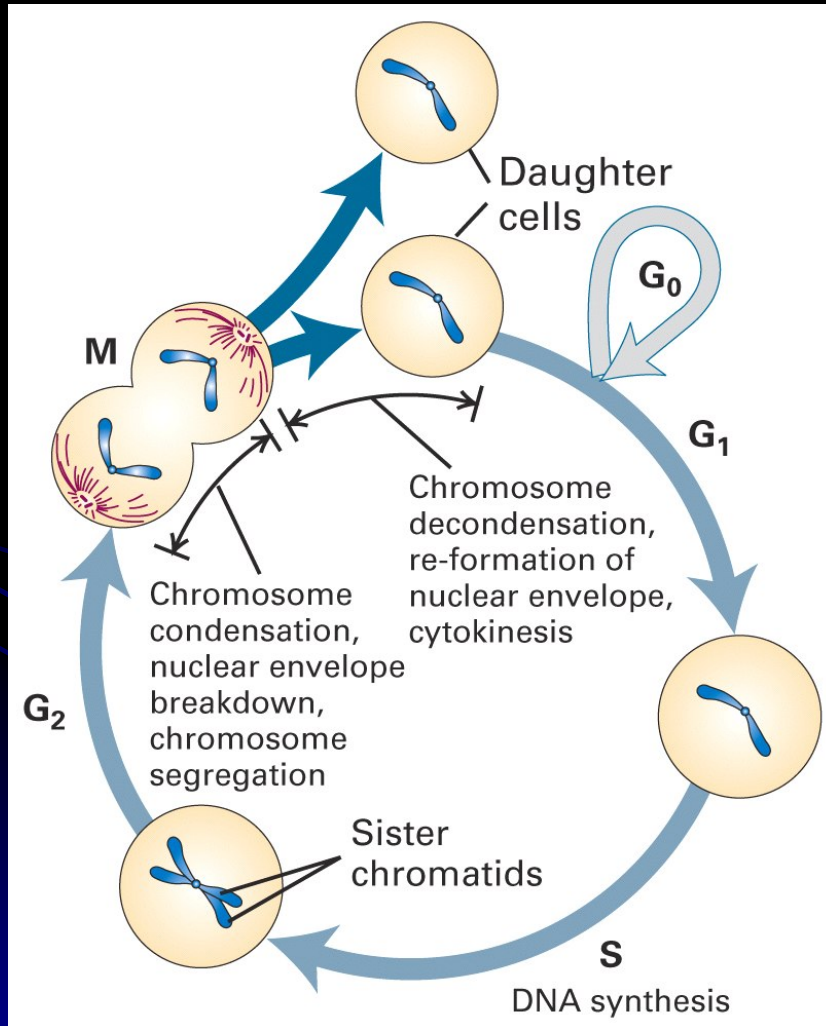


Figure 17-2

Cancer initiators promote growth



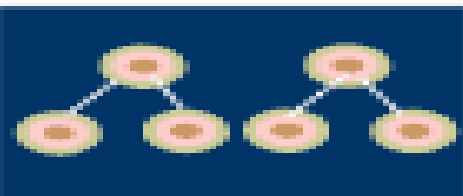
Cell Cycle

When cells grow and proliferate, they go through the cell cycle. This includes a replication of the DNA, and separation into two equal daughter cells.

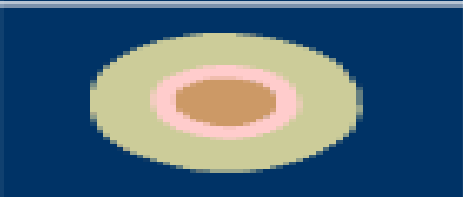
Epithelial cells hang out here in **G₀** once they have differentiated

Cell cycle regulation

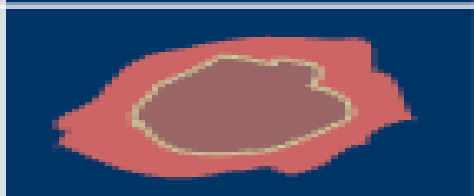
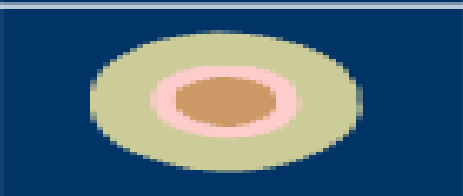
- **Cyclin**
 - transcribed in specific phase of cell cycle
 - unstable, resulting in transient activity
- **Cyclin-dependent protein kinase (CDK)**
 - substrate specificity and phosphorylation activity controlled by bound cyclin
 - phosphorylate serine or threonine of target protein
- Sequential activation of different CDK-cyclin complexes controls cell cycle progression

NORMAL**CANCER**

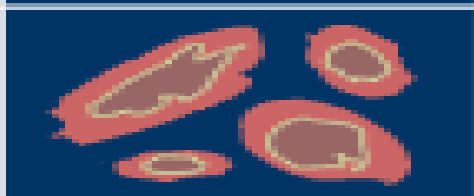
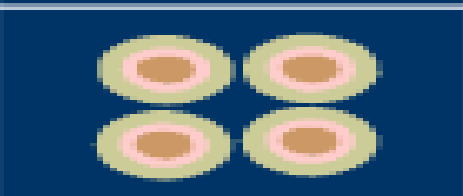
Large number of dividing cells



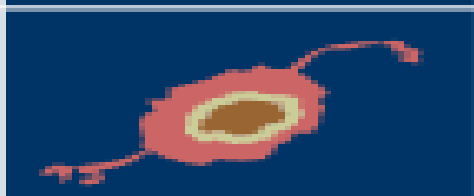
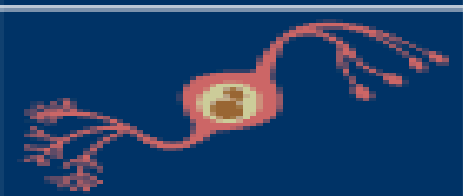
Large, variable shaped nuclei



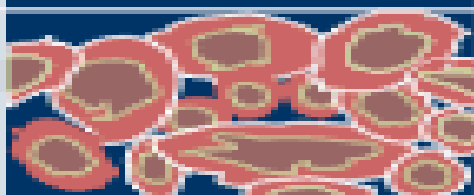
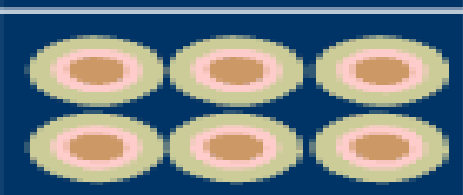
Small cytoplasmic volume relative to nuclei



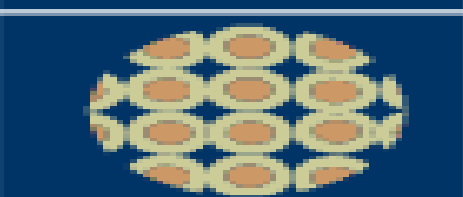
Variation in cell size and shape



Loss of normal specialized cell features



Disorganized arrangement of cells

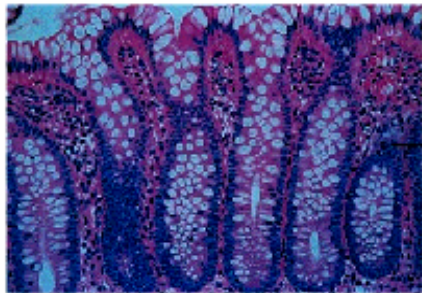


Poorly defined tumor boundary

Cancer

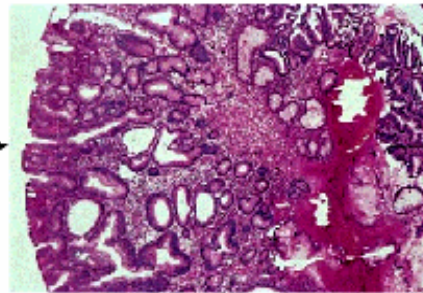
COLON CANCER

Loss of *apc* gene
(chromosome 5)



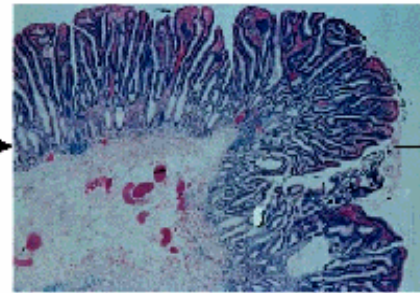
Normal colonic mucosa

Oncogenic mutation
of a *ras* gene
(chromosome 12)

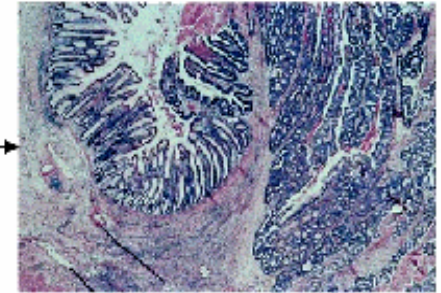


Benign
(early) adenoma

Loss of *p53* gene
(chromosome 17)
Loss of a gene (possibly
dcc) on chromosome 18



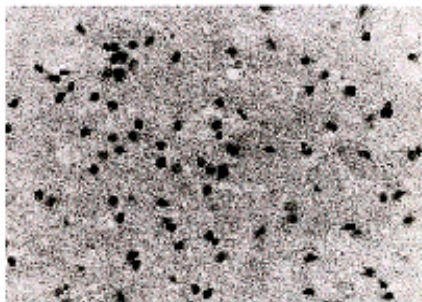
Benign
(late) adenoma



Malignant invasive carcinoma

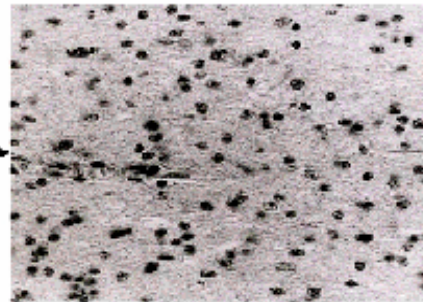
ASTROCYTOMA

Loss of *p53* gene



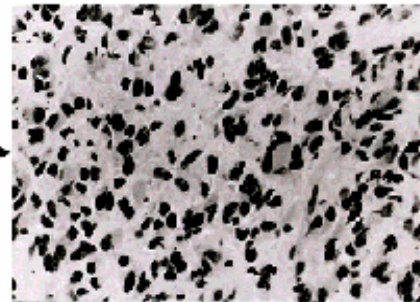
Normal tissue

Loss of a cluster of genes
on chromosome 9

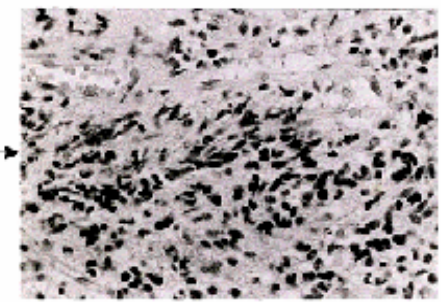


Low-grade tumor

Multiplication of gene for
epidermal growth factor
receptor (chromosome 7)
Loss of one copy of
chromosome 10

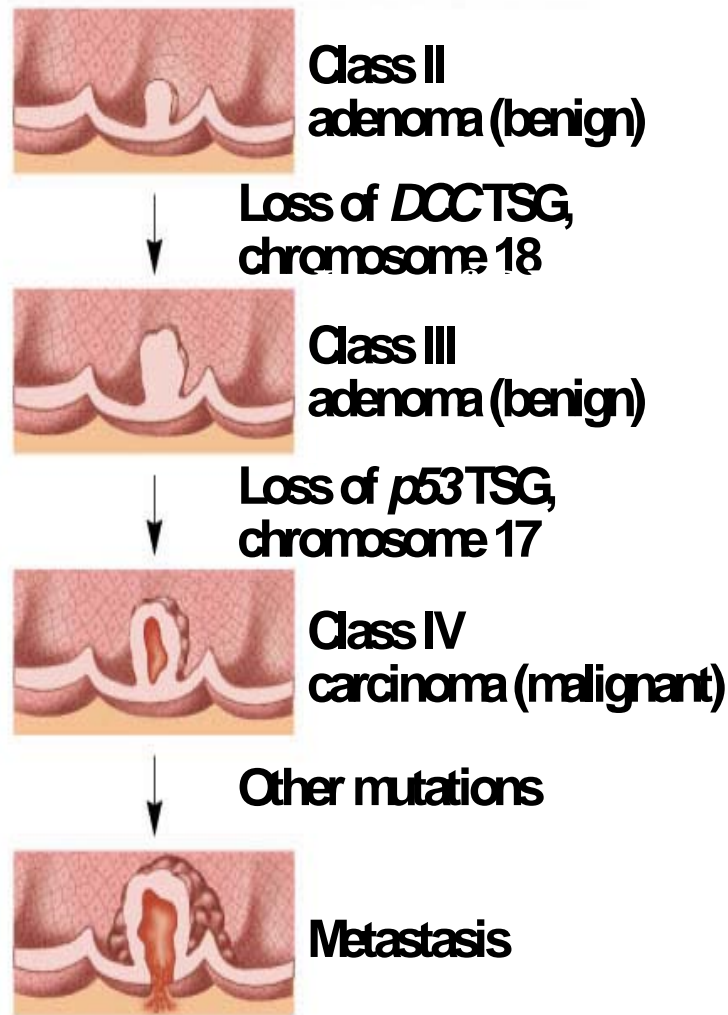
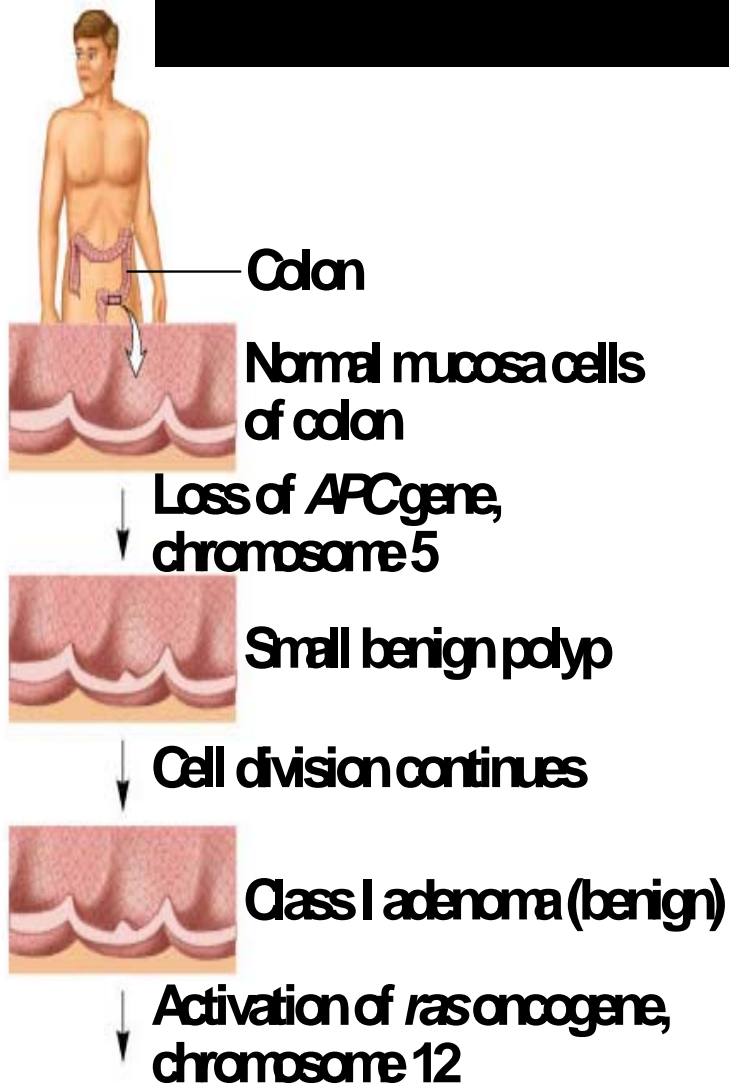


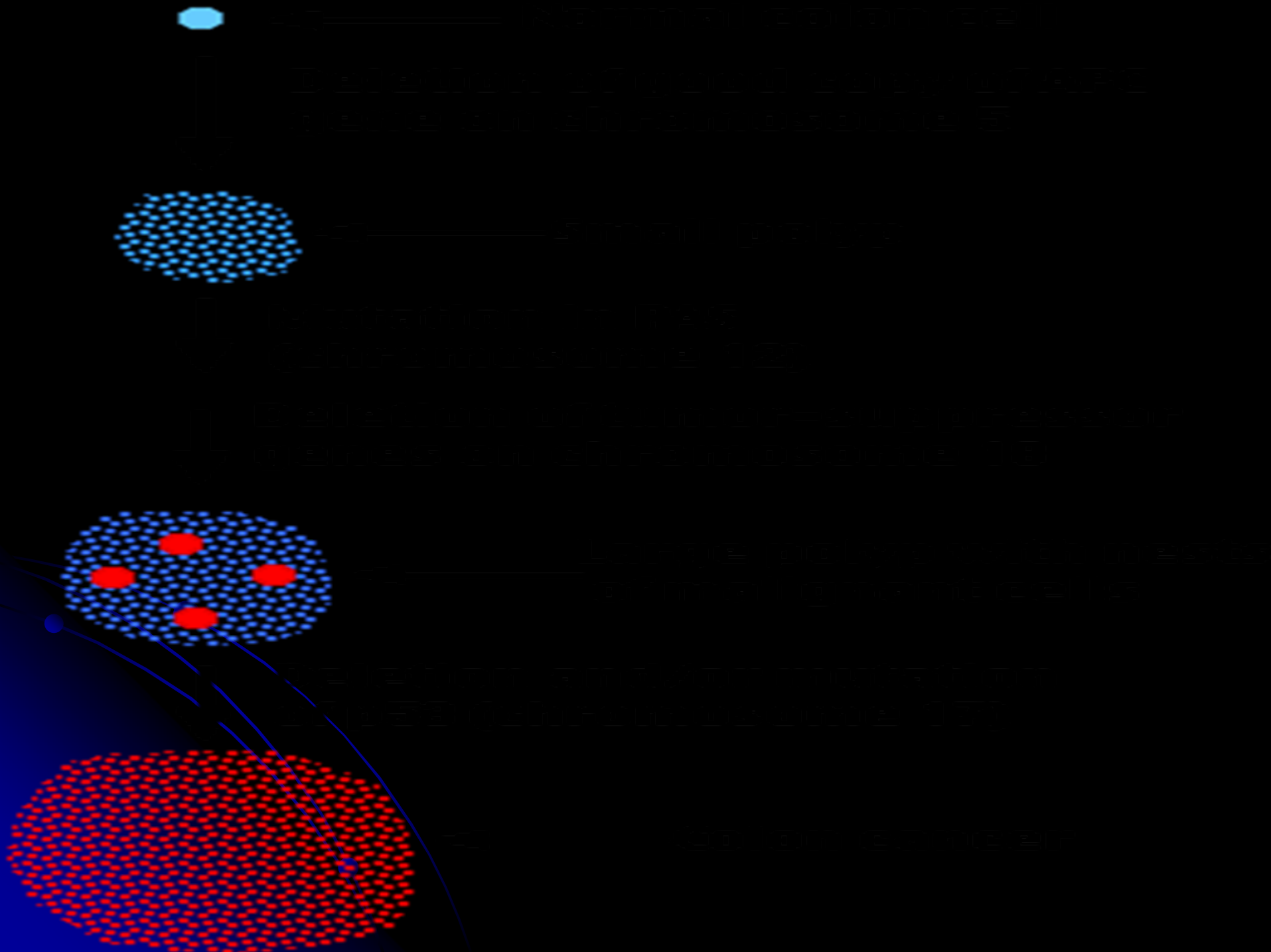
Higher-grade tumor



Most aggressive form of tumor

Cancer





Mutations in cancer cells

- Two categories
 - **oncogenes (onc)**, typically dominant
 - **tumour-suppressor genes (tsg)**, typically recessive
- Sometimes associated with chromosomal abnormalities
 - e.g. translocation that brings gene under control of another gene's strong enhancer (*onc*)
 - e.g. deletion of, or break point within (*tsg*)
- Cells that continuously proliferate or lose ability to undergo apoptosis have longer time to accumulate tumour-promoting mutations

Interactions

- **Genes do not “cause” diseases. It is wrong to claim they do. Genes instruct the manufacture of proteins, which may or may not advantage or disadvantage the organism under certain conditions.**
- **Similarly, no single disease can be attributed to environment. Even poisoning is influenced by phenotypical detoxification, which is genetically modulated.**
- **Lifestyle is even more complex than either genes or environment.**

(a) MOST NORMAL CELLS

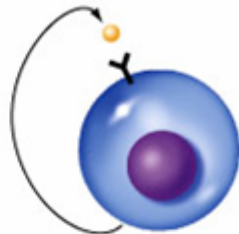
MANY CANCER CELLS

1.

Autocrine stimulation



Absent



Present

2.

Contact inhibition



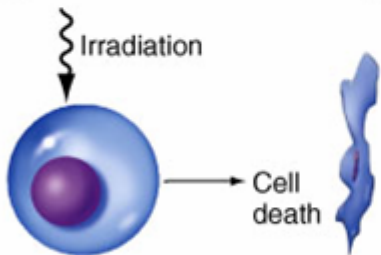
Present



Absent

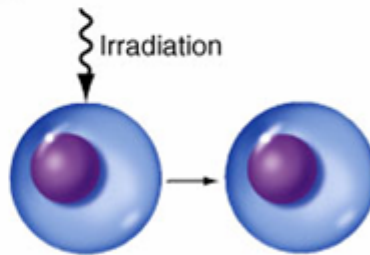
3.

Cell death



Cell death

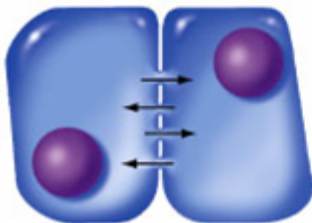
Present



Absent

4.

Gap junctions



Present



Absent

Cancer

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

Cancer

- **cancer will occur when 5-10 ordinary genes develop mutations in a single cell over a person's lifetime.**
- **Consists of cells that divide over and over.**
- **Cumulative exposure to damage (sun, etc.) increases likelihood of a mutation.**



spread of cancer

- the key reason we die from it.
- when the cancer cells invade other tissues they interfere with vital systems of the body





Figure 1. Acquired Capabilities of Cancer

We suggest that most if not all cancers have acquired the same set of functional capabilities during their development, albeit through various mechanistic strategies.

Basic research in cancer

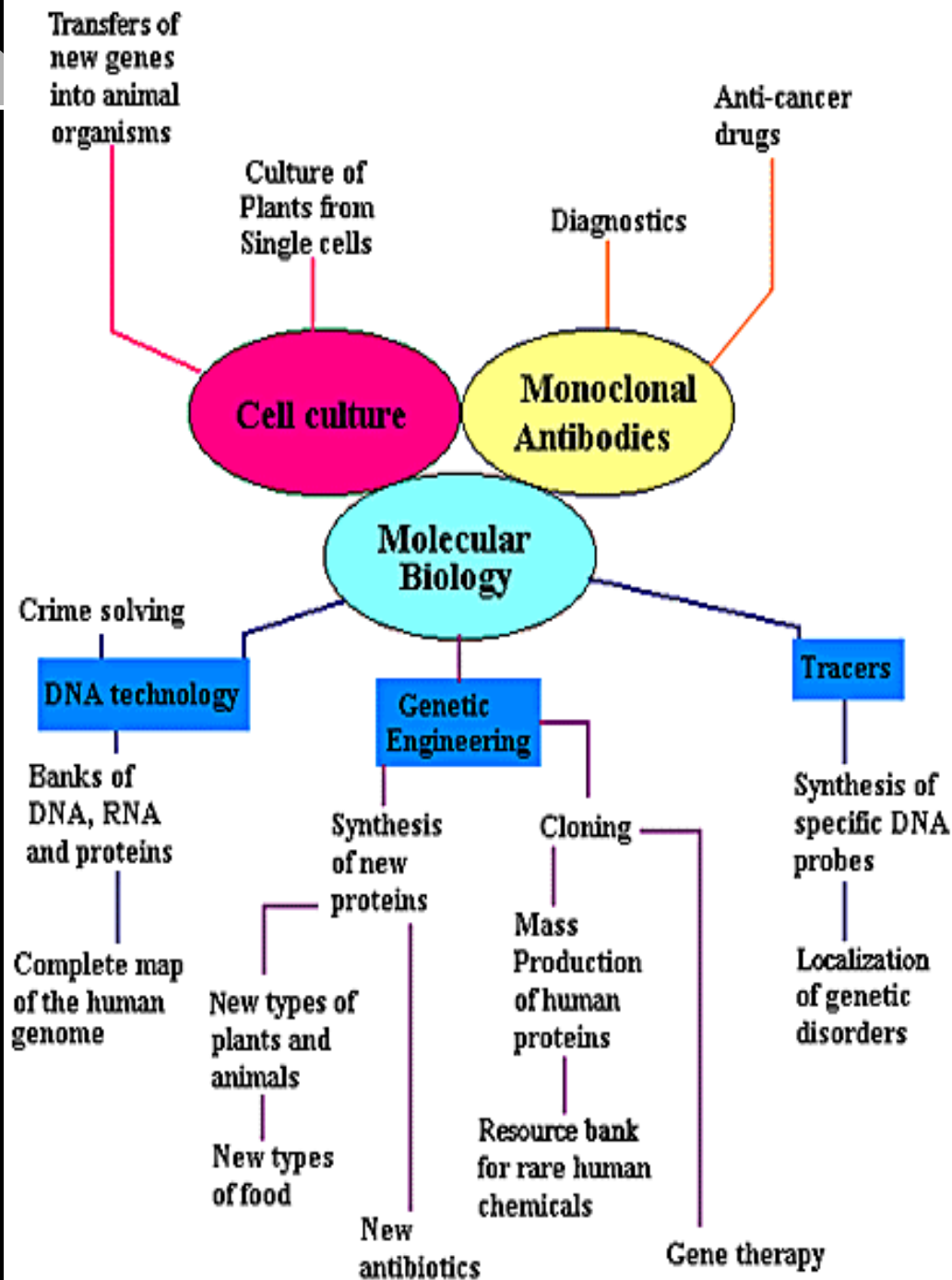
Carcinogenesis

Viruses

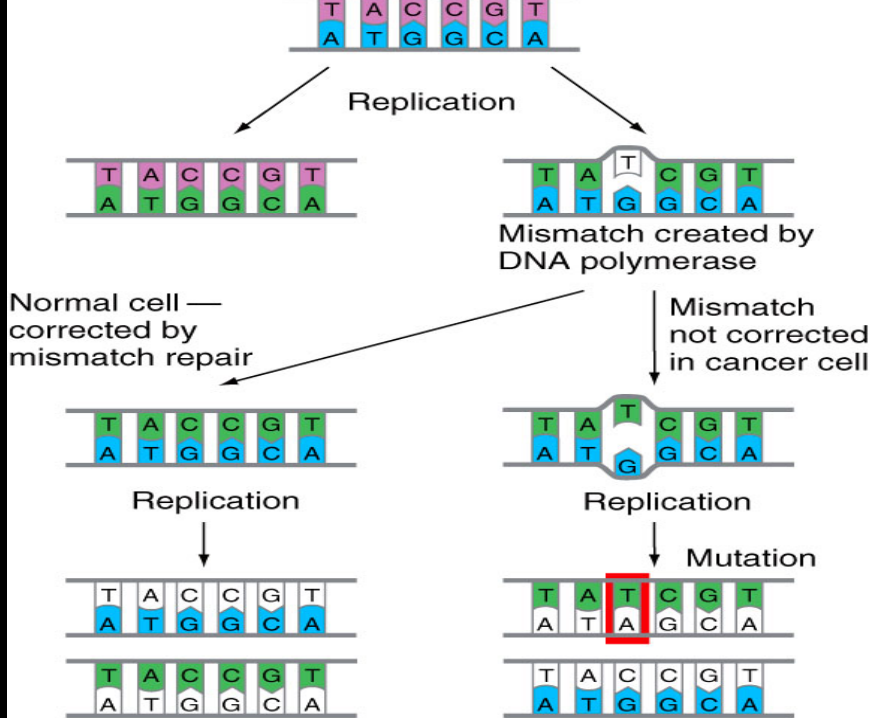
Molecular
epidemiology

The genetics

revolution



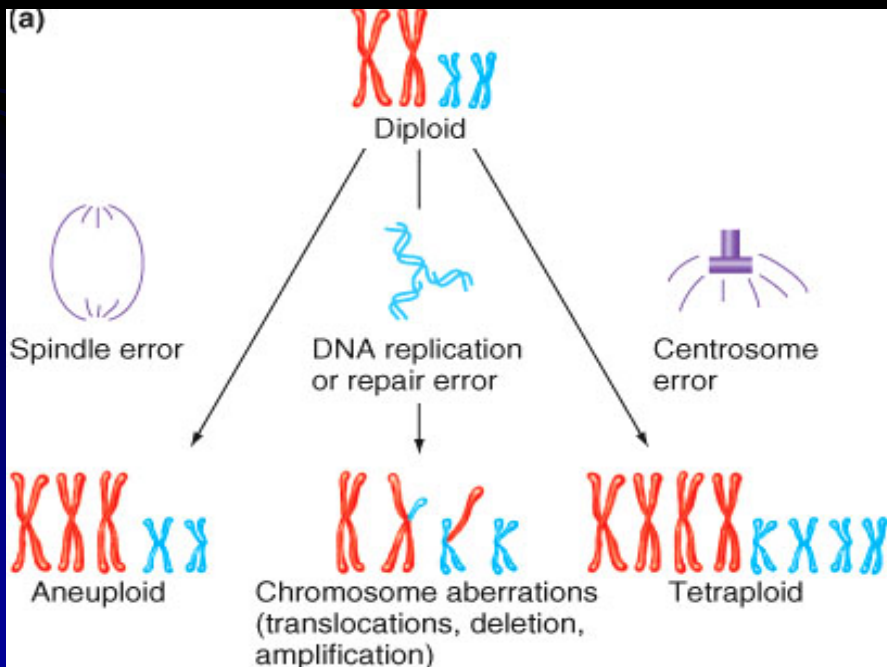
Cancer



■ Genomic and karyotypic instability:

■ Defects in DNA replication machinery – lost capability to reproduce genome faithfully

■ Increase rate of chromosomal aberrations – fidelity of chromosome reproduction greatly diminished



What is the important information?

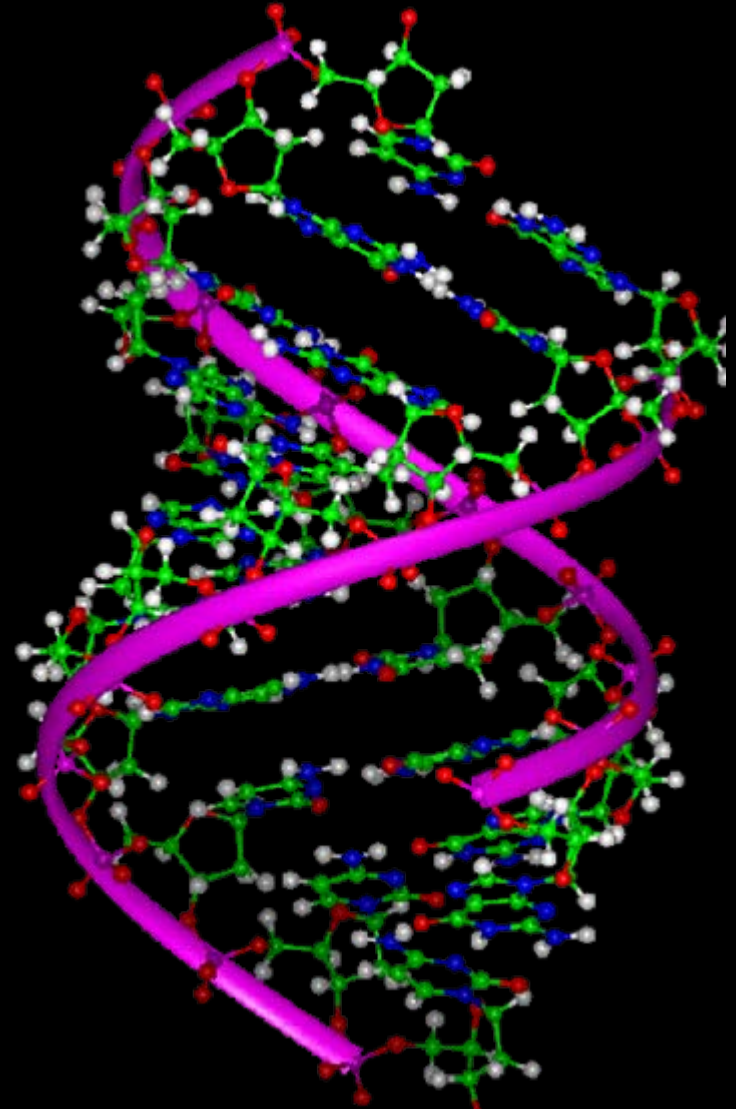
- **Number of affected relatives**

vs.

Small families

vs.

Population incidence

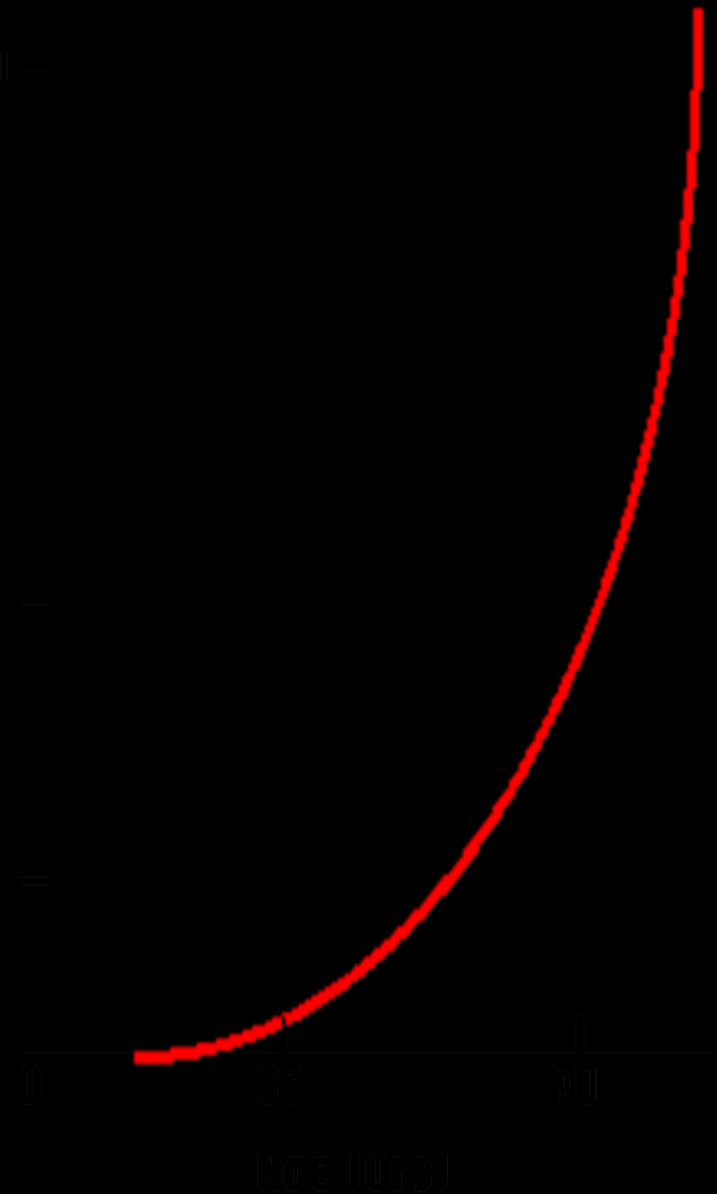


What is the important information?

Age at diagnosis

Early onset

compared to typical
age of onset



What is the important information?

Specific constellation of cancers

Leading Sites of New Cancer Cases



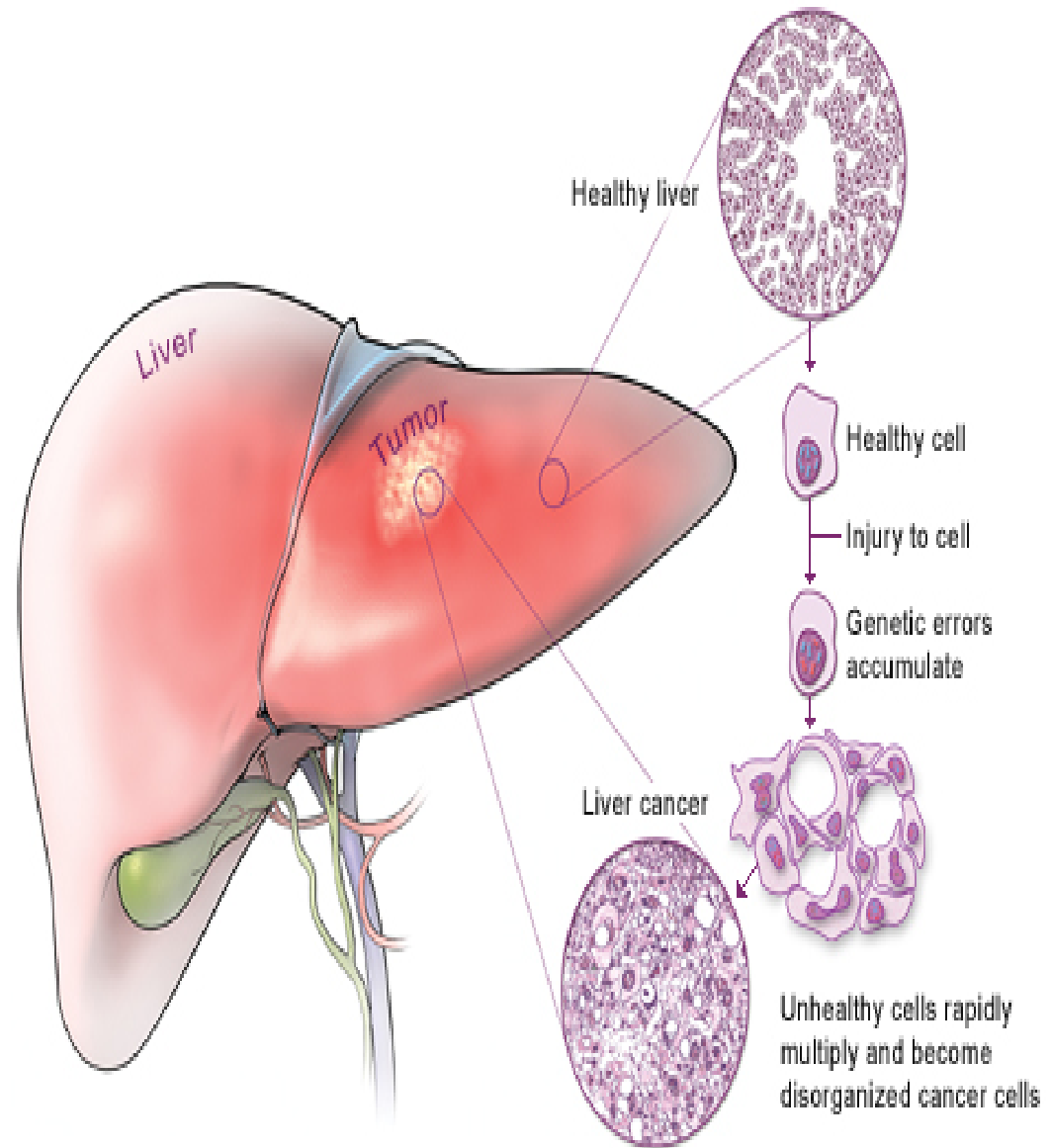
Adapted from American Cancer Society, Inc., Cancer Facts and Figures 2003

What is the important information?

Bilaterality

Multiple primary tumors

Rare cancers

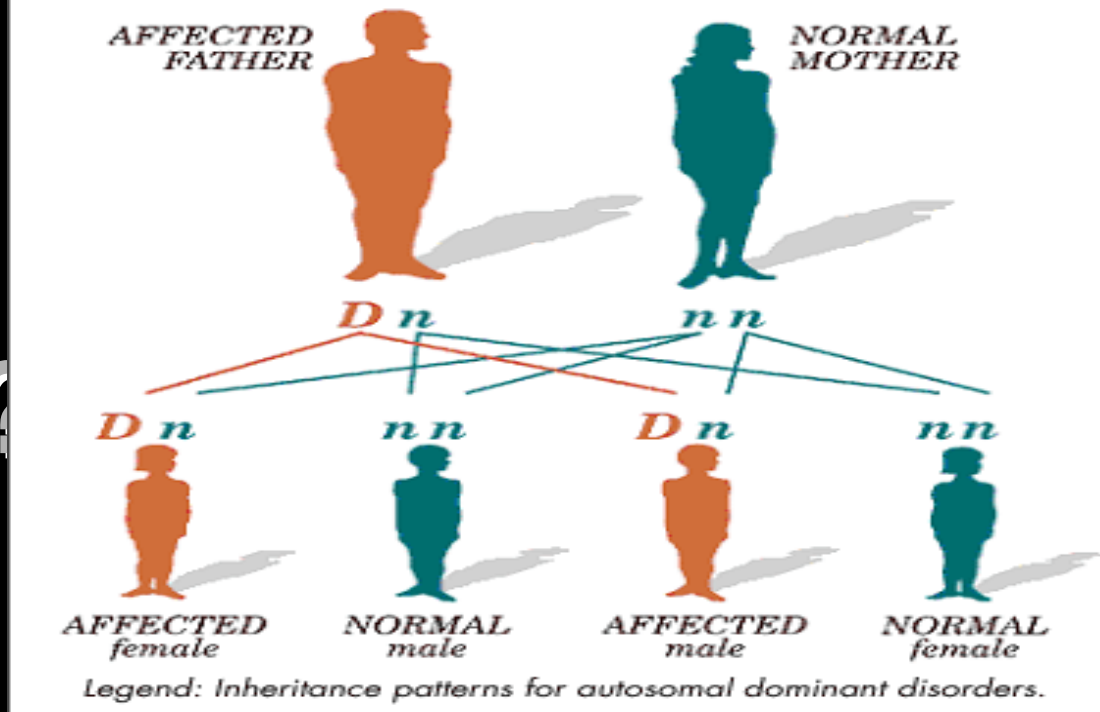


What is the
important
information
?

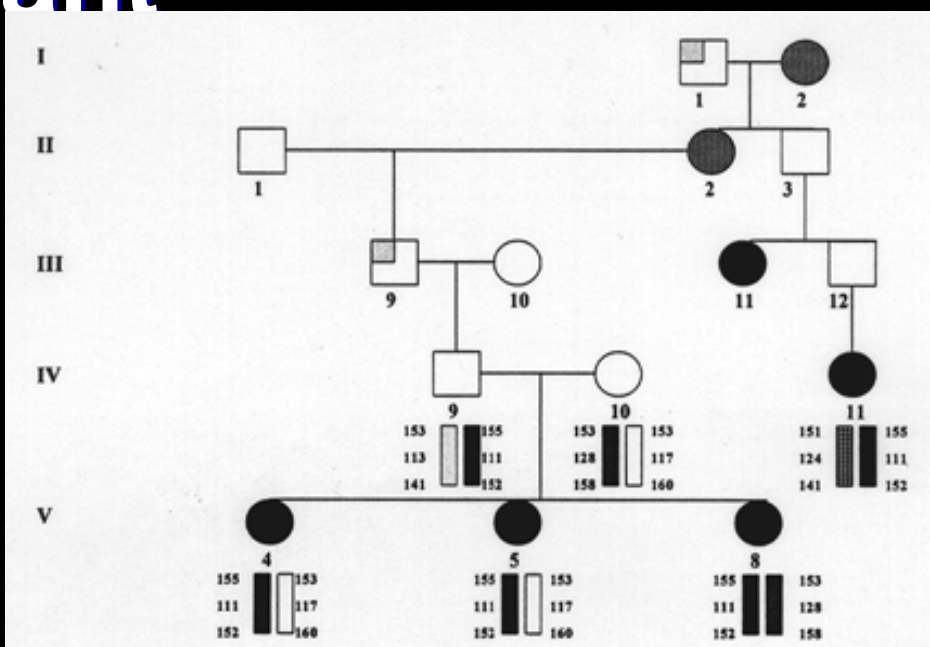
Ethnic
background



What is the important information?



Autosomal Dominant transmission vs. Sex limited expression



What proportion of cancer is due to “cancer-causing genes”?

- Can you see what is wrong with this question?
- Only ~10% of cancers are believed to be related to specific “cancer causing” genes, e.g. BRCA1;
- Of these, most are “interactive”, accounted for by e.g. Ca prostate (~40% of risk due to heritable factors; Ca Br. 27%; colorectal, 35%).
- Very few, rare cancers, e.g. retinoblastoma

Apoptosis

Healthy cell



Injury to cell

Genetic errors result from injury



Cell attempts to repair errors



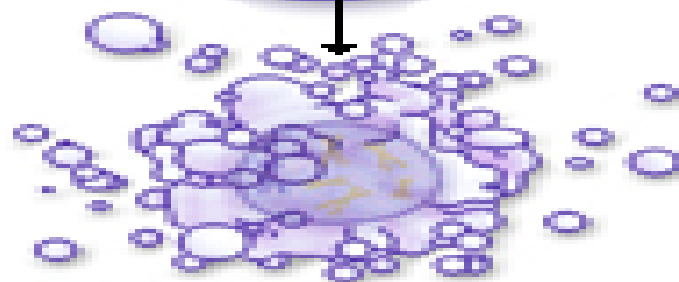
All errors repaired

Some errors remain



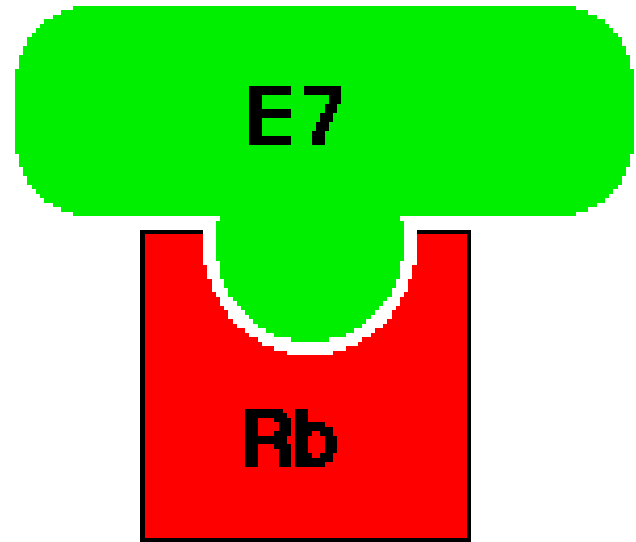
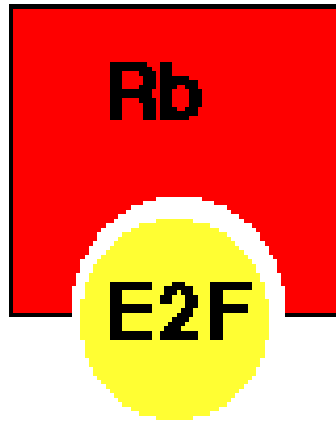
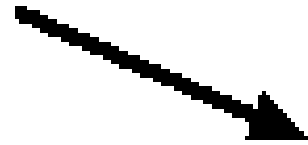
Additional injury to cell

Cell unable to repair errors



Cell programs itself to die via apoptosis

E7 - an oncogene product of one of the human papilloma viruses



DNA

DNA

Promoters

Promoters

Promoters "off";
cell remains in G0

Promoters "on";
cell begins mitosis

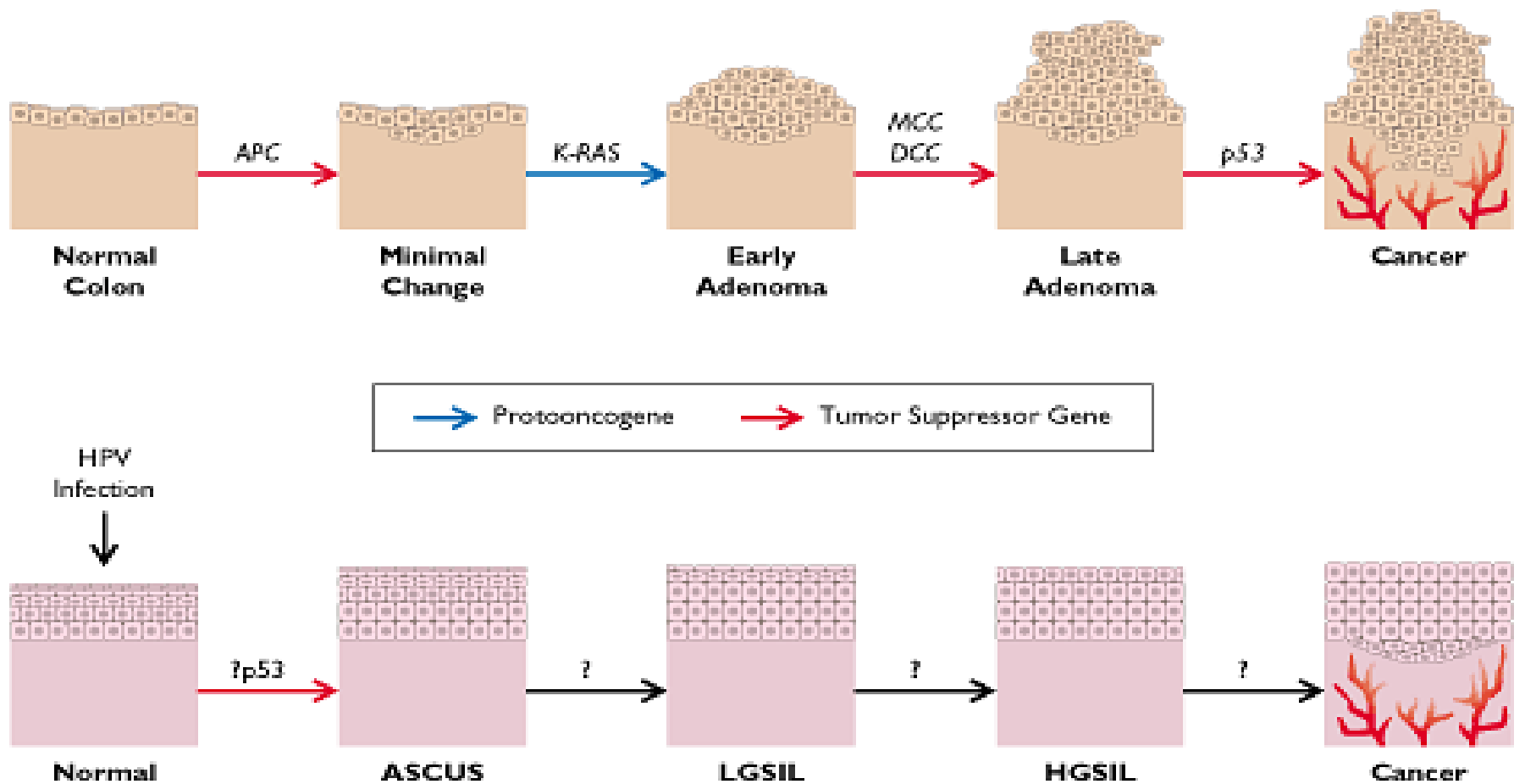


Illustration: Seward Hung

Figure 4. Mutation sequence responsible for the eventual emergence of a malignancy is implied by the succession of histologic changes seen in the evolution of colon and cervical cancer. In colon cancer (top), the mutated genes are at least partly known. With the exception of *k-ras*, a protooncogene, they are all tumor suppressor genes. In cervical cancer (bottom), the genes

remain largely unknown. On the other hand, the primary cause of cervical cancer is now recognized to be a viral pathogen. Infection by human papillomavirus (HPV) suppresses the protein encoded by *p53*—the functional equivalent of “hits” derailing both alleles of the gene itself. In colon cancer, *p53* knockout is a late event; in cervical cancer it may be the earliest.

Tumor Suppressor Gene Proteins

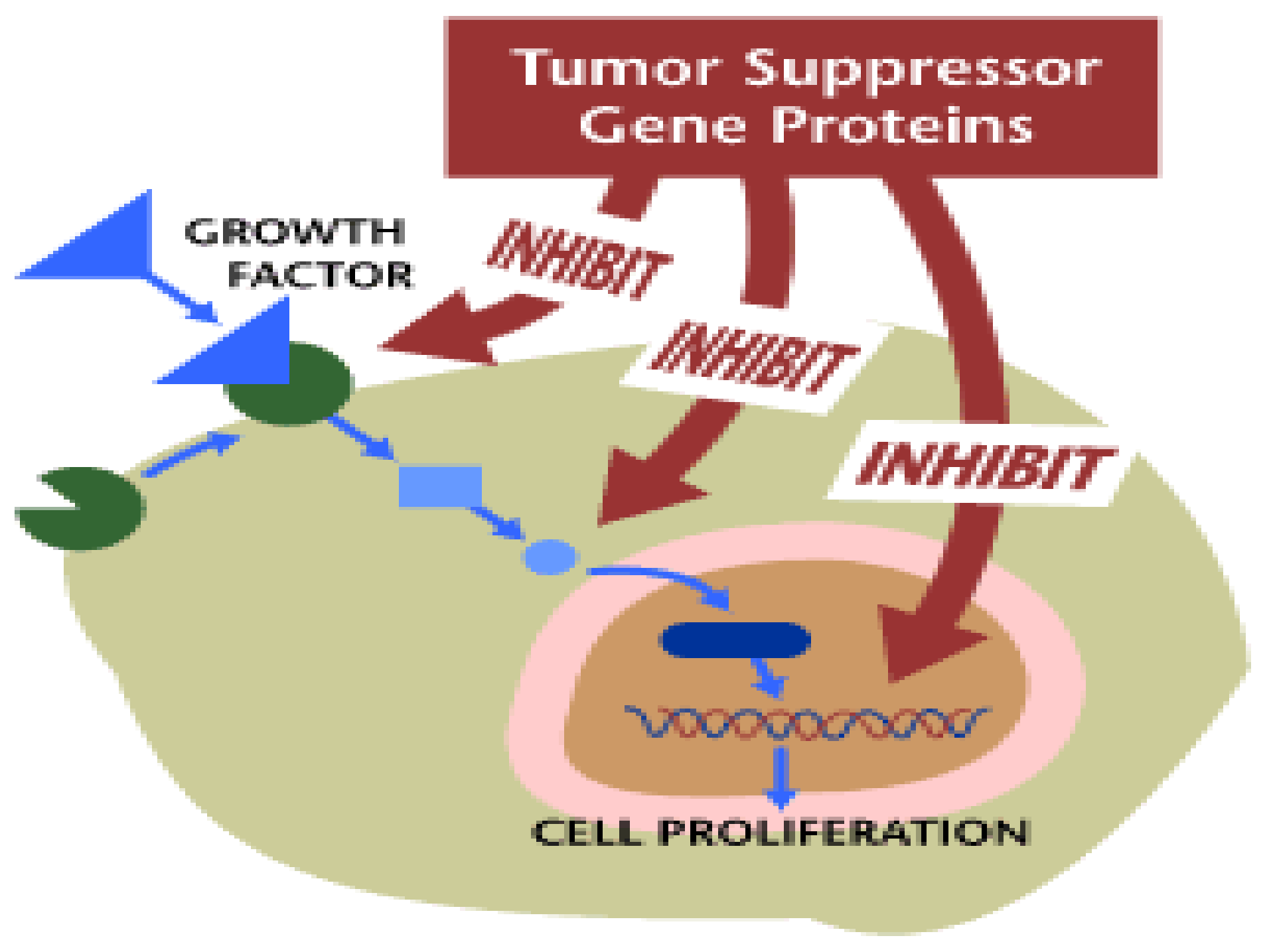
GROWTH
FACTOR

INHIBIT

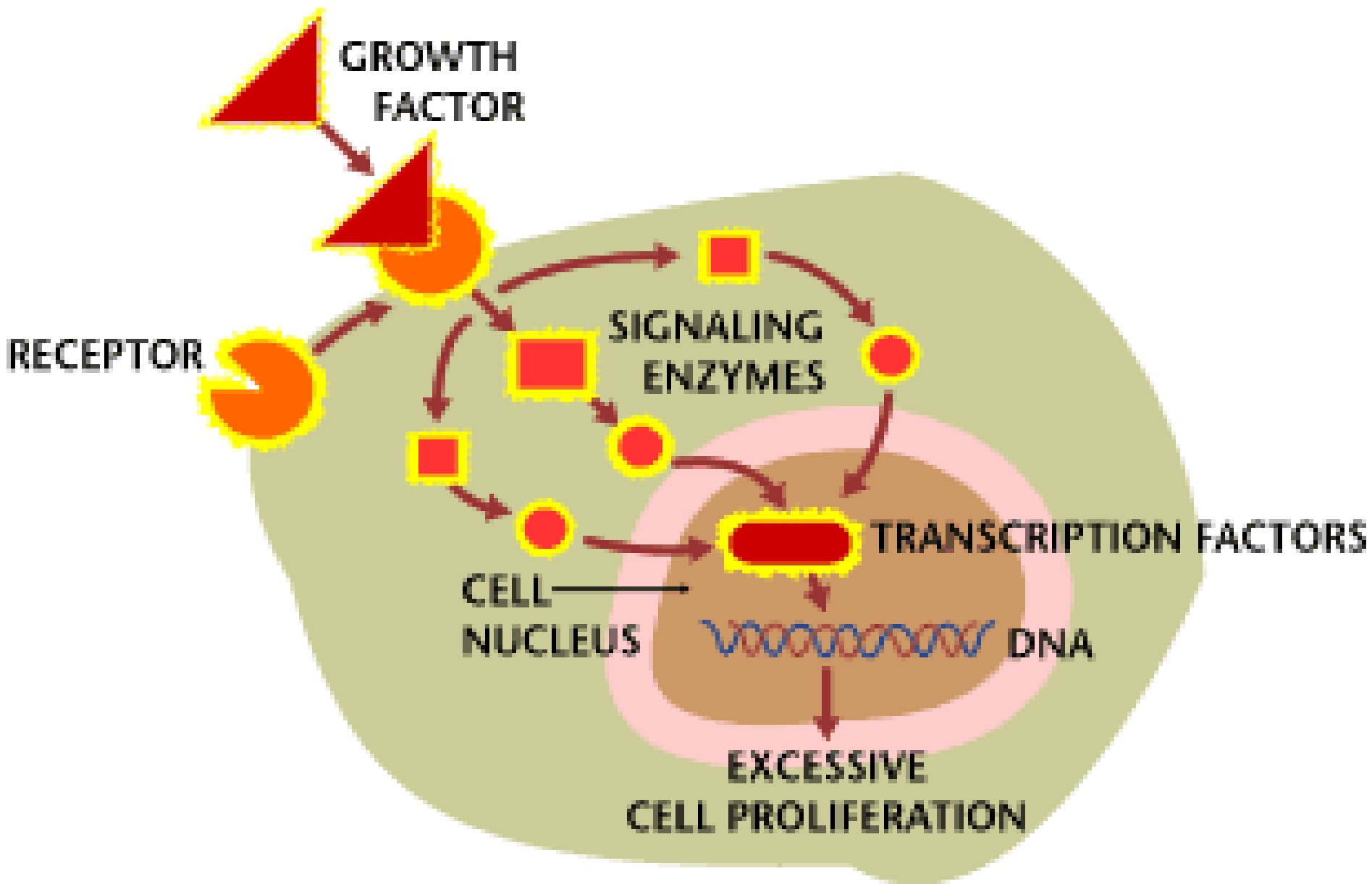
INHIBIT

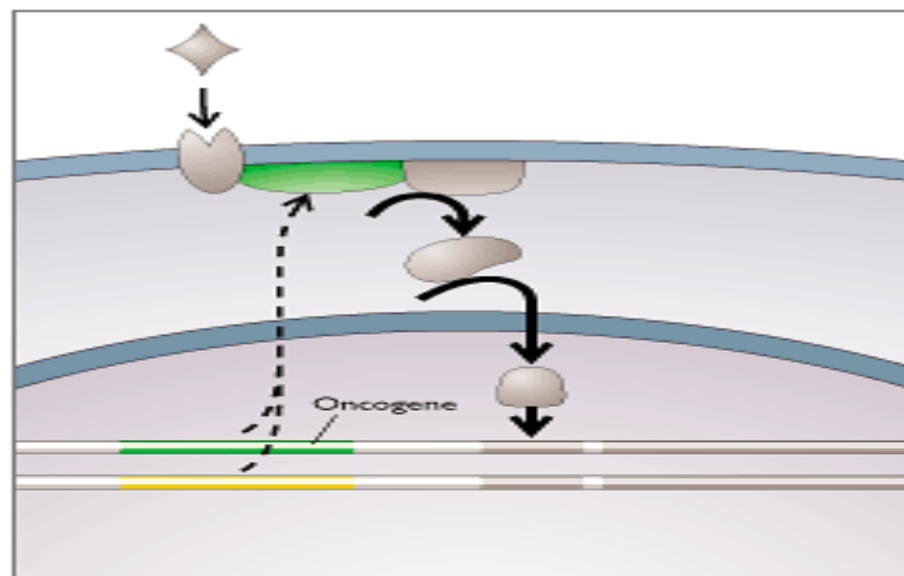
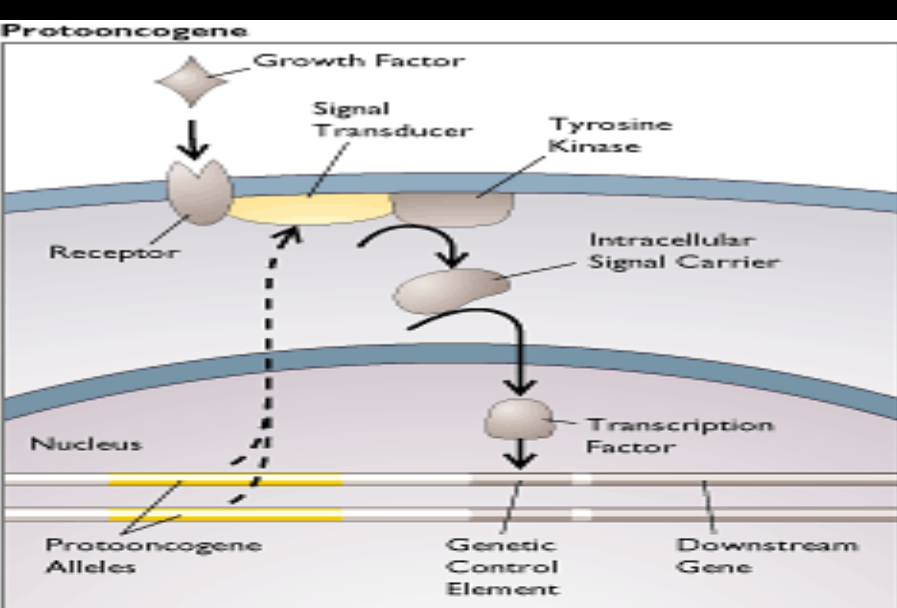
INHIBIT

CELL PROLIFERATION



Hyperactive growth-control pathway





Tumor Suppressor Gene

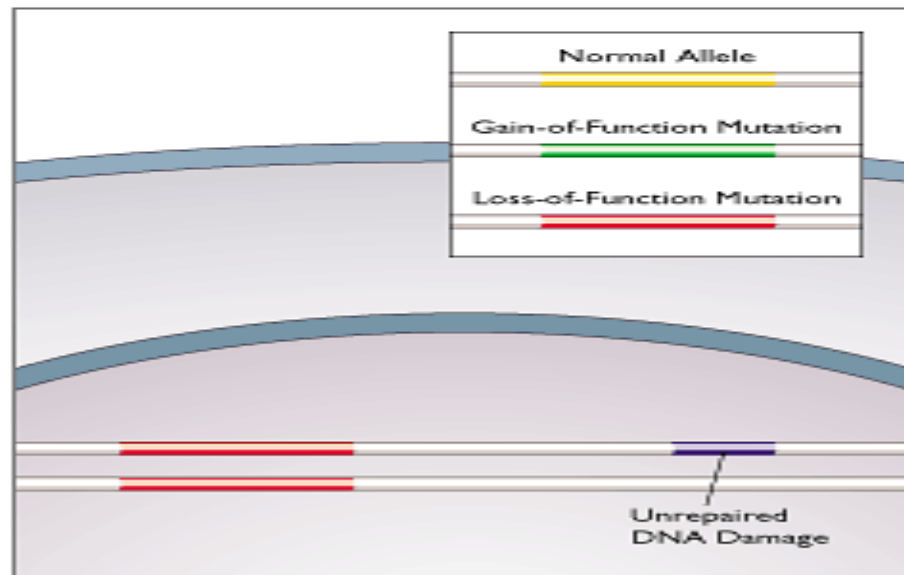
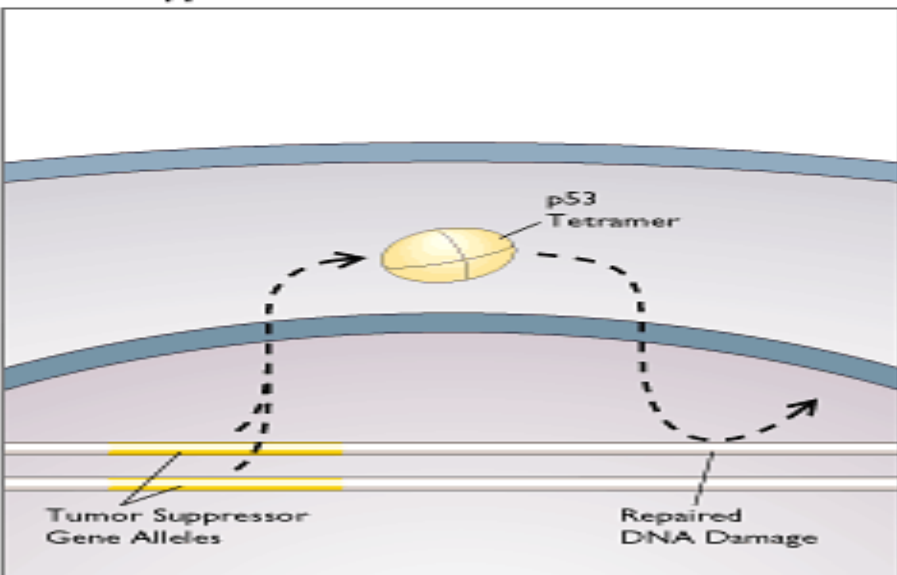
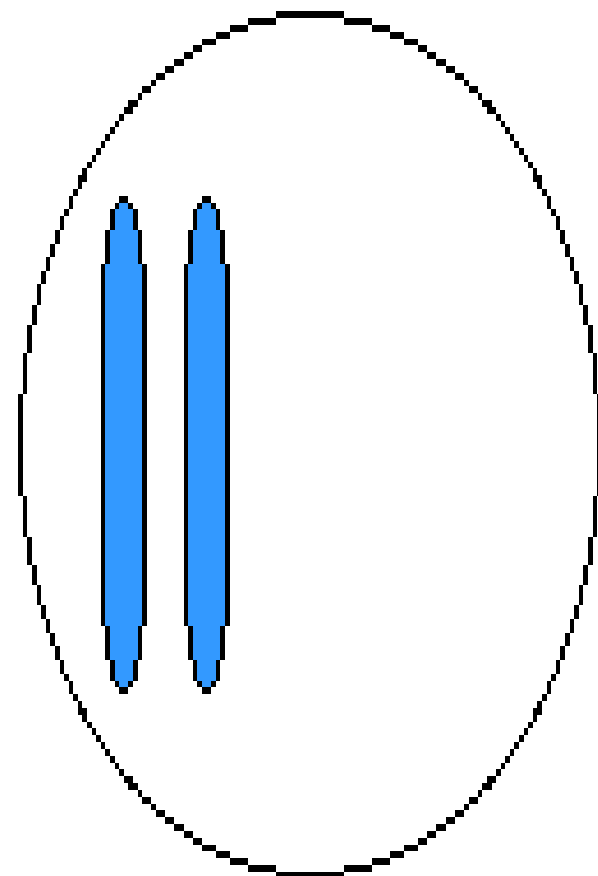
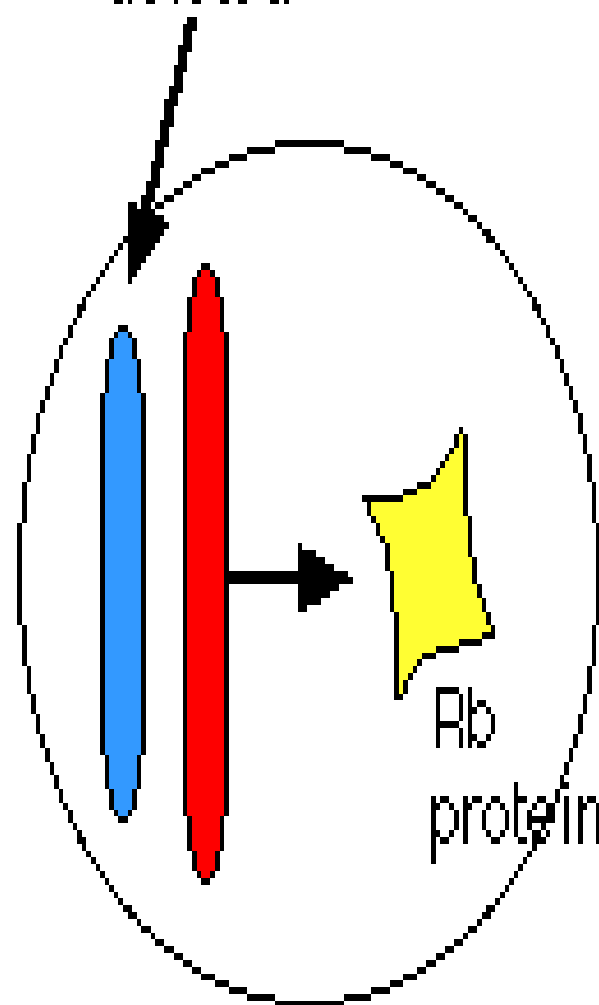
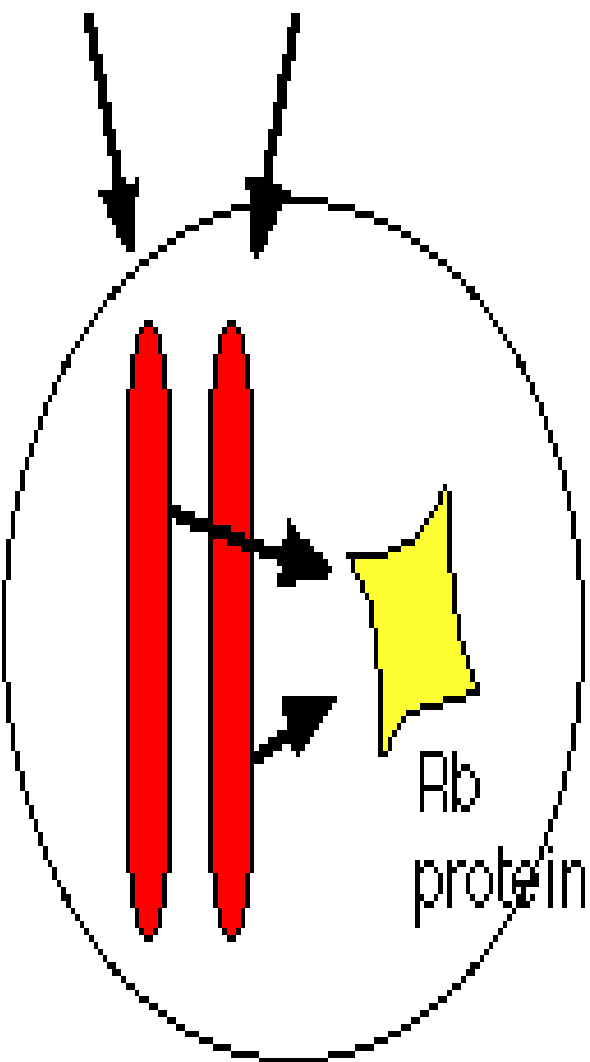


Figure 2. Genes that contribute to oncogenesis are of two types, protooncogenes and tumor suppressor genes. Normally, the alleles of a protooncogene (top left) specify constituents of signal pathways leading from external growth stimuli to growth-related genes in the cell nucleus. The example shown is a membrane-bound signal transducer. In oncogenesis, a mutation makes one allele a hyperfunctional oncogene (top right). Normally, the al-

leles of a tumor suppressor gene (bottom left) specify proteins involved in DNA maintenance. The example shown is the p53 tetramer, which recognizes genomic damage and promotes repair (or, failing that, cell suicide). In oncogenesis, mutations make both alleles nonfunctional (bottom right). The only exception (not shown) is a tumor-suppressor-gene mutation that makes the product of one allele block that of the other allele.

Normal chromosome 13

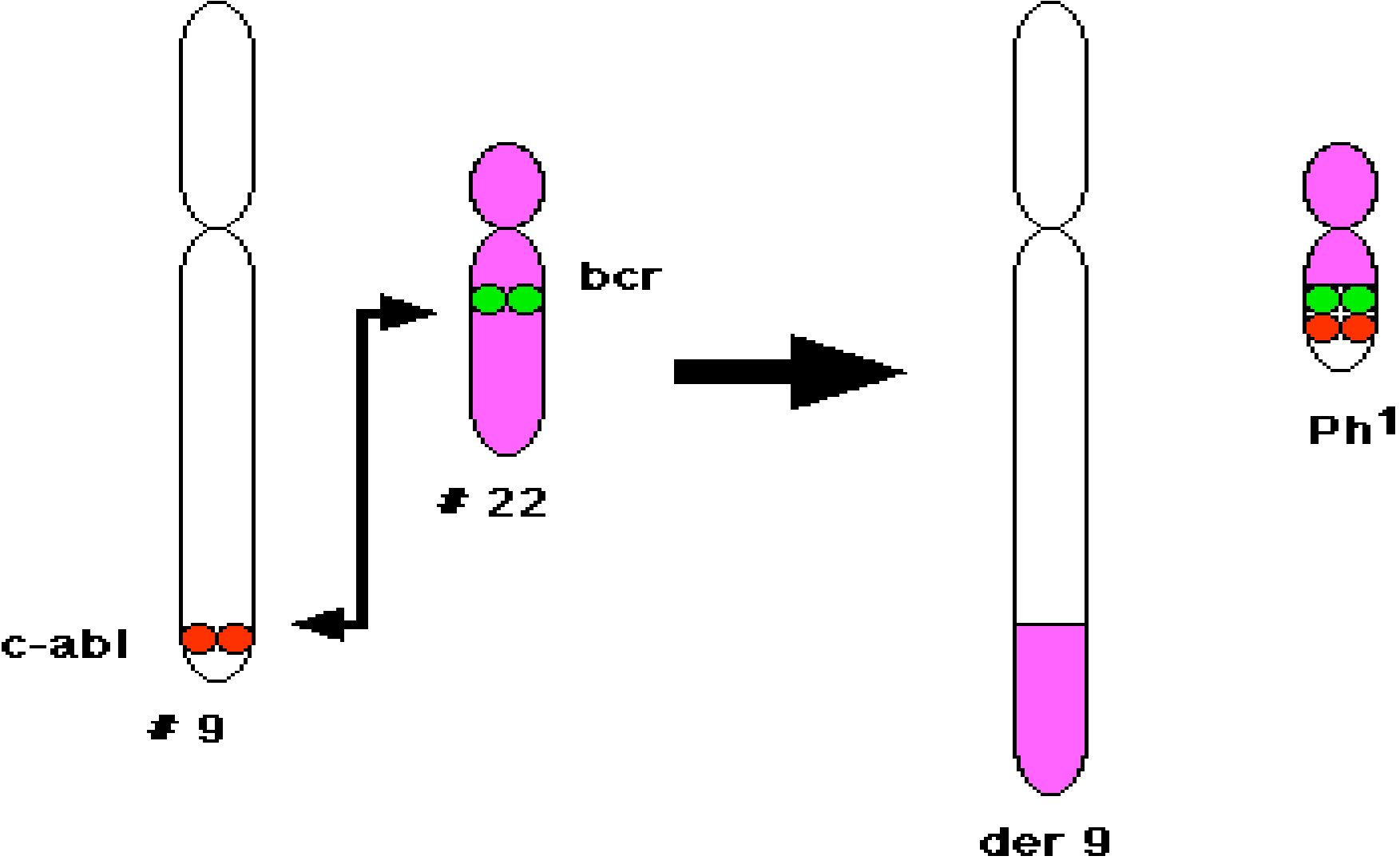
Chromosome 13 with RB locus
deleted



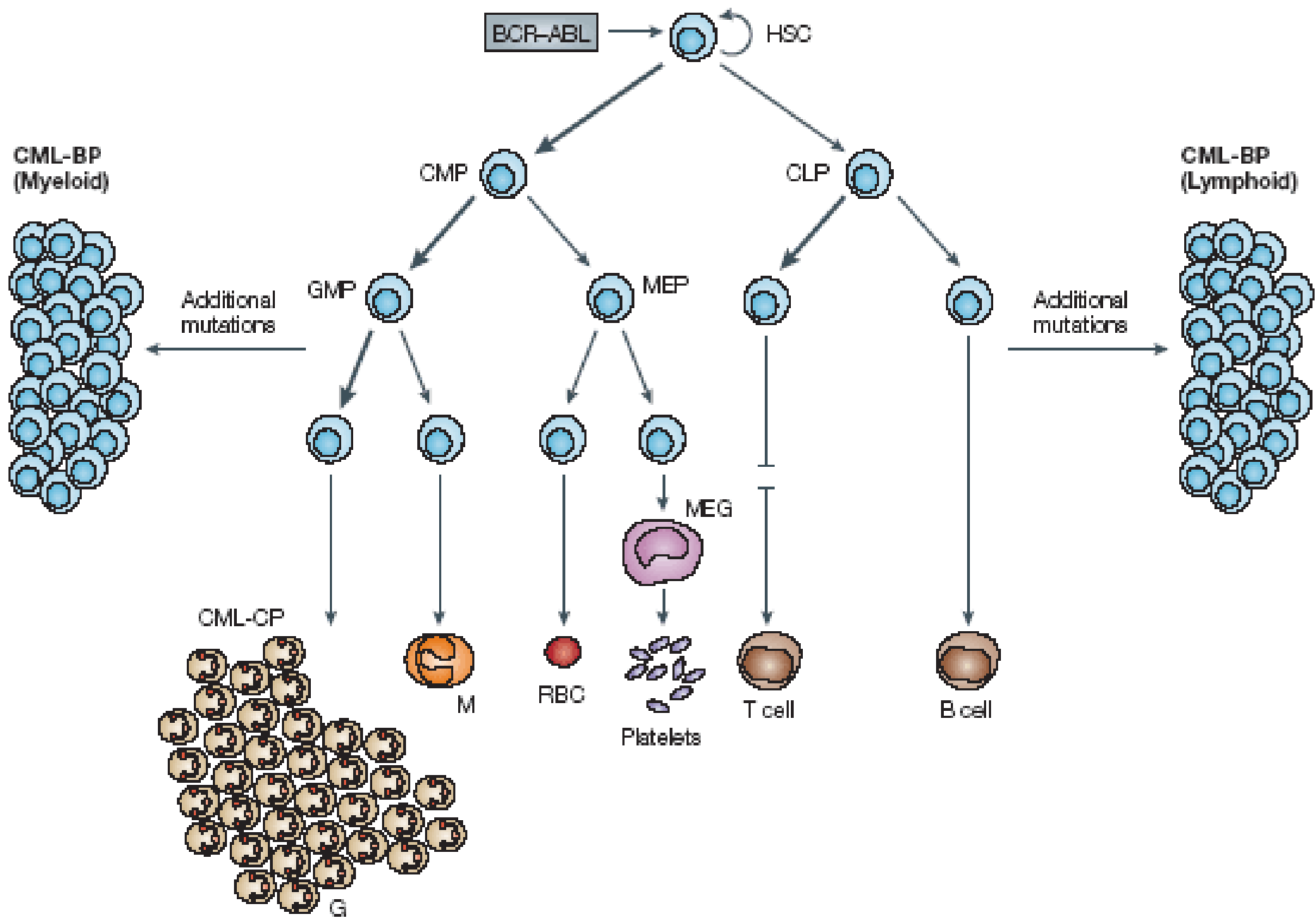
Normal retinal
cell

Retinal cell at
risk

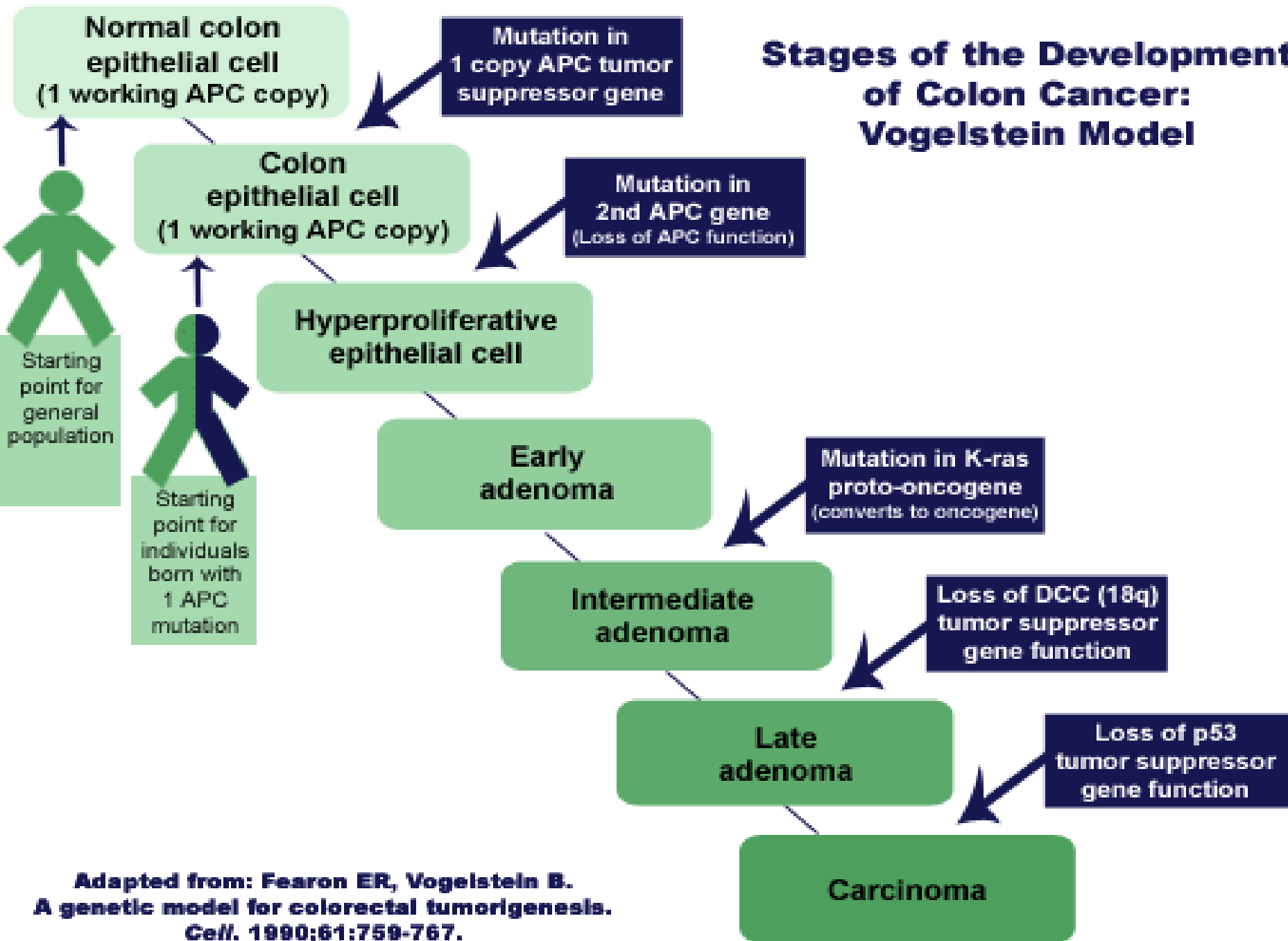
Retinoblastoma
cell



Reciprocal translocation between one # 9 and one #22 chromosome forms an extra-long chromosome 9 ("der 9") and the Philadelphia chromosome (Ph¹) containing the fused abl-bcr gene. This is a schematic view representing metaphase chromosomes.

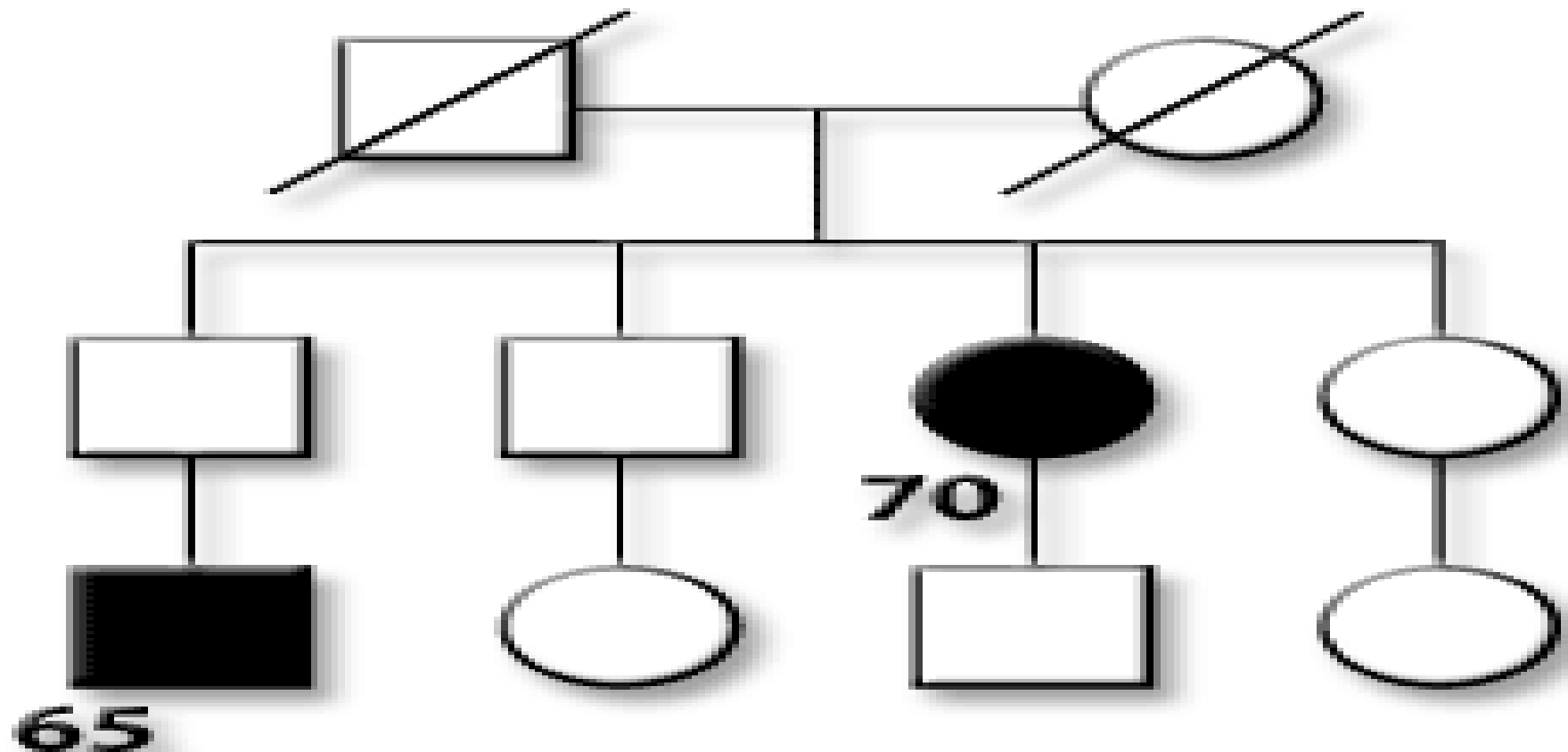


Stages of the Development of Colon Cancer: Vogelstein Model

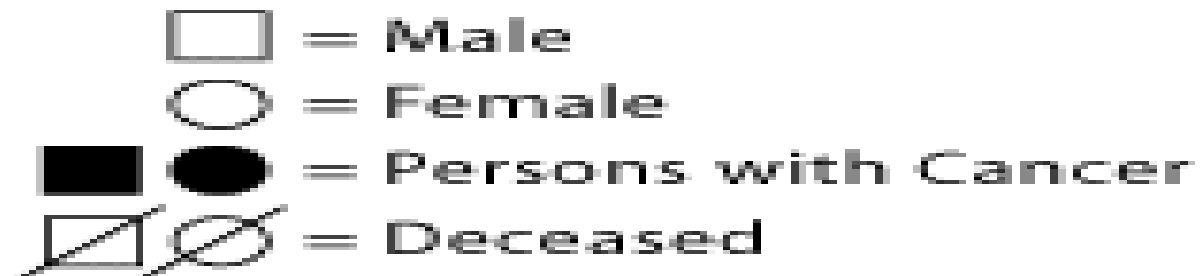


Adapted from: Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. *Cell*. 1990;61:759-767.

Familial Cancer History





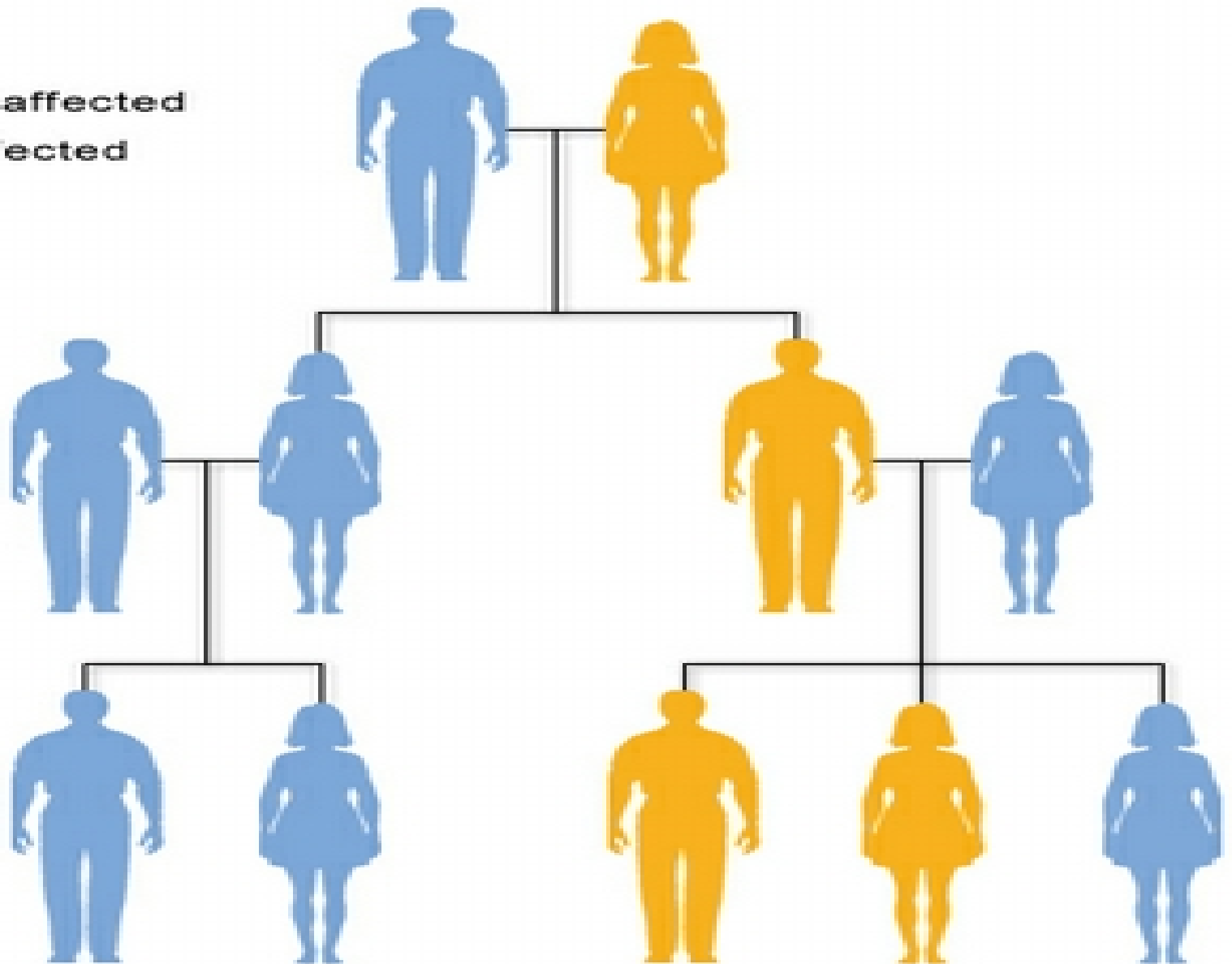
Key:



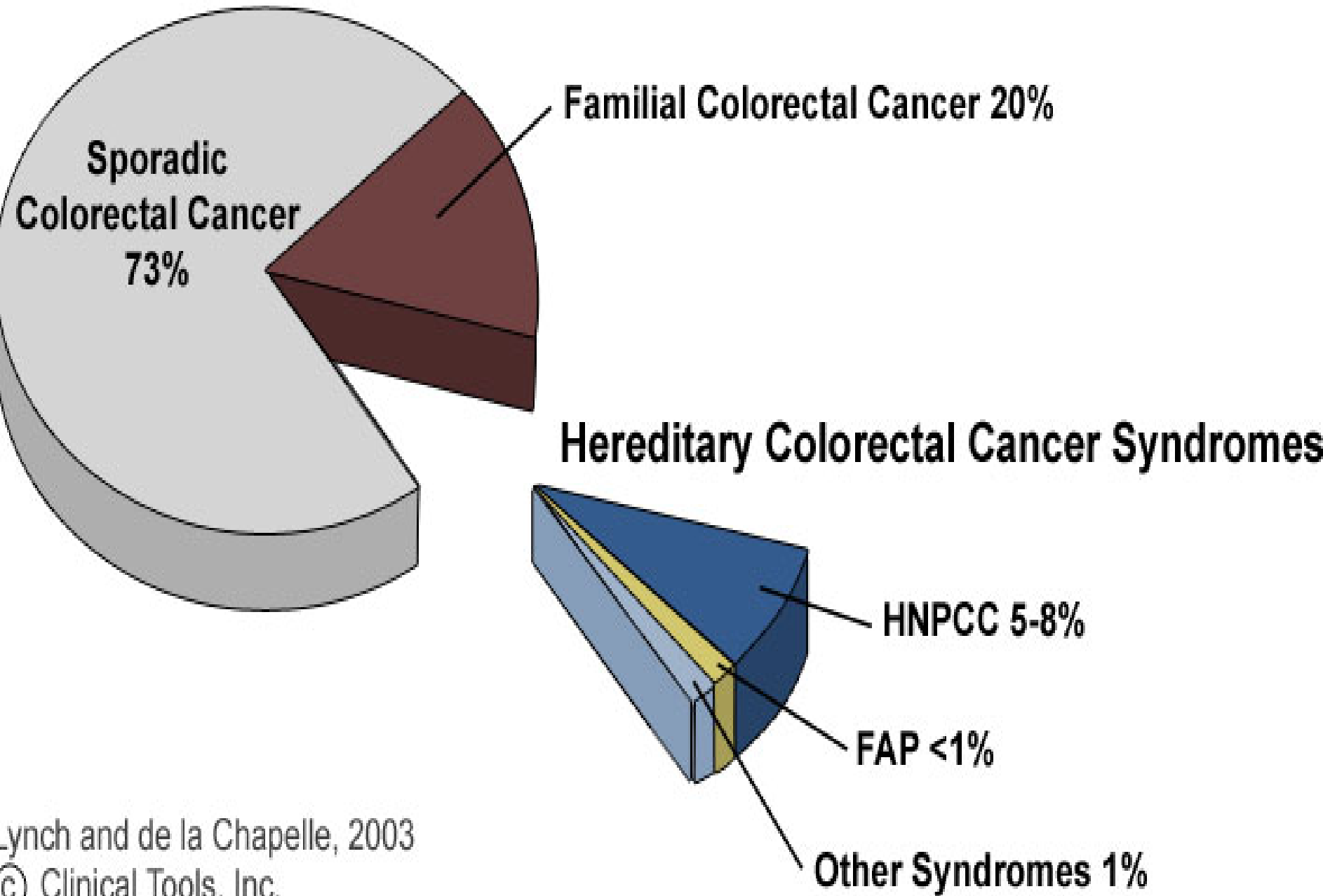
Numbers are ages of onset of cancer.

Condition affecting members of a family

 unaffected
 affected



Contribution of Familial and Hereditary Factors to Colorectal Cancer Cases



Lynch and de la Chapelle, 2003
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Some General Guidelines for Family History Taking



- Use standardized pedigree symbols when constructing a pedigree
- Elicit a three generation family history
- Document ethnicity
- Use a legend to show or explain any symbols
- Ask about adoptions
- Ask about consanguinity (Are you and your partner related in anyway other than marriage?)

Family history

- **Family history of a disease, e.g. cancer, is seen as indicating “high-risk” status.**
- **But...**
 - **those dying younger have less chance to manifest disease, so offspring have “less” family history**
 - **those living longer more likely to develop disease, but longevity ignored as benefit to offspring.**

Benefits of genetic testing in high risk patients

- Patients with a family history of cancer can have a predictive test to tell whether they carry the normal or abnormal parental gene
- If normal gene: can be reassured
- Abnormal gene carriers can be placed in a prevention programme
- Affected patients can have tailored screening and treatment

During the last 5 years

- **Early (Stage I) ovarian cancers have been detected**
- **Early breast cancers have been detected**
- **Several bowel polyps have been removed**
- **Over 200 patients have had genetic testing and have been reassured**
- **Over 200 patients have been found to carry a breast, ovary, bowel or other familial cancer gene and have been placed in a prevention programme**

Challenges - next 20 years

- **Even more genes for breast and colon cancer in patients with medium risk family history**
- **gene tests for other hereditary cancers including testicular, thyroid, prostate, endometrial cancers**
- **Solid tumour work – haematological genetics**
- **Costs of screening in cancer units (balanced by more efficiency)**

MUCHAS

GRACIAS

