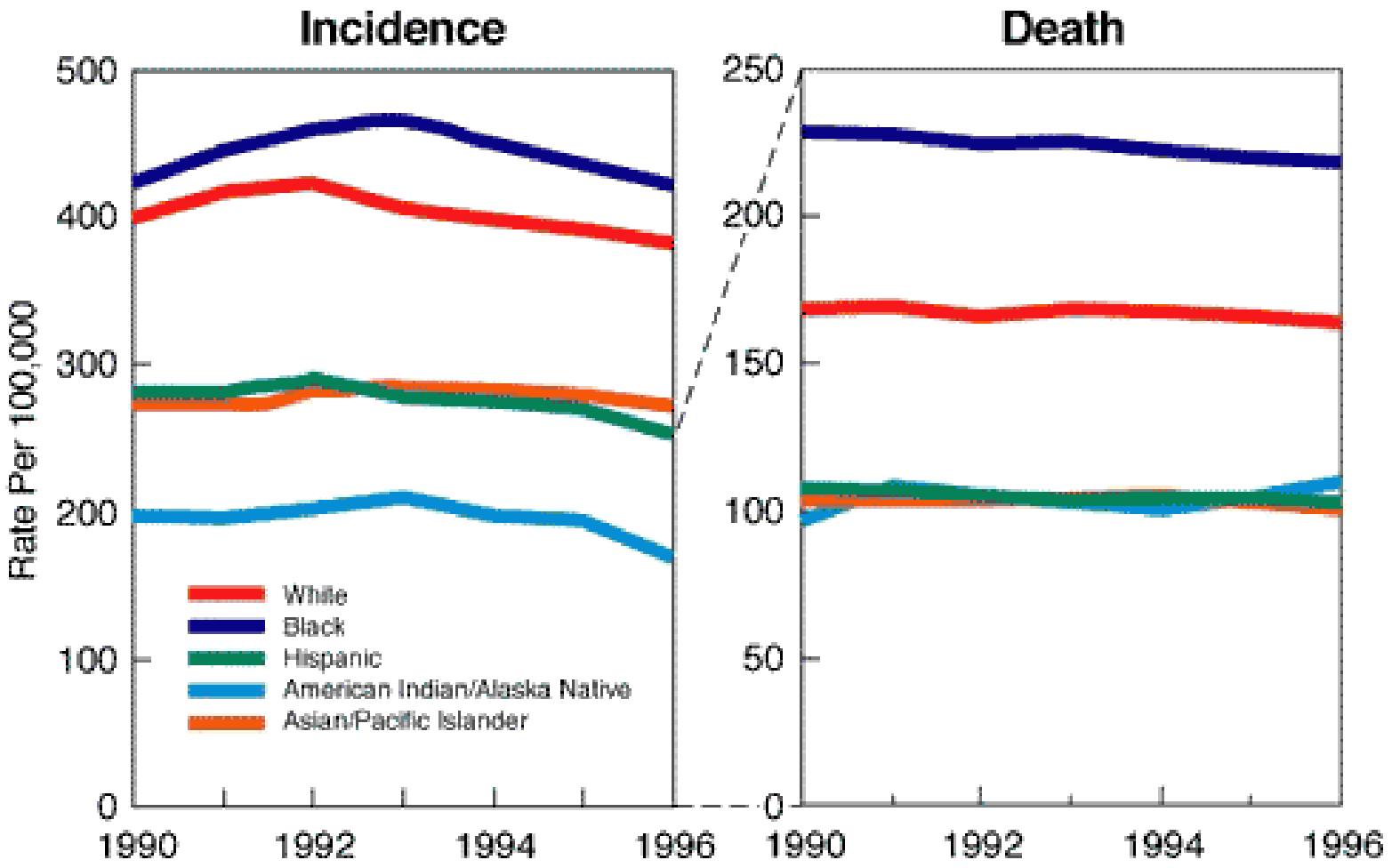
Mechanisms of Mutagenesis & Carcinogenesis

Lecturer: Pr. Aitkhazha Bigaliyev

Cancer Incidence and U.S. Death Rates*, 1990-1996



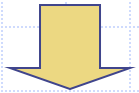
*Rates are age-adjusted by 5-year age groups to the 1970 U.S. standard million population
Source: SEER and NCHS data

Maintenance of homeostasis

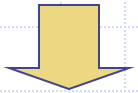
- Adult human maintains ~10^{15} cells
- Stem cells undergo ~10^{12} divisions per day
- There is a balance between cell birth and cell death
- Random mutations disrupt homeostasis

Molecular basis for cancer progression

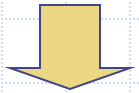
DNA damage



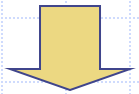
Failure to repair damage



Failure to destroy cells with DNA damage

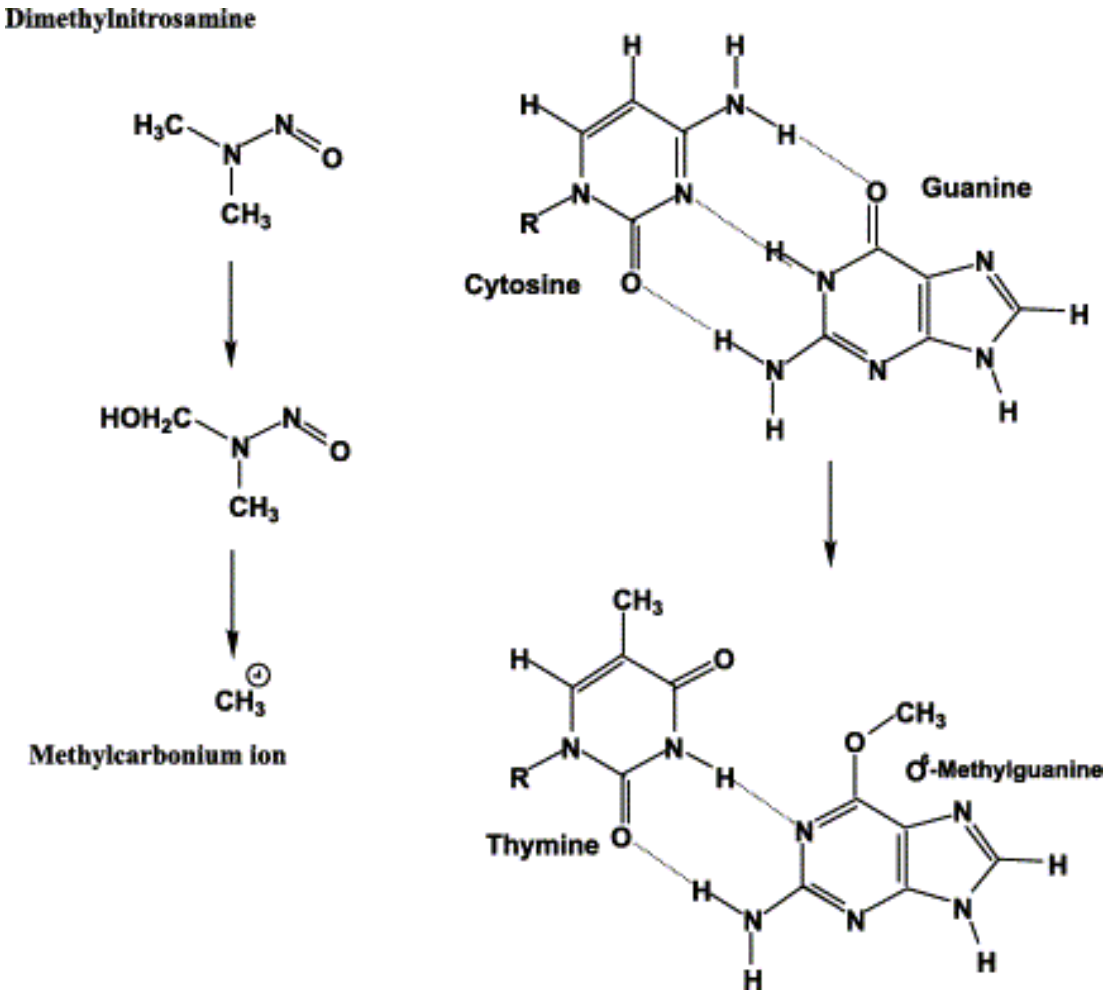


Mutation



Selection advantage

Example of DNA damage



From Bertram, Molecular Aspects of Medicine 21, 2001, 161-223

List of carcinogens

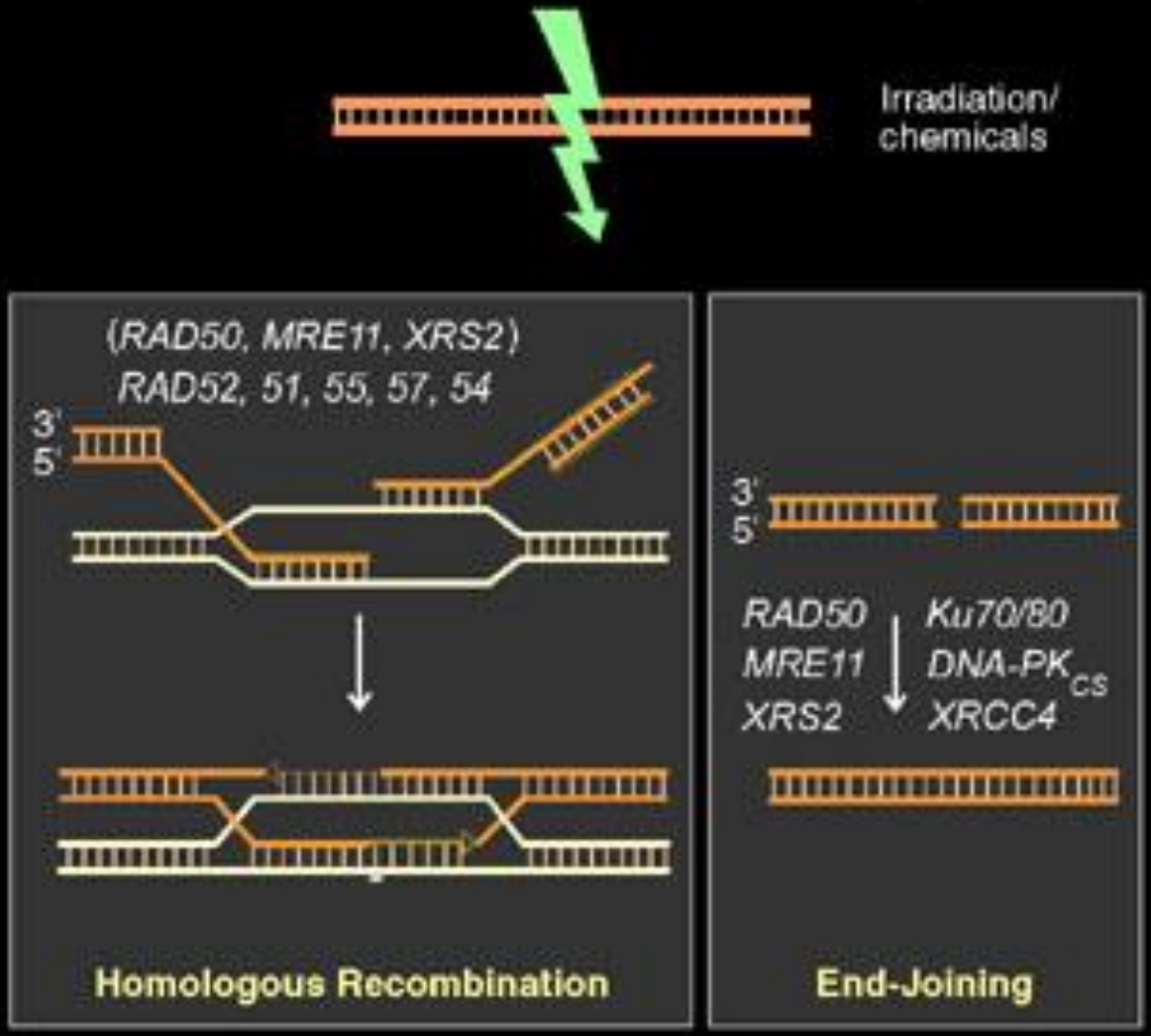
Chemical

- Asbestos
- Arsenic
- Chromium
- Polyaromatic hydocarbons
- dichlorodiphenyl-trichloroethane (DDT)

Physical

- Gamma radiation
- UV light
- Radon
- X-rays
- Viruses*

Double-Strand Break Repair Pathways in Eukaryotes



http://www.eur.nl/fgg/ch1/gen_research/dbr-man.html

Hereditary form of colon cancer

Case 1:

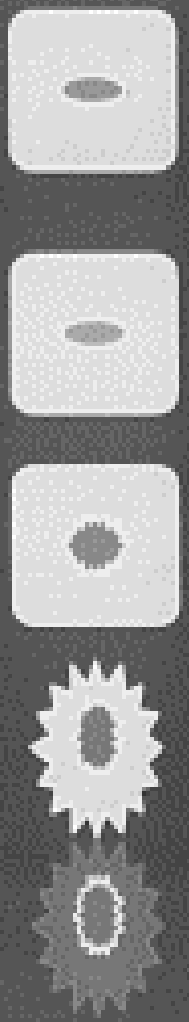
Beth M.'s father died of colon cancer, as did her grandmother. Now two of her brothers, both in their 40's, have been diagnosed with colon cancer. Beth, age 37, feels a curse is hanging over her family and is worried about her future and that of her children.

Case 2:

Paul C. was 35 when his doctor told him the grim news: he had advanced colon cancer. As far as he knew, Paul had no family history of the disease. But after checking, Paul learned that several aunts and uncles had died of colon cancer at an early age.

Diagnosis:	hereditary nonpolyposis colorectal cancer (HNPCC)
Frequency:	1 in 6 colorectal cancer cases
Cause of the disease:	*hMLH1* or *hMSH2* mutations. Genes responsible for DNA mismatch repair

Multistep Carcinogenesis: requirement for DNA damage and proliferation



Rare mutations [10^{-6}] in a large population [10^{8}] of normal cells: initiation frequent.

Initiated cell- single mutation

Proliferation to 10^{6} cells required for second event

Preneoplasia

Proliferation to 10^{6} cells required for third event

Proliferation for 4th, 5th event, etc.

Cancer

Induction of mutator phenotype will increase mutation rate

From Bertram, Molecular Aspects of Medicine 21, 2001, 161-223

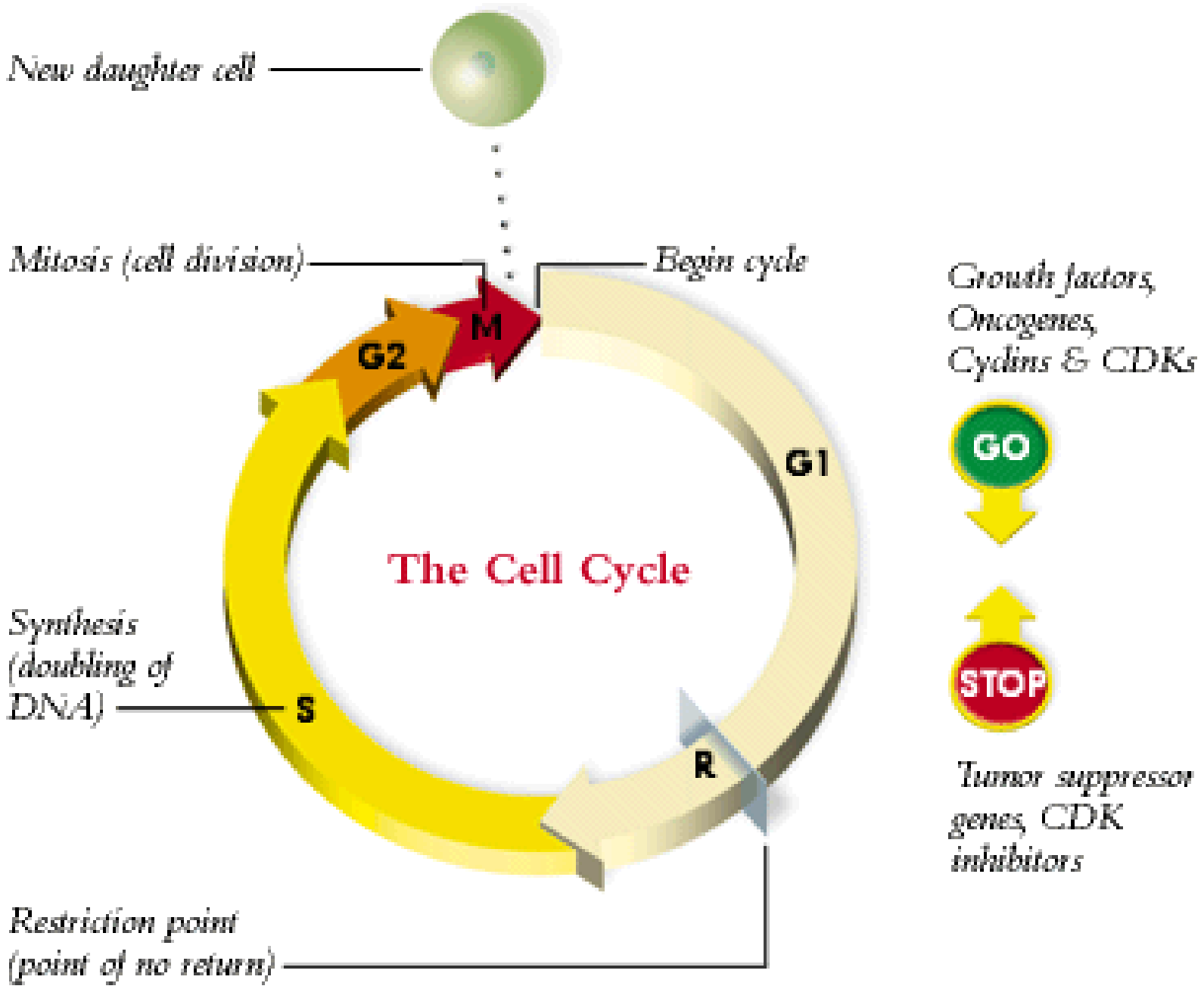
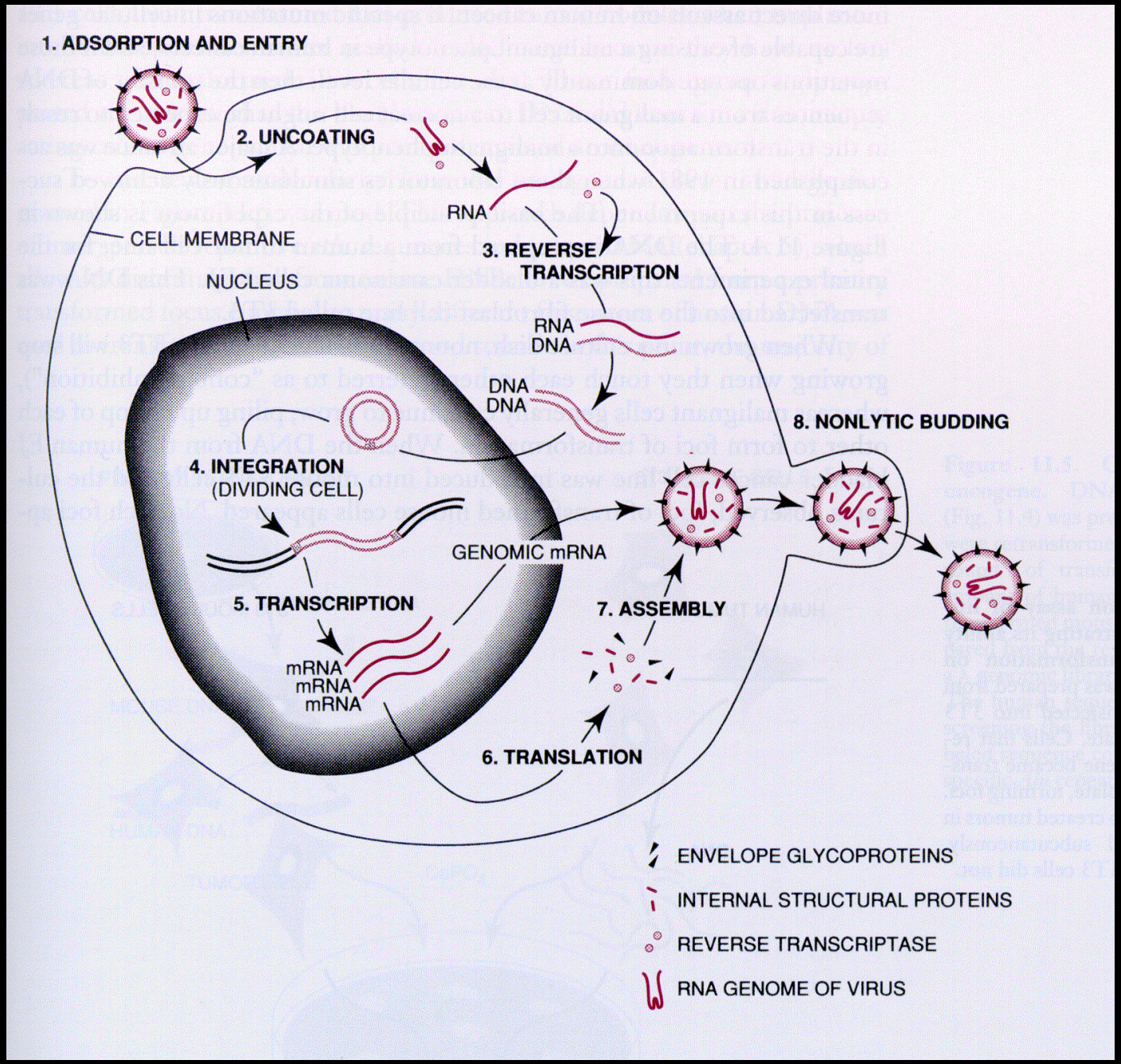


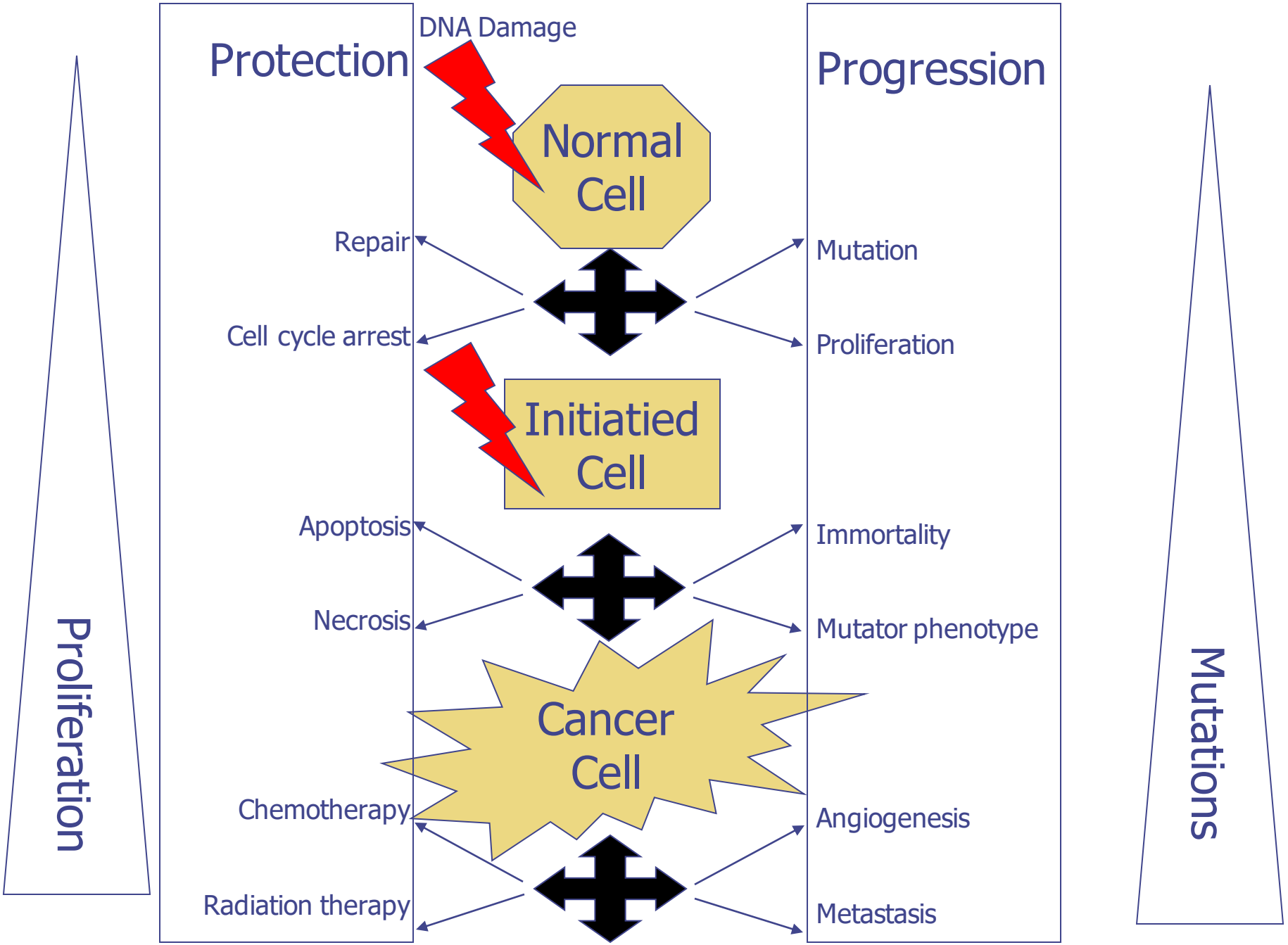
illustration by George Eade

http://www.hhmi.org/communic/annrep/research/regulate.htm

Viruses and cancer

- Viruses account for 15% of all cancers
- DNA viruses
  - Epstein-Barr virus
  - Human papilloma virus
  - Hepatitis B virus
- RNA viruses
  - HIV-1
  - HTLV-1
  - HTLV-2

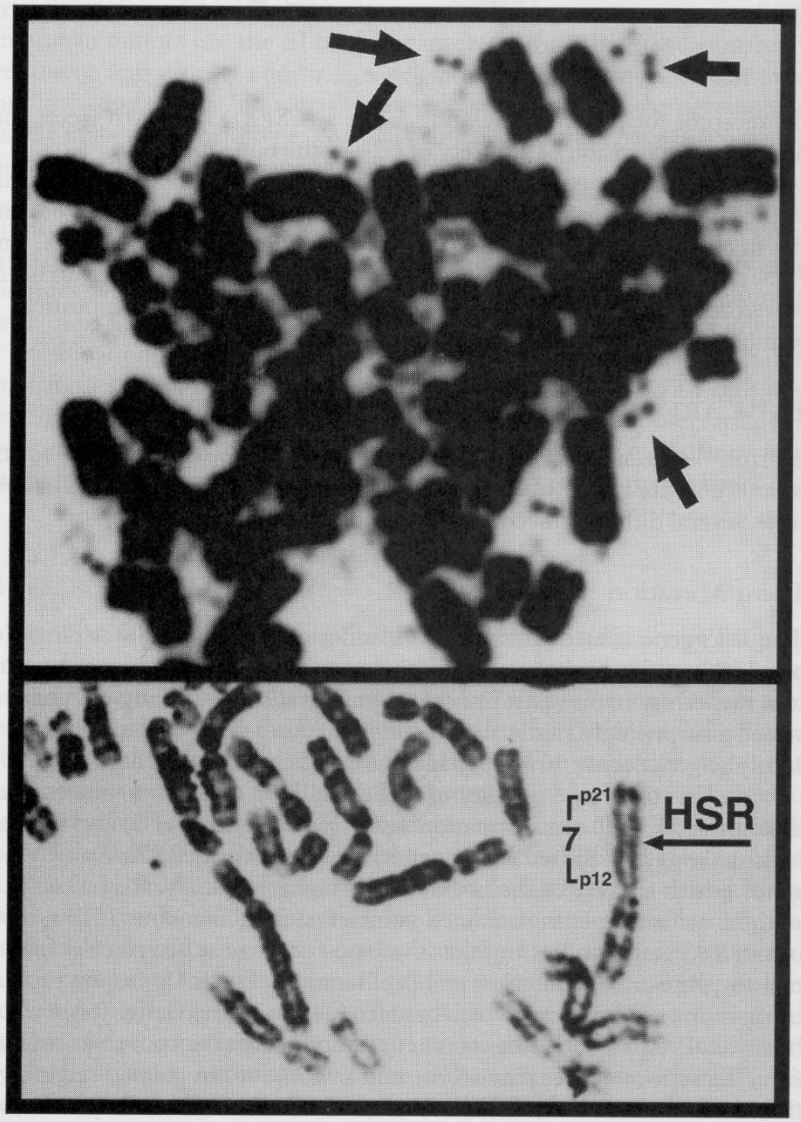

1. ADSORPTION AND ENTRY
2. UNCOATING
RNA
CELL MEMBRANE
3. REVERSE TRANSCRIPTION
NUCLEUS
RNA
DNA
DNA
DNA
8. NONLYTIC BUDDING
4. INTEGRATION
(DIVIDING CELL)
GENOMIC mRNA
5. TRANSCRIPTION
7. ASSEMBLY
mRNA
mRNA
mRNA
6. TRANSLATION
ENVELOPE GLYCOPROTEINS
INTERNAL STRUCTURAL PROTEINS
REVERSE TRANSCRIPTASE
RNA GENOME OF VIRUS



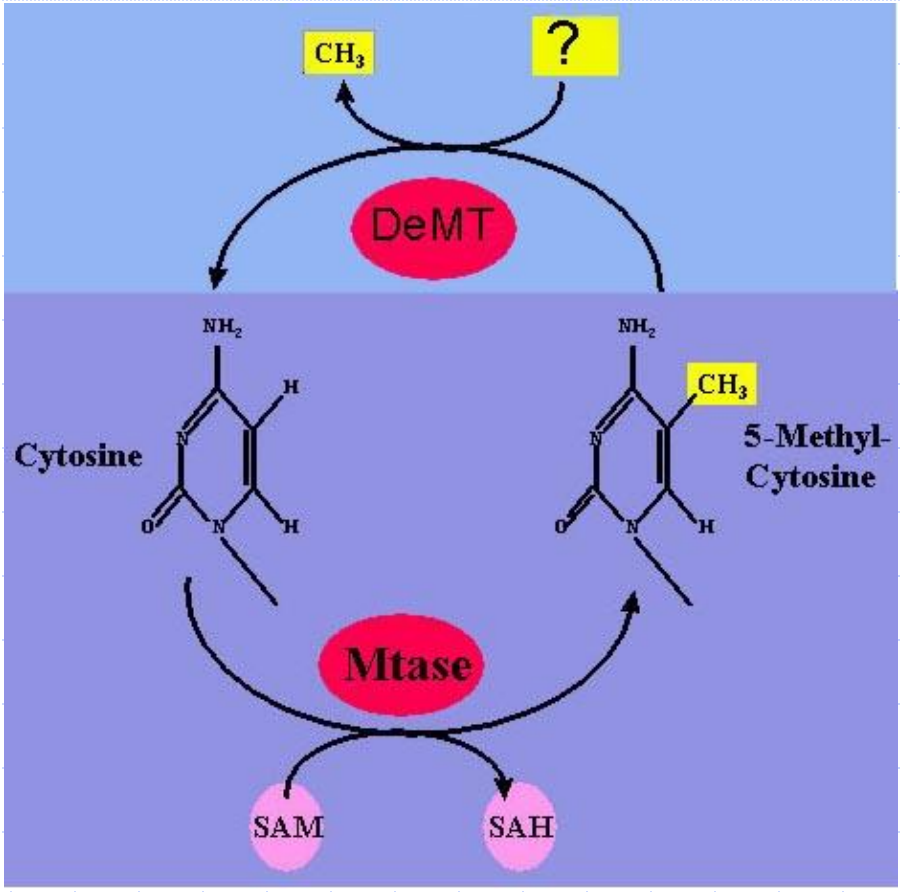
Adapted from Bertram, Molecular Aspects of Medicine 21, 2001, 161-223

DNA Amplification

Figure 11.8. Activation of proto-oncogenes by amplification. A. Multiple copies of "double minutes" (*arrows*) are seen in this tumor cell metaphase stained with Giemsa. **B.** An HSR (*arrow*) is seen here on the short arm of chromosome 7 in this G-banded tumor cell metaphase. (Reprinted with permission from Beaudet AL, Scriver CR, Sly WS, Valle D, (eds.) The metabolic and molecular bases of inherited disease. CD version. New York: Mgraw-Hill, 1997.)



DNA Methylation and Demethylation-ways to control expression of genes



Point mutation activation of Ras

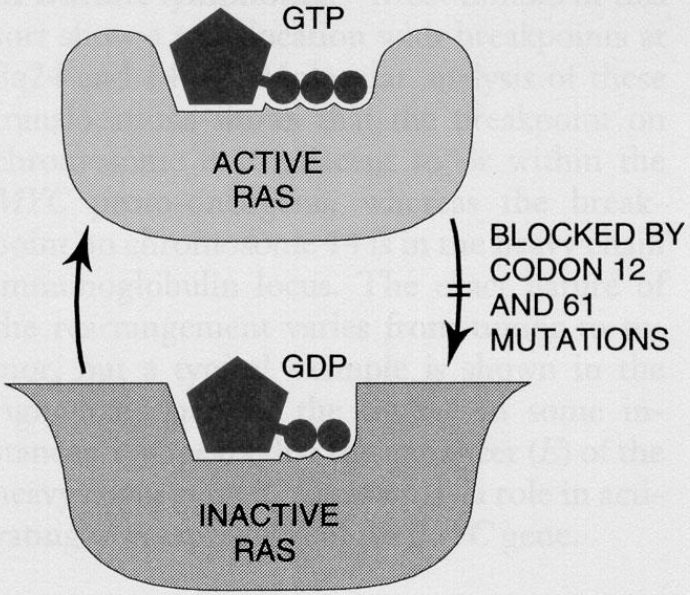
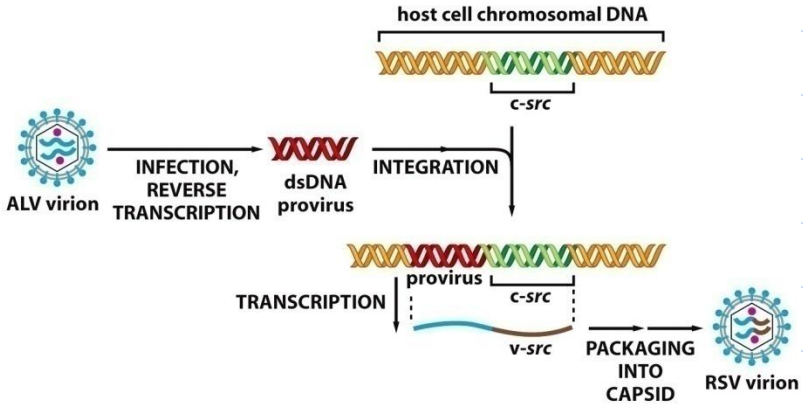


Figure 11.7. Proposed regulation of activation of the RAS protein. The active form binds GTP, whereas the inactive form binds GDP. Apparently the point mutations in codons 12 and 61, which convert *RAS* to a transforming gene, prevent the conversion from the active to the inactive form, so the protein is left in a "locked-on" position.

Viral oncogenes paved the way

c-src
proto-oncogene

v-src
oncogene



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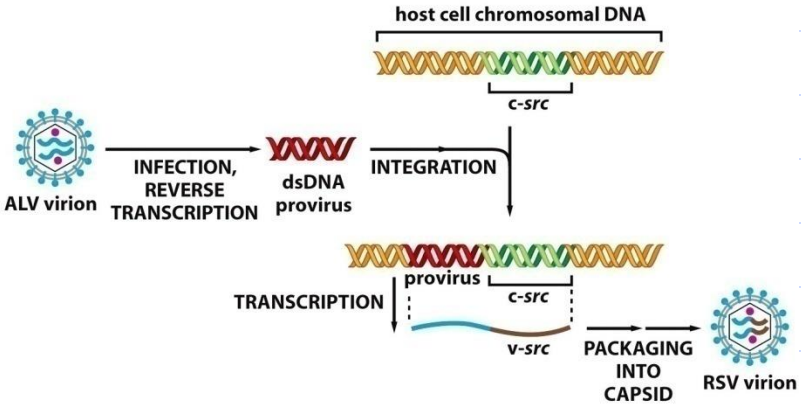


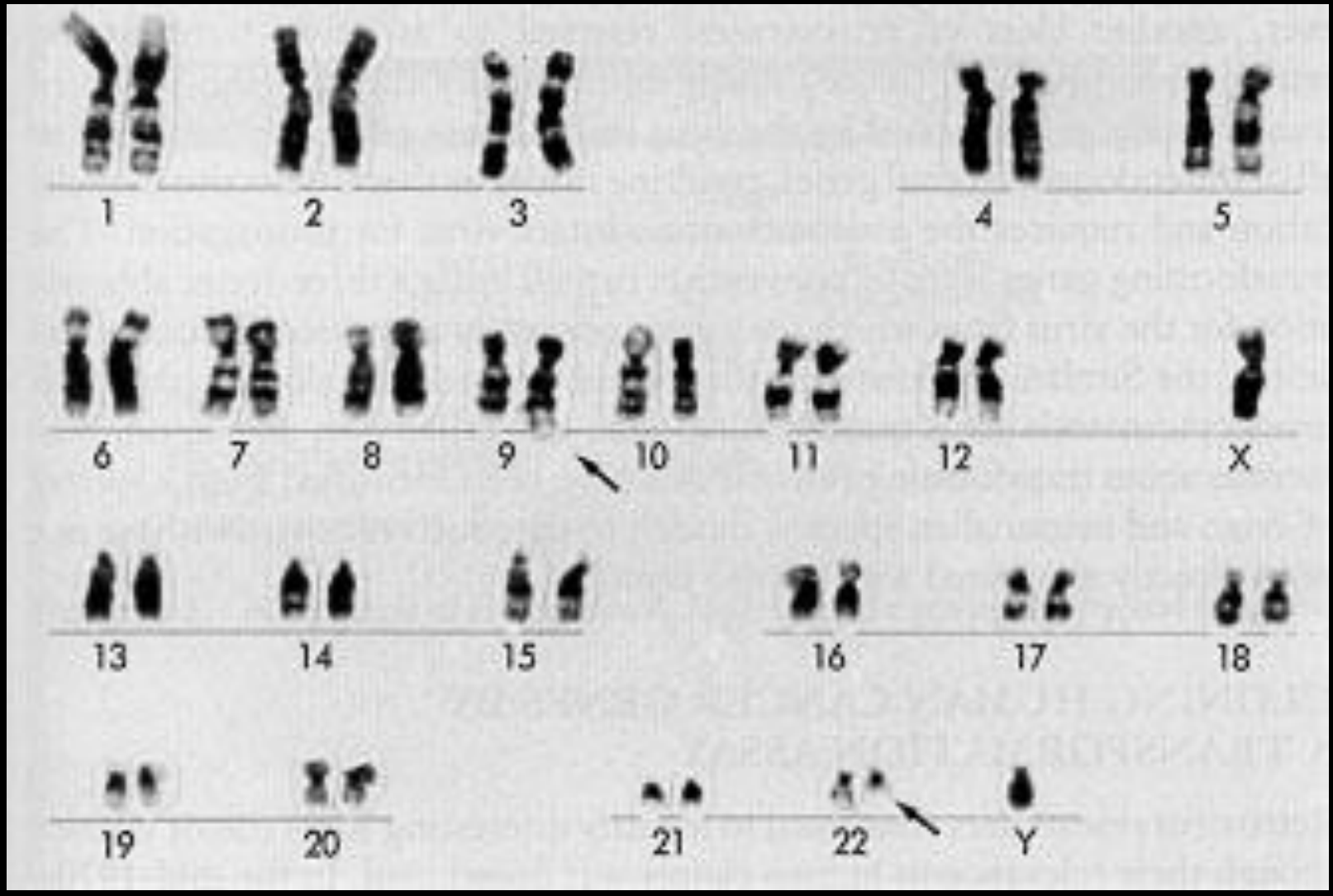
The concept:

-Viruses kidnap a normal proto-oncogene

-During the “kidnapping”,
the mutated proto-oncogene became an oncogene

-A new viral infection inserted an oncogene into the recipient, leading to cancer

The Philadelphia Chromosome

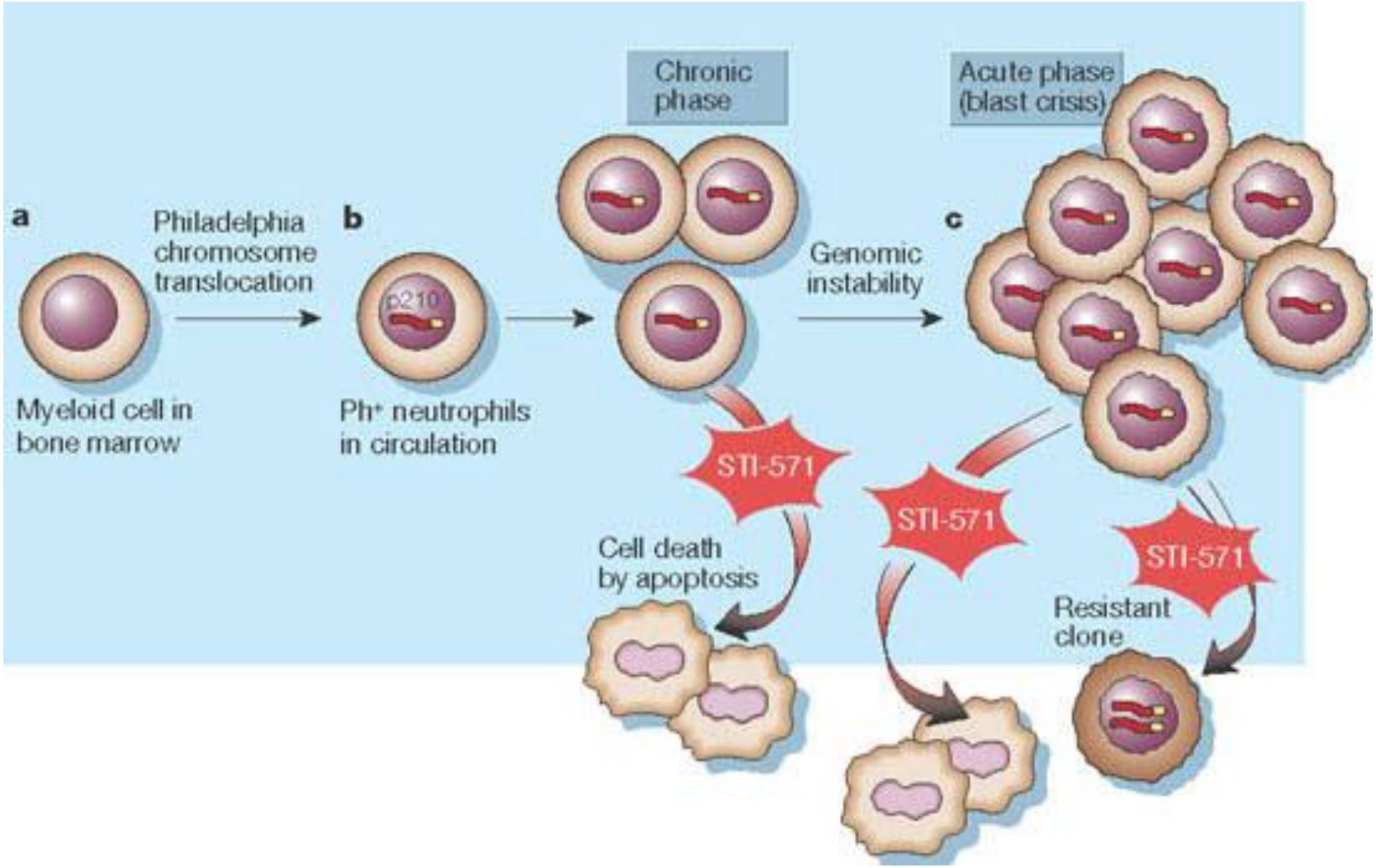


BCR-ABL translocation and expression

In CML, a translocation of genes upsets regulation of cell division

http://www.kent.k12.wa.us/staff/vhoward/apbio/oncogenes/brc-ablcartoon.gif

STI-571--an inhibitor of BCR-ABL function



http://www.blc.arizona.edu/courses/181gh/Lectures_WJG.01/cell_signaling.01/Applications.html

How are oncogenes activated?

- Point mutation-Eg. *K-ras,*
- Amplification-Eg. *N-myc, MDM2, Her2/neu/ErbB2*
- Chromosome translocation-Eg. *bcr-abl*
- Overexpression due to DNA demethylation

Thank you!