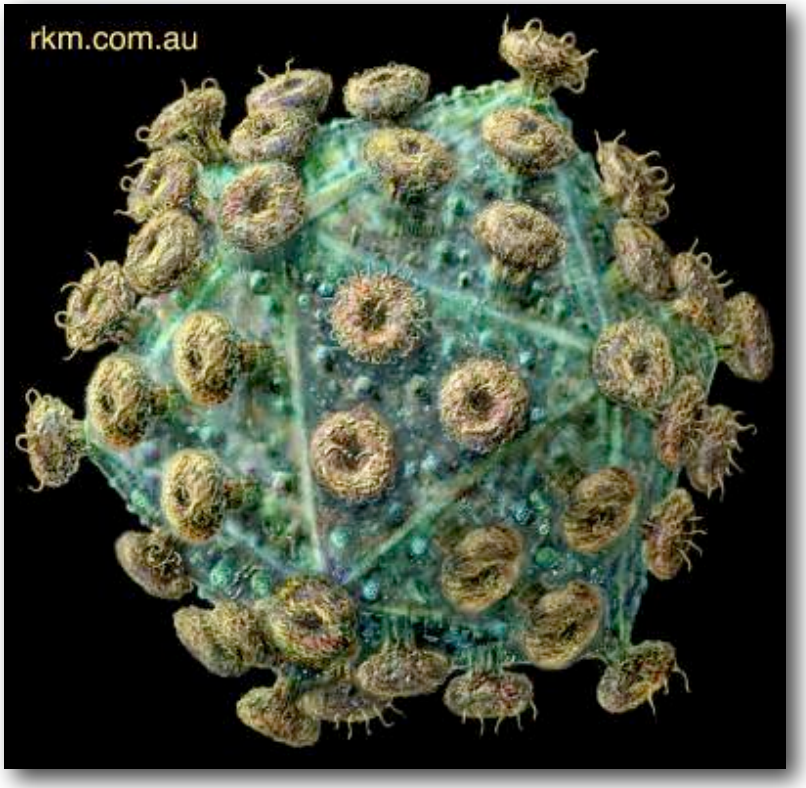
# Mutations and Cancer

189-199 and
Chapter 14





# Mutation: change to genetic material (DNA)

A mutation to genetic material is usually not beneficial. Mutagens are things that cause mutations, they include:

1. Certain Toxic Chemicals (pesticides, benzene etc)
2. Radiation (nuclear, man-made, solar)

Several common place items are capable of causing mutations:
Pesticide-treated foods
Smoke
BBQed food
(Dental) X-Rays (it is estimated that 0.9% of cancer cases in the US are caused by X-Ray exposure)

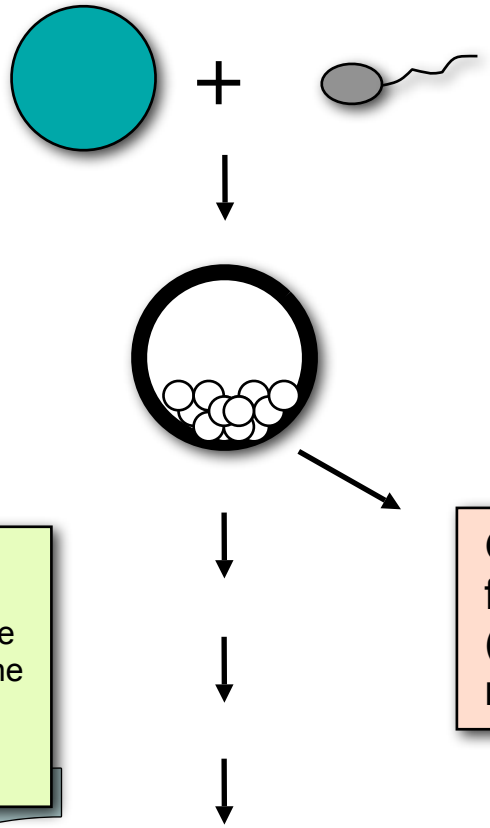
# Somatic-Cell vs Germ-Cell Mutations

All people have random acquired mutation in cells. Such mutations are termed somatic. Such mutations play important roles in cancer

Germ mutations occur, or are present in the sperm or egg producing cells. These mutations are inheritable and present in all cells of an organism. These mutations are the drivers of evolution

# Somatic Cells/Germ line mutations

This has nothing to do with bugs



## Mutations

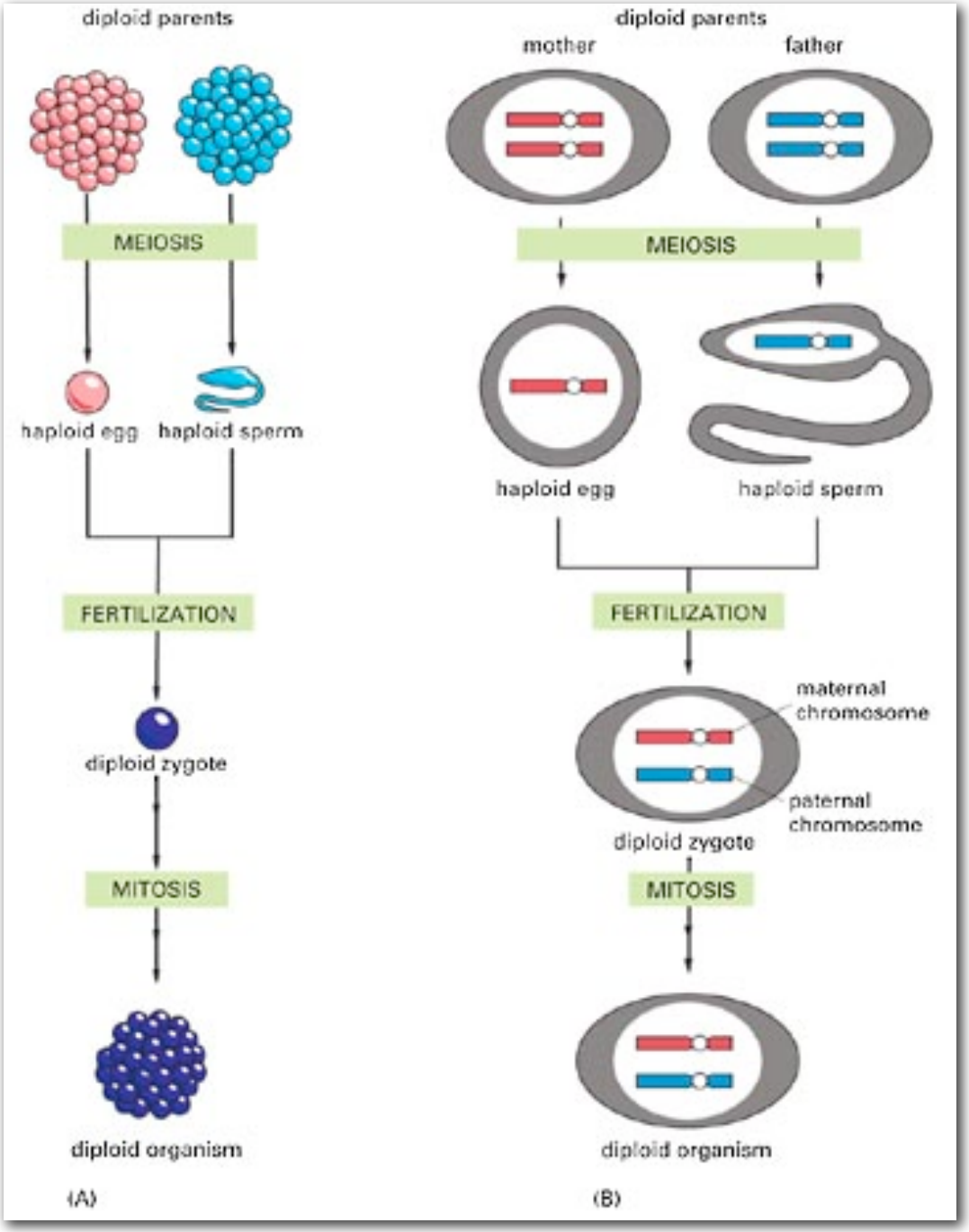
passed on to progeny, all tissues, Mendelian

GERM LINE
female: eggs (precursors)
male: sperm

## Mutations

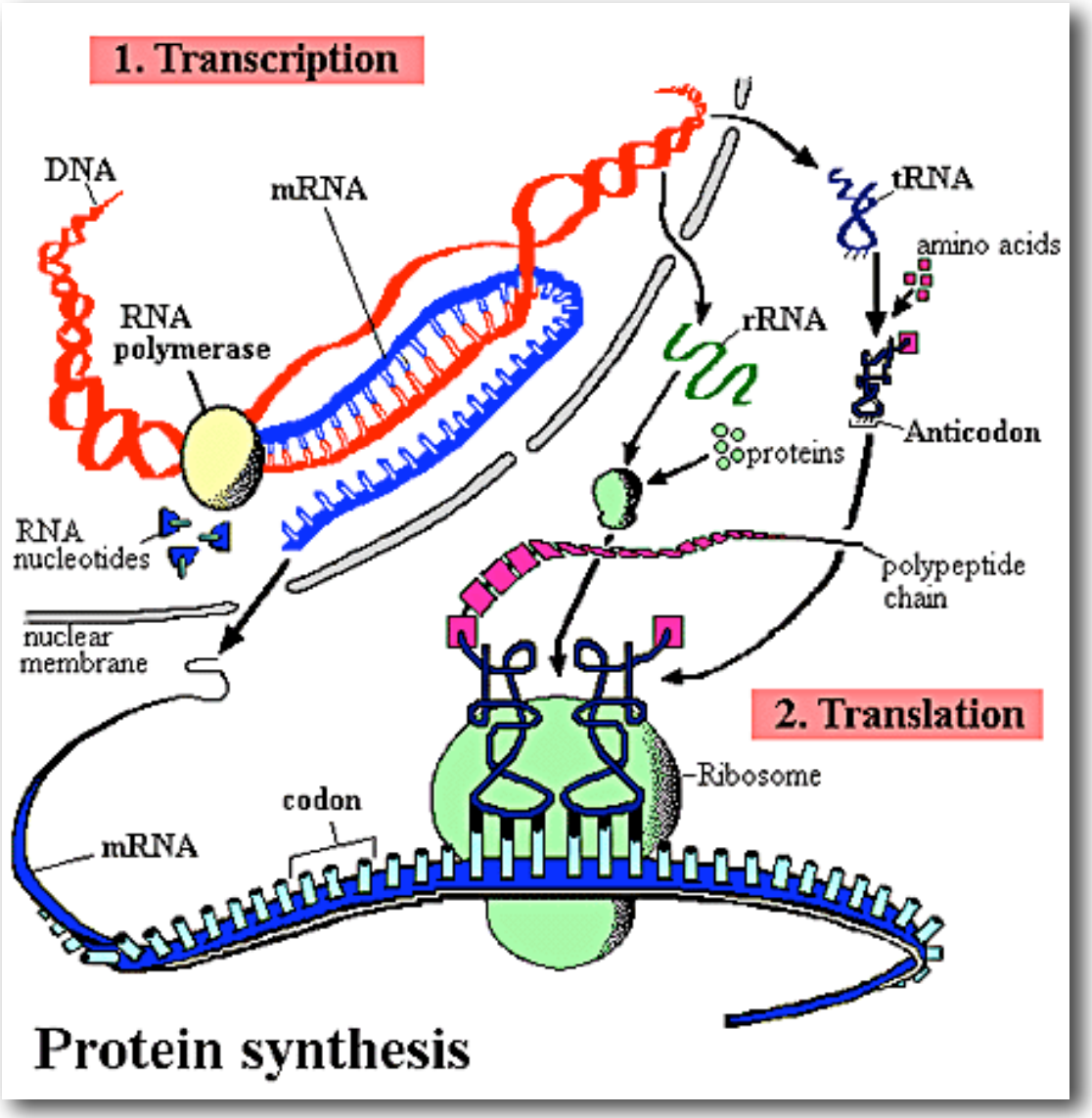
usually little effect, cell death for damaged cell; however, all cancers arise from somatic cell mutation, one cell confined to one tissue

SOMATIC CELLS
embryo proper
all tissues




Meiosis is a important time for mutations to occur. The germ mutations that occur during meiosis could be passed on during a fertilization

# Mutations can affect protein structure

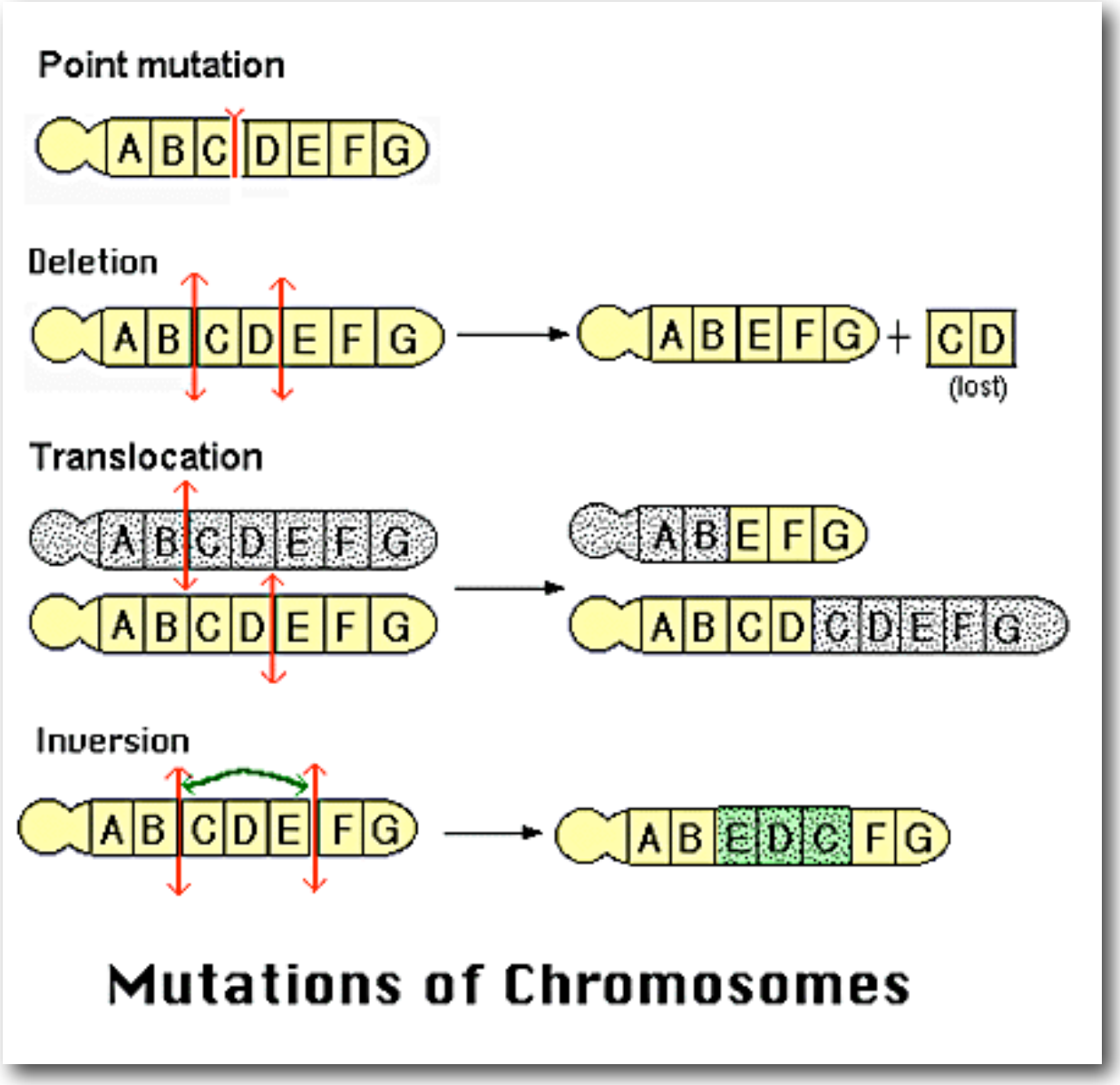


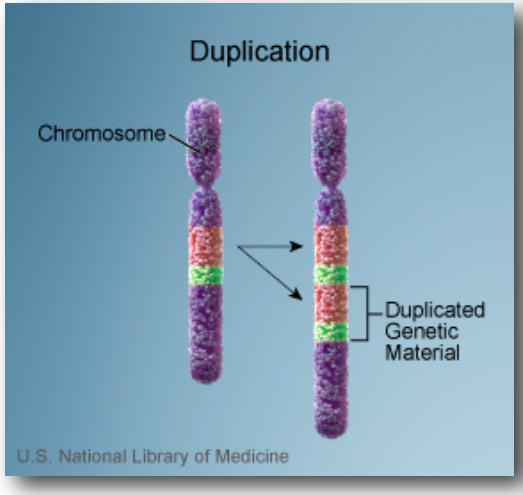

Transcription: Mutated DNA will produce different mRNA, possibly leading to the production of an altered, or even a bad protein.

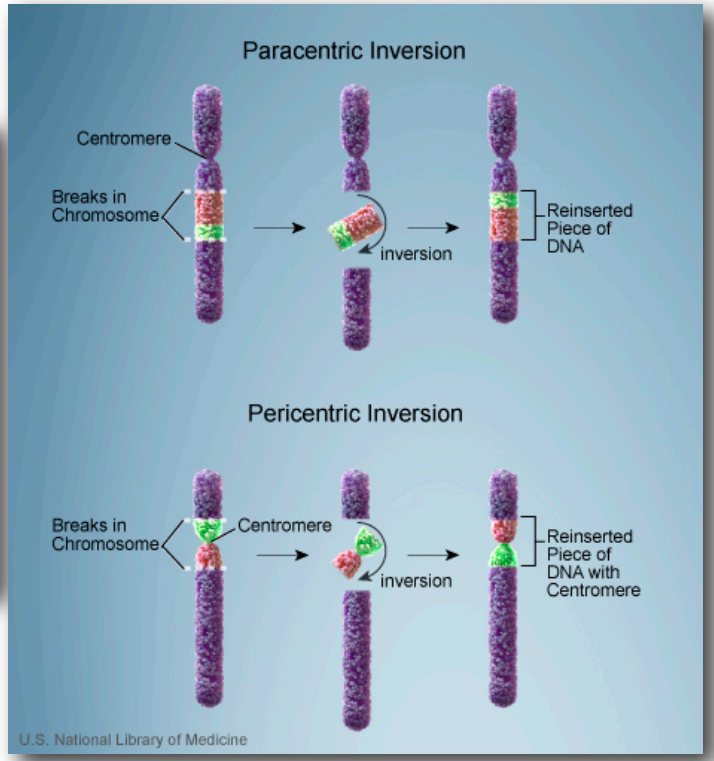
**Most mutations are neutral!!!**

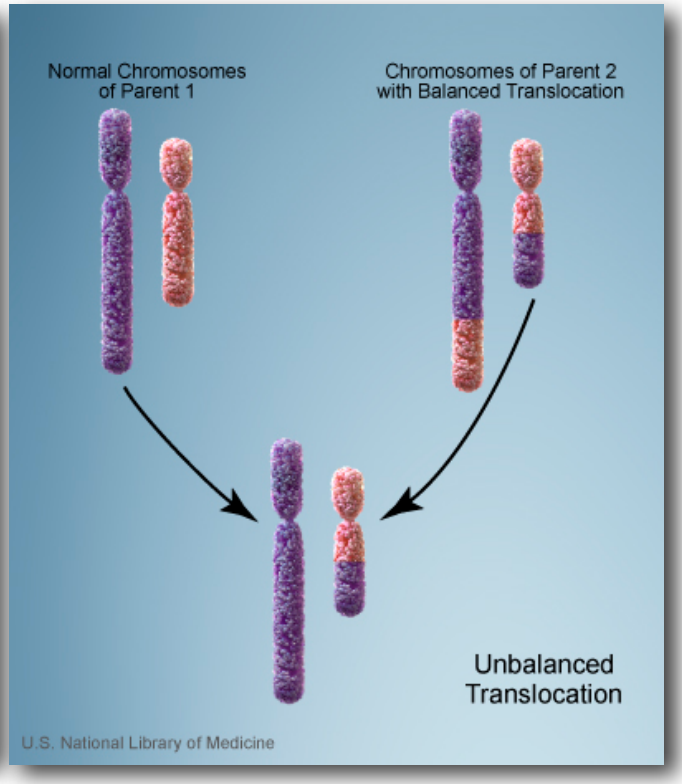
After all, 1% of the genome codes for protein, 99% does not

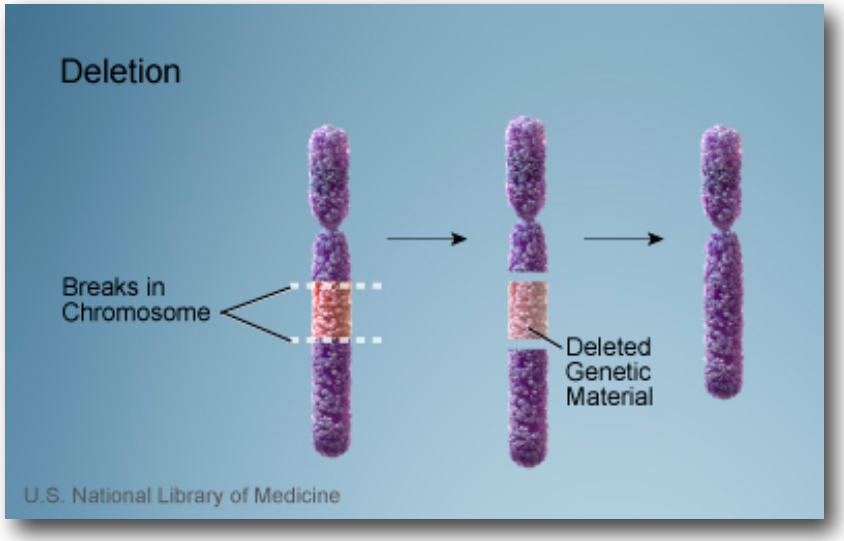
# Types of mutations

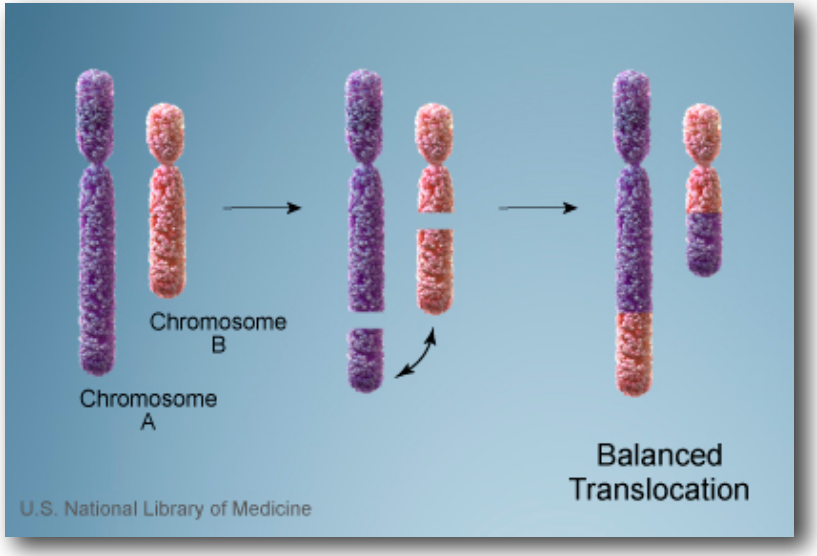



Duplication
Chromosome
Duplicated Genetic Material
U.S. National Library of Medicine

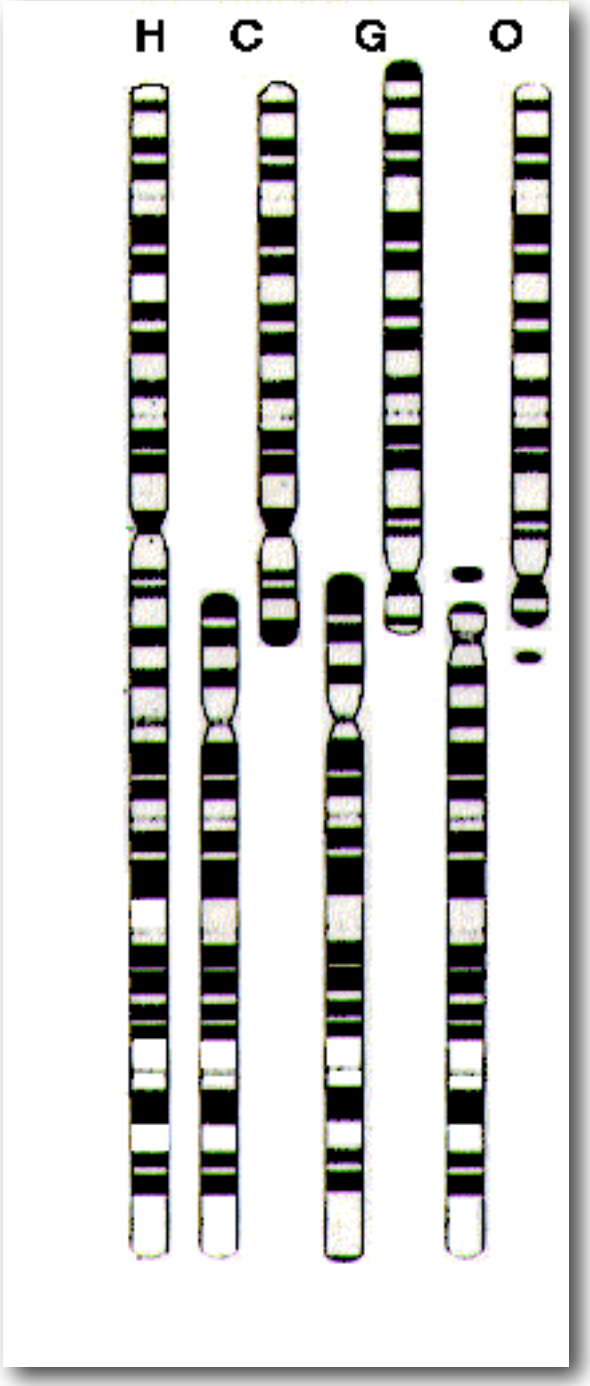

Paracentric Inversion
Centromere
Breaks in Chromosome
inversion
Reinserted Piece of DNA
Pericentric Inversion
Breaks in Chromosome
Centromere
inversion
Reinserted Piece of DNA with Centromere
U.S. National Library of Medicine


Normal Chromosomes of Parent 1
Chromosomes of Parent 2 with Balanced Translocation
Unbalanced Translocation
U.S. National Library of Medicine


Deletion
Breaks in Chromosome
Deleted Genetic Material
U.S. National Library of Medicine


Chromosome B
Chromosome A
Balanced Translocation
U.S. National Library of Medicine

A principal difference between humans and the other great apes is a rearrangement that made chromosome 2



# A closer look at some of these “small” mutations

**Point mutation** - when a base is replaced with a different base.

CGG CCC AAT to CGG CGC AAT

Guanine for Cytosine

**Insertion** - when one ore more nucleotides are added

CGG CCC AAT to CGG CGC CAA T

Guanine is added

**Deletion** - the loss of one or more nucleotides

CGG CCC AAT to CGG CCA A T

loss of Cytosine

# Frame Shift mutations

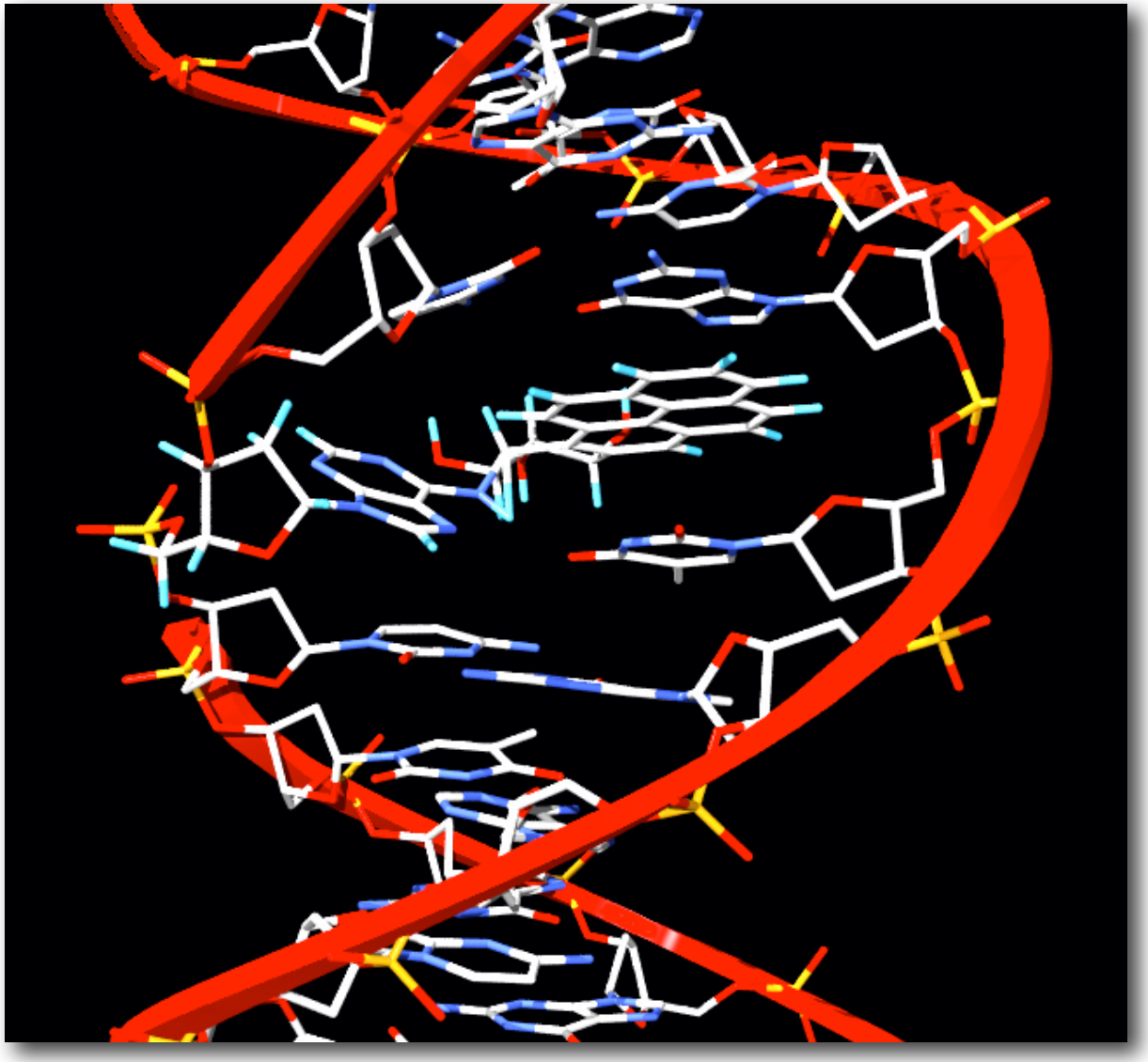
- A frame shift mutation results from a base deletion or insertion. Each of these changes the triplets that follow the mutation.

  CGG CCC AAT GAC AAG

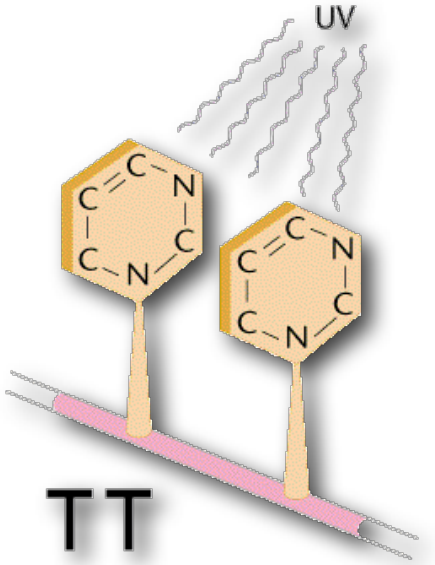
  CGG CGC CAA TGA CAA G

- Frame shift mutations have greater effects than a point mutation (nucleotide change) because they completely change the rest of the coding sequence

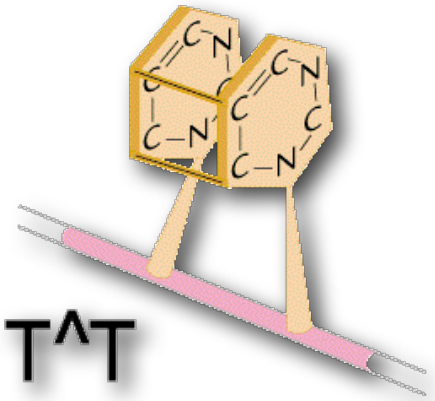
# A Mutagen in smoke

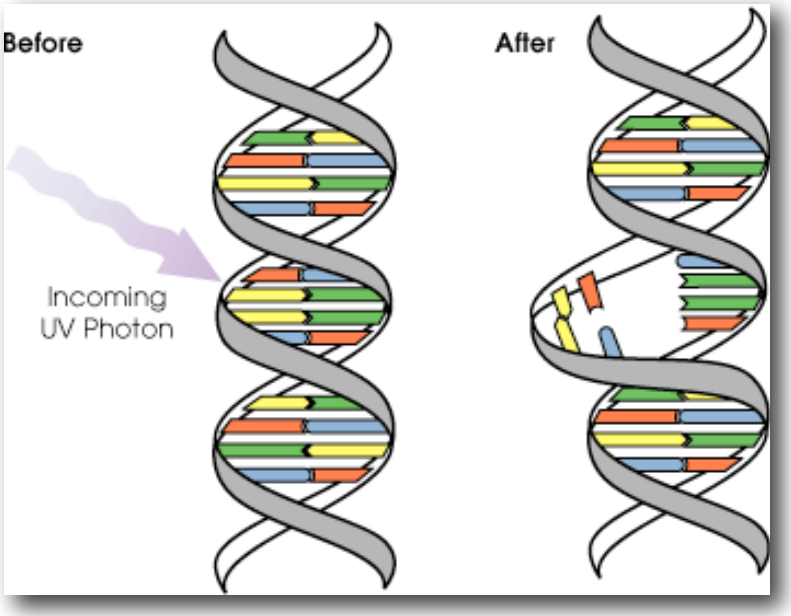


# Sunbathing




Thymidine Dimers




DNA damage increases melanin production

Cancer caused by changes in the DNA

Strong Mutagens have often been found by epidemiological research on cancer

Smoking
Radiation

# Shoe fitting in the 1930s

## CERTIFICATE

SHOE-FITTING TEST DATA FOR _____

1. **ANKLE ROLL** GOOD ☐ FAIR ☐ POOR ☐

2. **WEIGHT DISTRIBUTION**

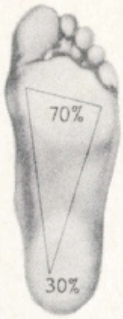

RIGHT WAY


LEFT RIGHT

____% BALL ____%

____% OUTER ____%

____% HEEL ____%




WRONG WAY

3. **X-RAY FITTING TEST**

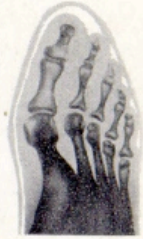
RIGHT WAY


LEFT RIGHT

☐ GOOD ☐

☐ FAIR ☐

☐ POOR ☐



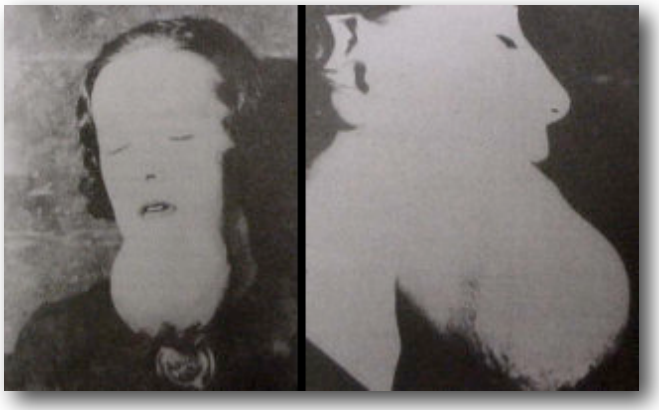
WRONG WAY

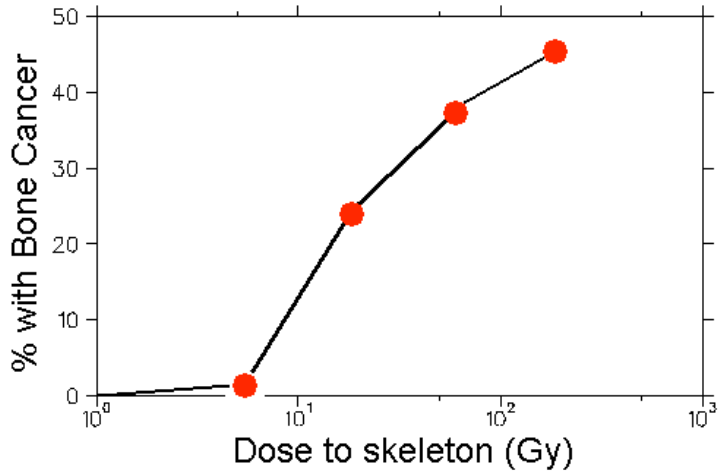
**This scientific way of approaching the problem of poorly-fitted shoes eliminates guesswork. Now you can see for yourself!**

Radium girls

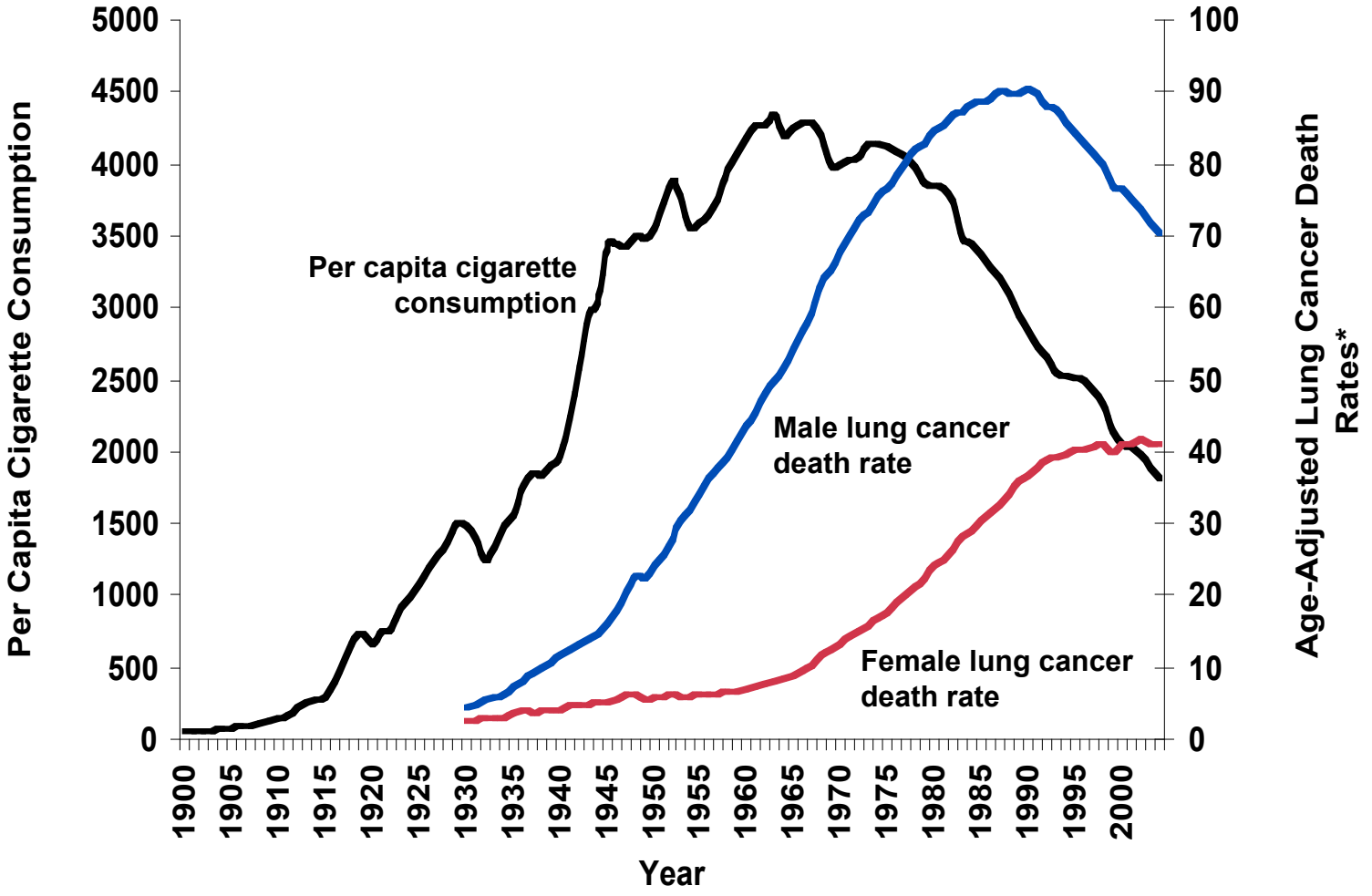
1910s


RUDDER
BLINKER
OXYGEN FLOW
INDICATOR
OFF ON
WESTCLOX
POCKET BEN
LEAR
DIRECTIONAL GYRO




% with Bone Cancer
Dose to skeleton (Gy)
0
10
20
30
40
50
$10^0$
$10^1$
$10^2$
$10^3$

# Tobacco Use in the US, 1900-2004




*Age-adjusted to 2000 US standard population.

Source: Death rates: US Mortality Data, 1960-2004, US Mortality Volumes, 1930-1959, National Center for Health Statistics, Centers for Disease Control and Prevention, 2006. Cigarette consumption: US Department of Agriculture, 1900-2004.

# CANCER overview

- Class of diseases
- Uncontrolled cell division
- Originates from a single or a few cells
- Is a microevolutionary process
- Is caused by mutations (with sometimes a viral involvement)

METASTASIS
cancer cells spread by
bloodstream or lymphatic system

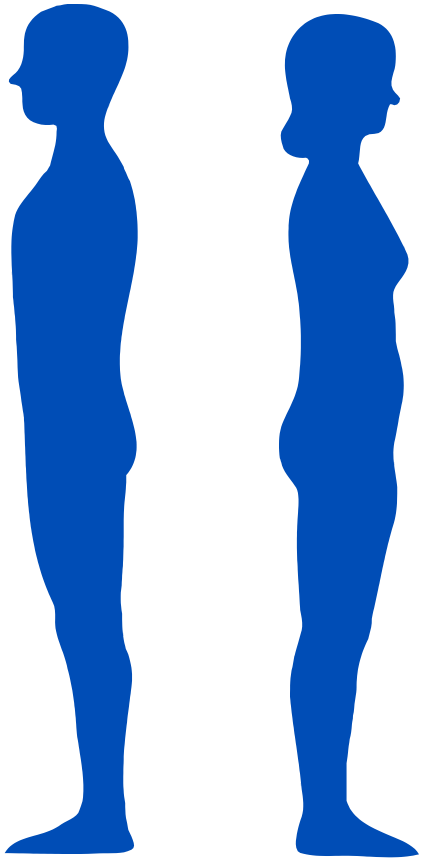
Cancer often derive from tissue that undergo renewal/growth in the adult

- Breast Cancer
- Skin Cancer
- Lung Cancer
- Colon Cancer
- Prostate Cancer

# 2008 Estimated US Cancer Cases*

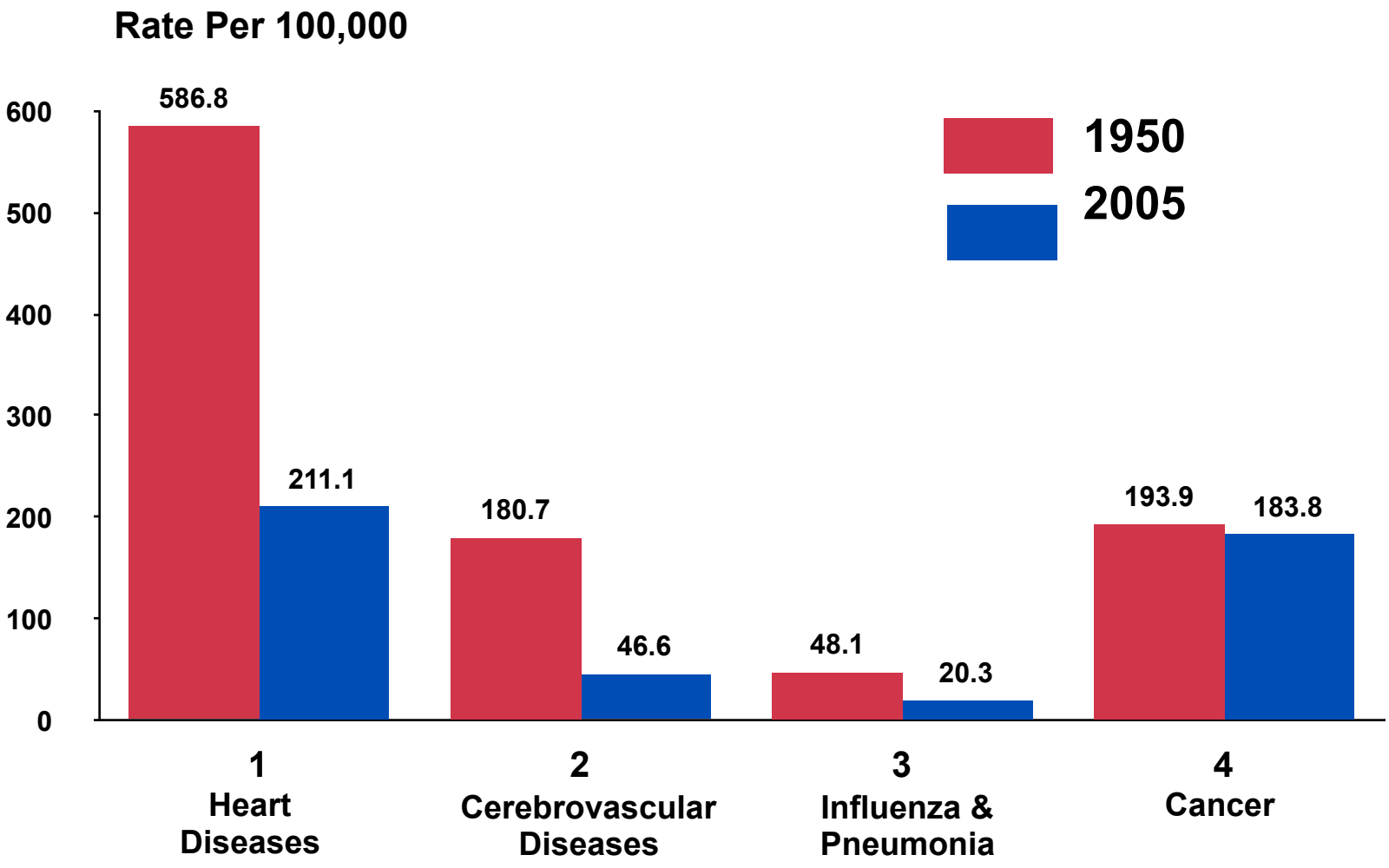
Basal Skin Cancer: almost 1 million cases/year

| Men 745,180 | | Women 692,000 | |
|---|---|---|---|
| Prostate | 25% | 26% | Breast |
| Lung & bronchus | 15% | 14% | Lung & bronchus |
| Colon & rectum | 10% | 10% | Colon & rectum |
| Urinary bladder | 7% | 6% | Uterine corpus |
| Non-Hodgkin lymphoma | 5% | 4% | Non-Hodgkin lymphoma |
| Melanoma of skin | 5% | 4% | Thyroid |
| Kidney & renal pelvis | 4% | 4% | Melanoma of skin |
| Oral cavity | 3% | 3% | Ovary |
| Leukemia | 3% | 3% | Kidney & renal pelvis |
| Pancreas | 3% | 3% | Leukemia |
| All Other Sites | 20% | 23% | All Other Sites |



***Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder.**
**Source: American Cancer Society, 2008.**

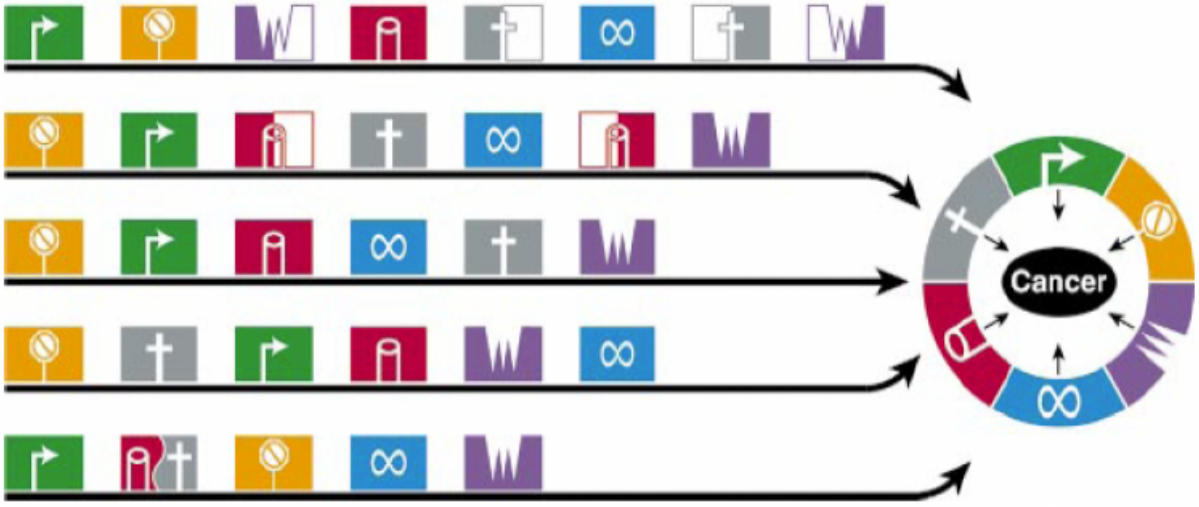
# Change in the US Death Rates* by Cause, 1950 & 2005




* Age-adjusted to 2000 US standard population.
Sources: 1950 Mortality Data - CDC/NCHS, NVSS, Mortality Revised.
2005 Mortality Data: US Mortality Data 2005, NCHS, Centers for Disease Control and Prevention, 2008.

| Component | Acquired Capability | Example of Mechanism |
|---|---|---|
| | Self-sufficiency in growth signals | Activate H-Ras oncogene |
| | Insensitivity to anti-growth signals | Lose retinoblastoma suppressor |
| | Evading apoptosis | Produce IGF survival factors |
| | Limitless replicative potential | Turn on telomerase |
| | Sustained angiogenesis | Produce VEGF inducer |
| | Tissue invasion & metastasis | Inactivate E-cadherin |

B



# Hallmark #1: Self-sufficiency in growth signals/Oncogenes

Originally coined as a genetic term to describe any gene capable of causing cancer.

Oncogenes refers to genes that contribute to cancer in a gain-of-function manner
– And are dominate at the cellular level.

Proto-oncogenes are the normal genes

Over 100 oncogenes have been identified

# Hallmark #2: Insensitvity to negative signals, often Tumor Suppressor Genes (TSGs)

TSGs are altered by inactivating mutations and this can lead to cancer
– Point mutations
– Delete regions of chromosomes
– Loss of heterozygosity
– Altered promotor activity

Remember, you need to inactivate both alleles of tumor suppressor genes

# Hallmark #3: Evasion of Apoptosis

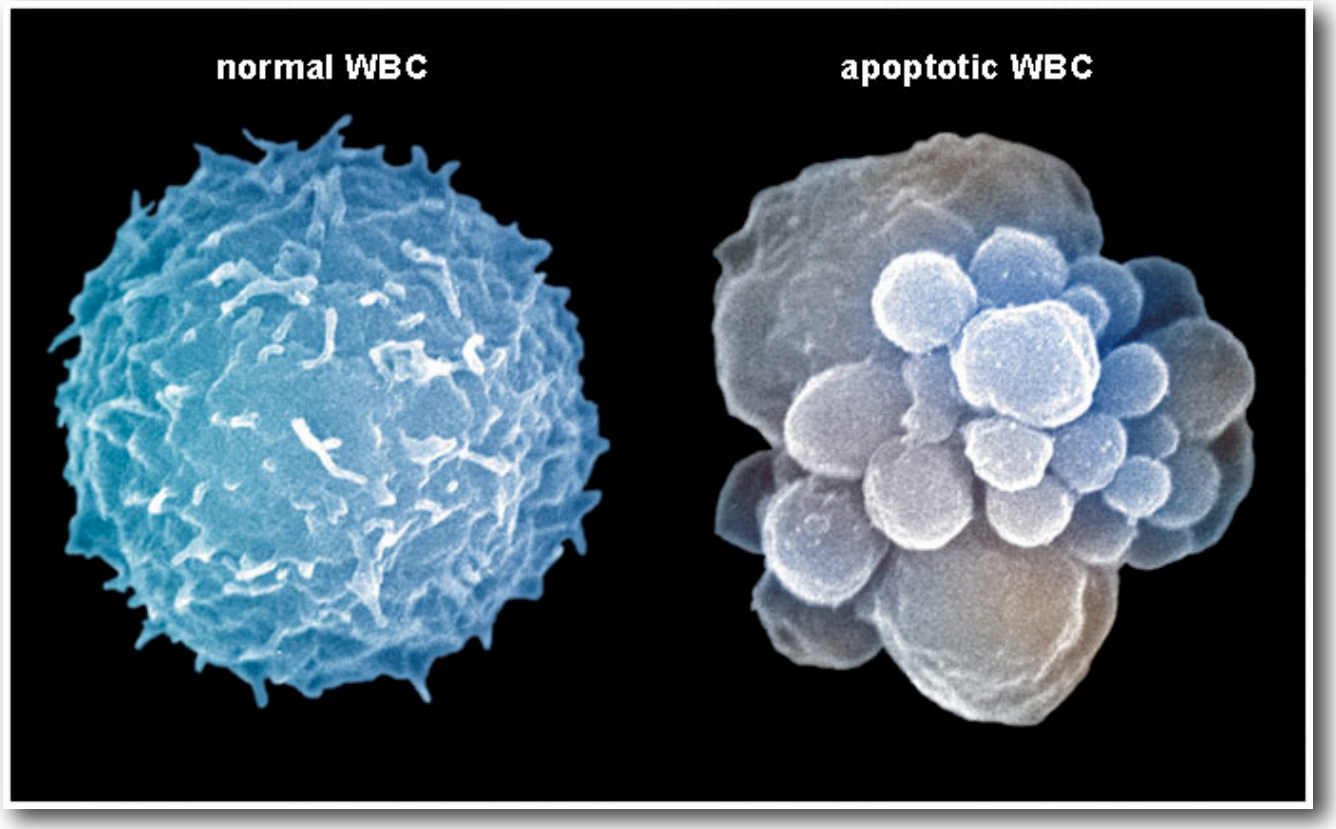
Apoptosis is programmed cell death

Damaged cells are effectively removed by this mechanism

Also, this is a mechanism by which cells that have an oncogenic mutations are removed

Many cancer drugs activate apoptosis

– Apoptosis is a critical defense against cancer, and aids cancer survival



## Hallmark #4: Acquisition of limitless proliferative capacity

grow the telomeres (activate telomerase)

## Hallmark #5: Angiogenesis

All tumors require a blood supply if they are to grow to a significant size

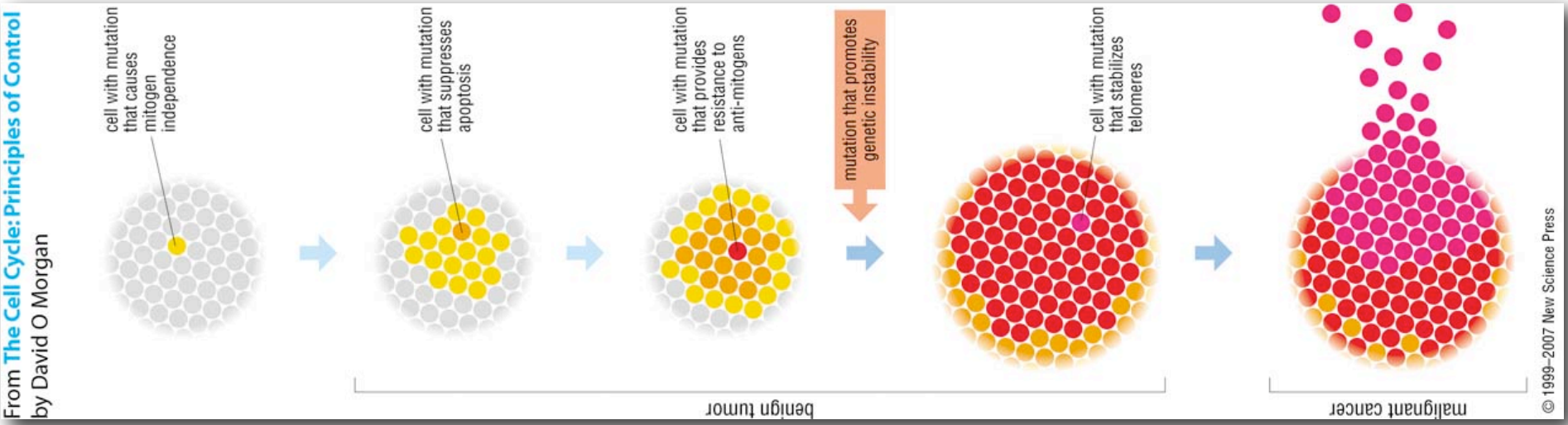
VEGF and FGF1 and FGF2 are activated in tumors and signal endothelial cell proliferation and growth of blood vessels.

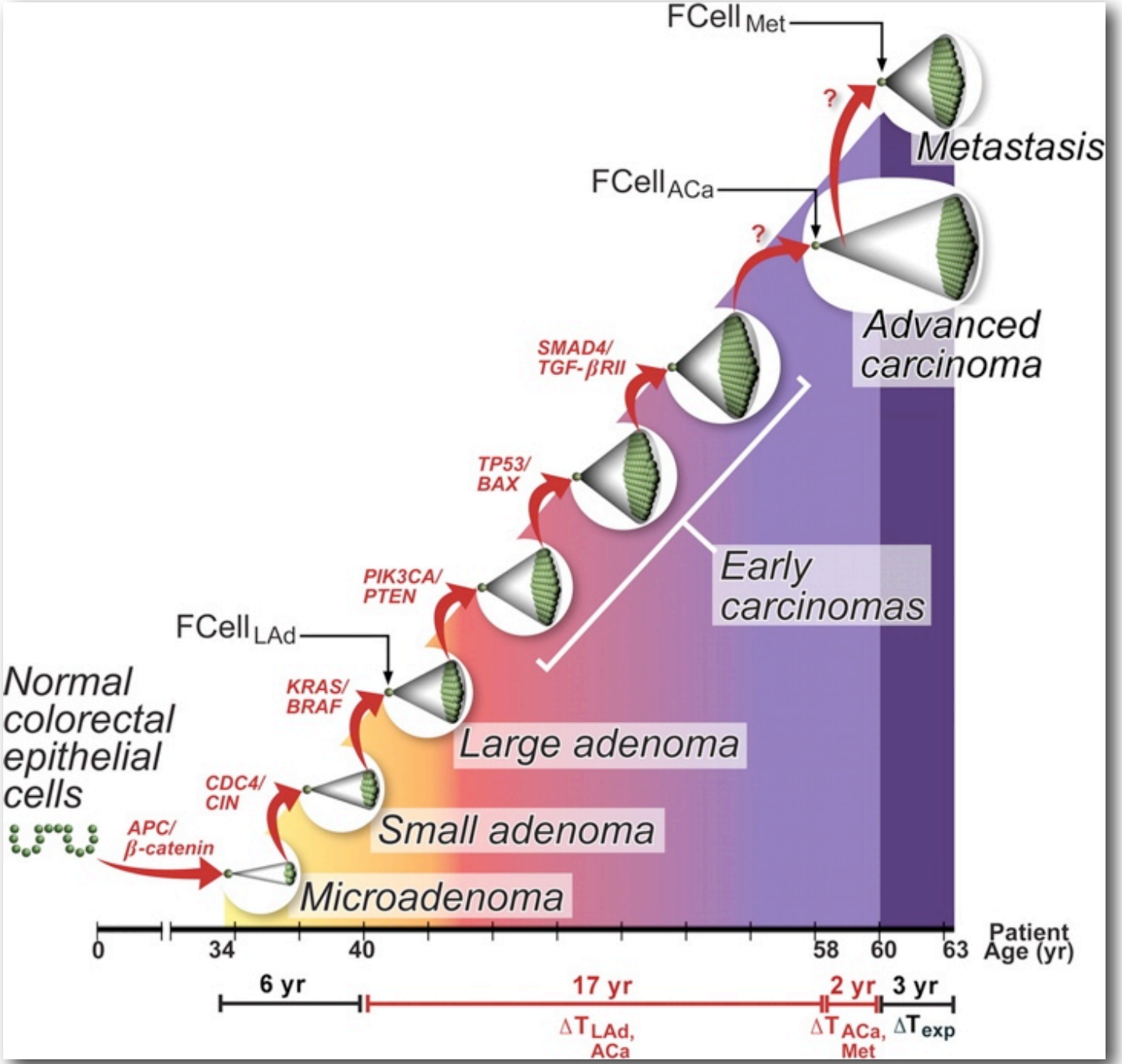
## Hallmark #6: Tissue invasion and metastasis

Altogether a poorly understood process

Cancer is a multistep process, and most step involve the acquisition of additional mutations.

Cancer is an evolutionary process and it can take decades for a microtumor to develop into cancer




FCell Met
?
Metastasis
FCell ACa
?
Advanced carcinoma
SMAD4/ TGF-βRII
TP53/ BAX
PIK3CA/ PTEN
Early carcinomas
FCell LAd
Normal colorectal epithelial cells
KRAS/ BRAF
Large adenoma
CDC4/ CIN
APC/ β-catenin
Small adenoma
Microadenoma
0
34
40
58
60
63
Patient Age (yr)
6 yr
17 yr
2 yr
3 yr
ΔT LAd, ACa
ΔT ACa, Met
ΔT exp