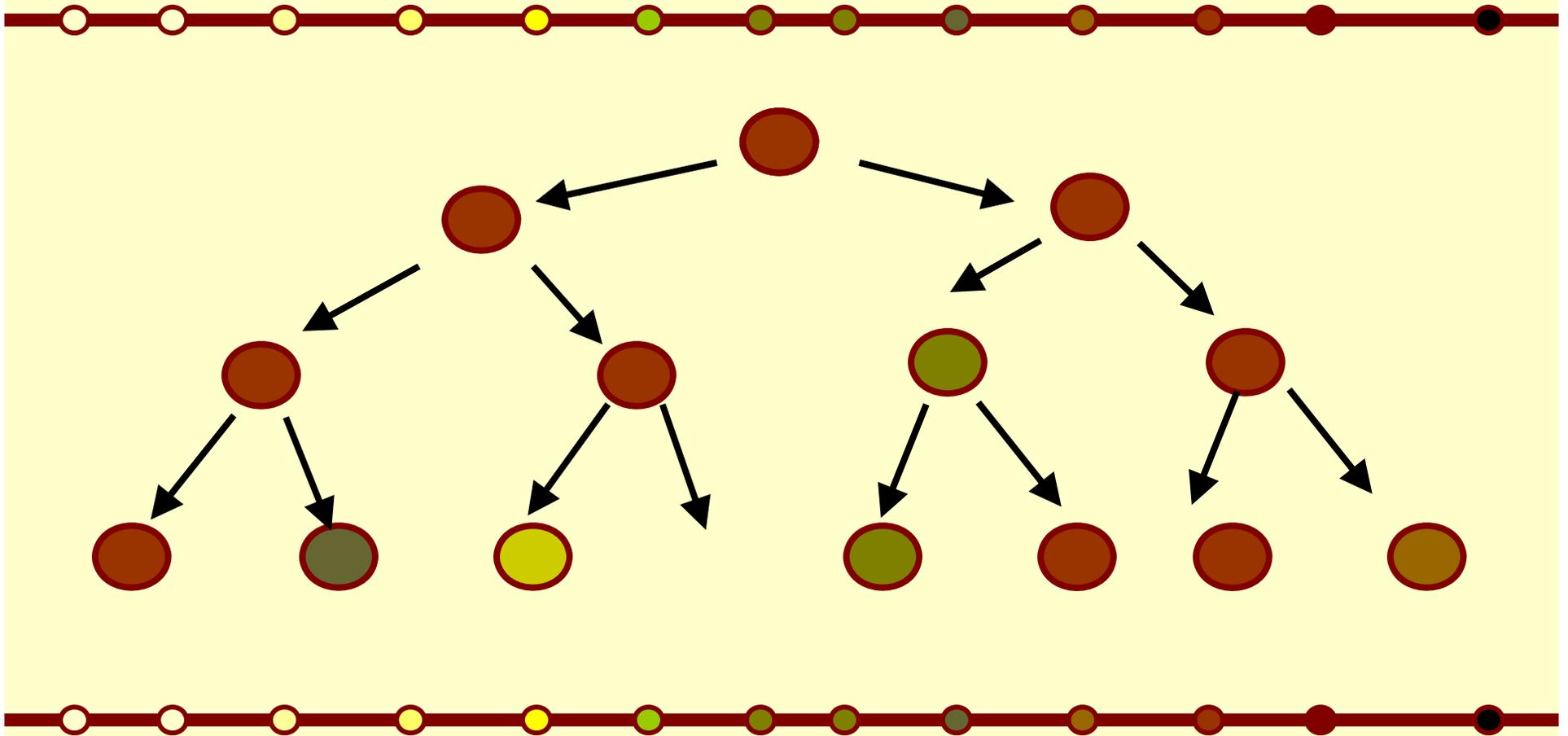


Genomic Instability

Delayed Genetic Effects



What is Genomic Instability?



- Often, after being damaged by radiation, cells are able to repair DNA damage and reproduce normally.
- However, sometimes damage may carry over for several generations before the unobserved damage causes the cell to lose control of its genome.
- At this point, cells may be unable to reproduce successfully. They may become genetically unstable, or become cancerous.

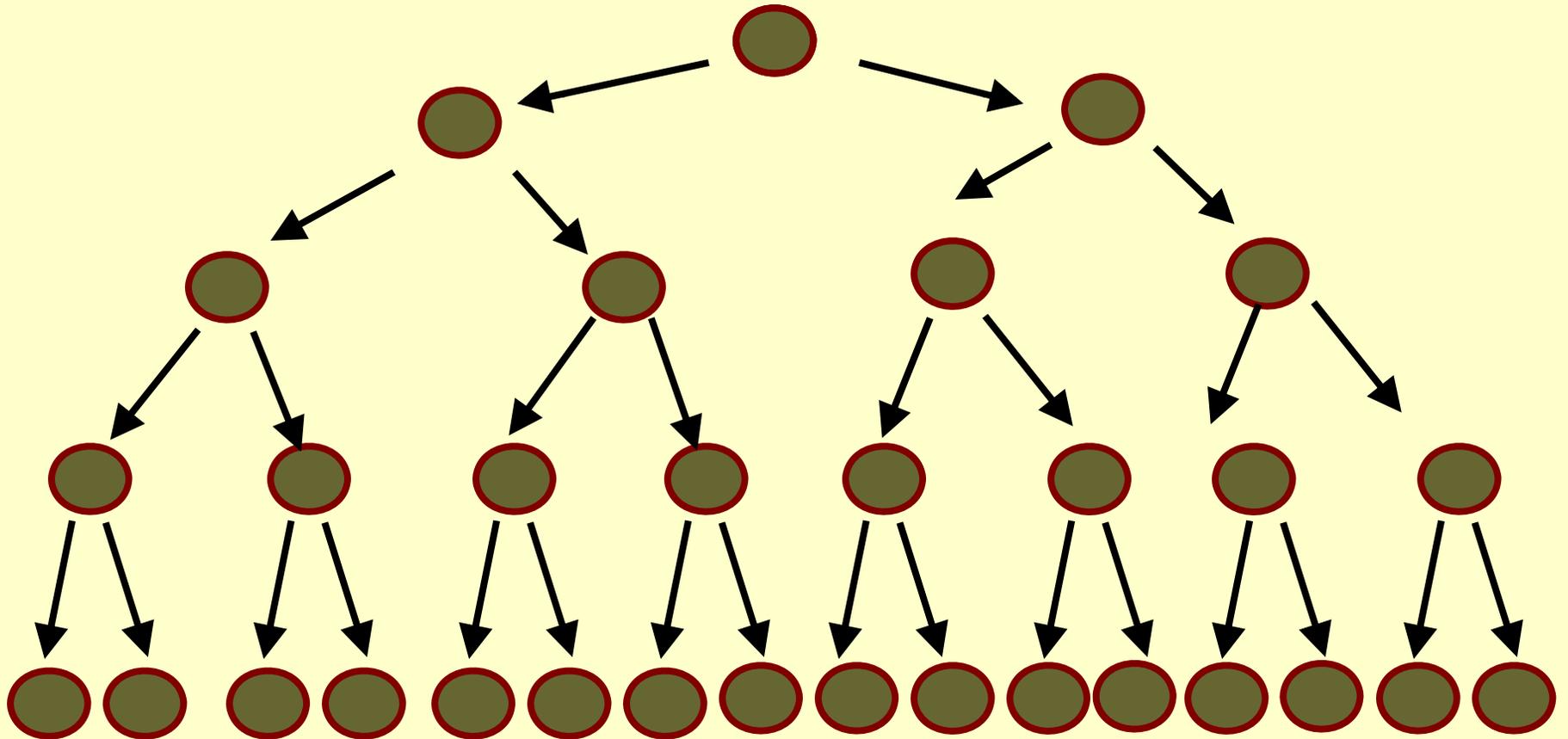
Radiation-induced Genetic Damage



Old Paradigm

After a cell is mutated by radiation, all of its prodigy are mutated

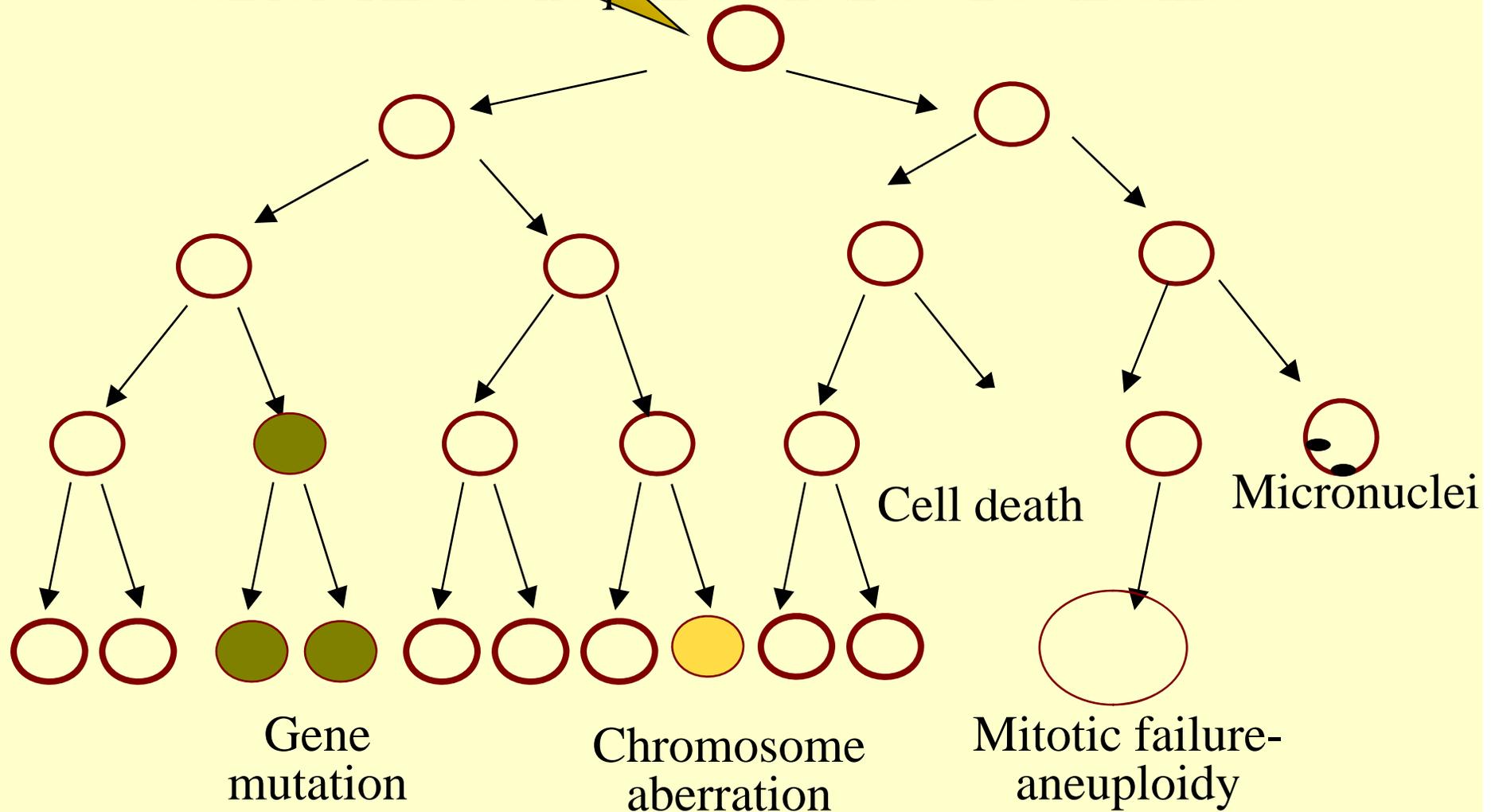
Mutation is a rare event that cannot be altered.



Genomic Instability

New Paradigm

After a cell is exposed to radiation, biological changes are produced that, after many cell divisions, result in loss of genetic control. This is a frequent event that can be modified.



Early effects seen in “hit” cell



Chromosomal rearrangements

Micronuclei

Gene mutations

Increased Reactive Oxygen Species (ROS)

Inflammatory responses

Change in gene expression

Effects seen in cell progeny



Chromosomal rearrangements

Micronuclei

Transformation

Chromosome amplification

Death inducing factors

Gene mutations

Cell death

Change in gene expression

Radiation-related Gene Induction



It has been shown that certain genes are inappropriately induced, or “turned on” or “turned off” by radiation. The consequence of the gene alteration sometimes shows up more frequently several generations after the initial radiation exposure.

Genomic Instability can be demonstrated in some strains of mice



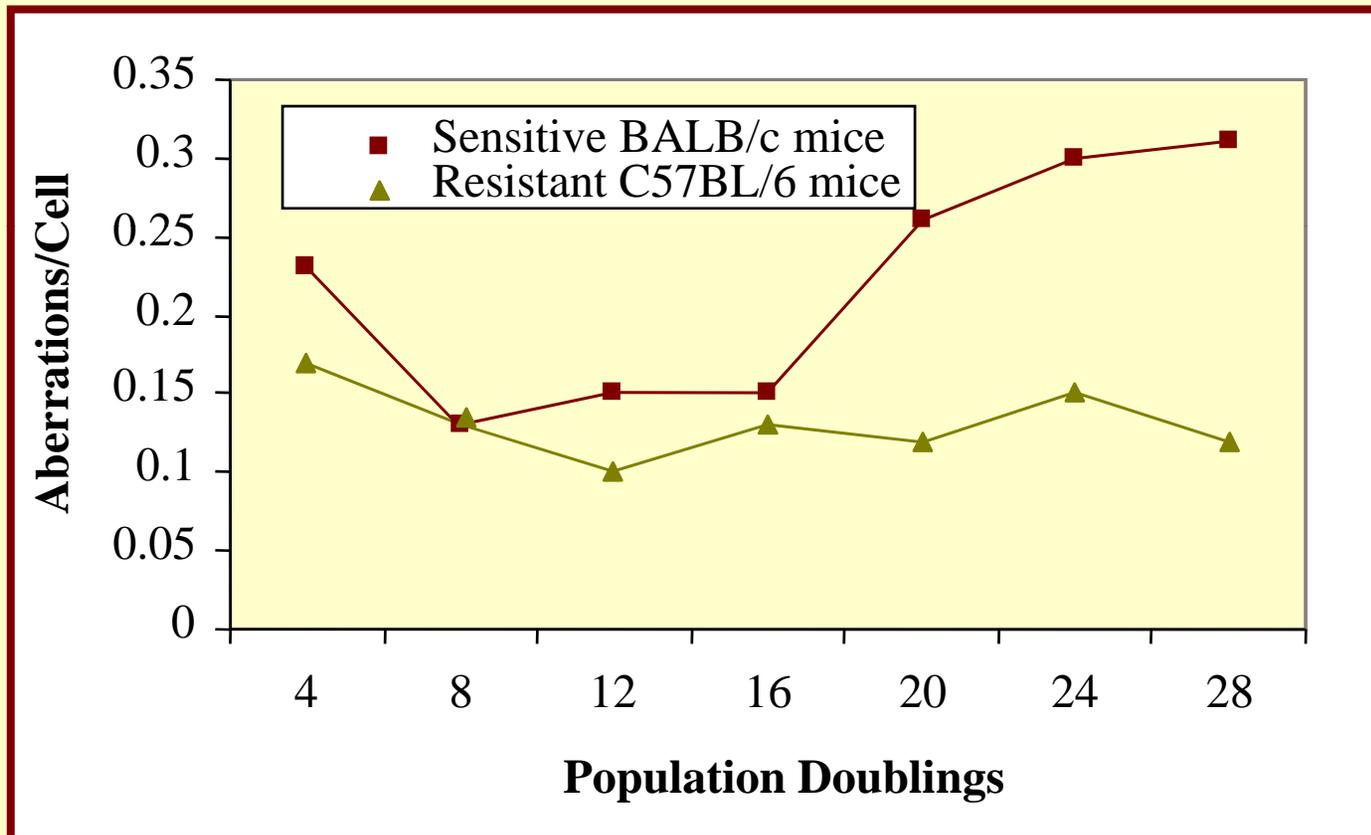
Hybrid Mouse Models



After only a few generations of apparently normal breast cell division, the cells of the sensitive mice, BALBc, show increased chromosome aberrations and genomic instability, while cells of the radiation resistant mice, C57BL/6, remain stable.

Cells of the sensitive BALBc mice are very sensitive to radiation-induced breast cancer. Other cells, such as those from the resistant C57BL/6 mice, are particularly resistance to this radiation-induced effect.

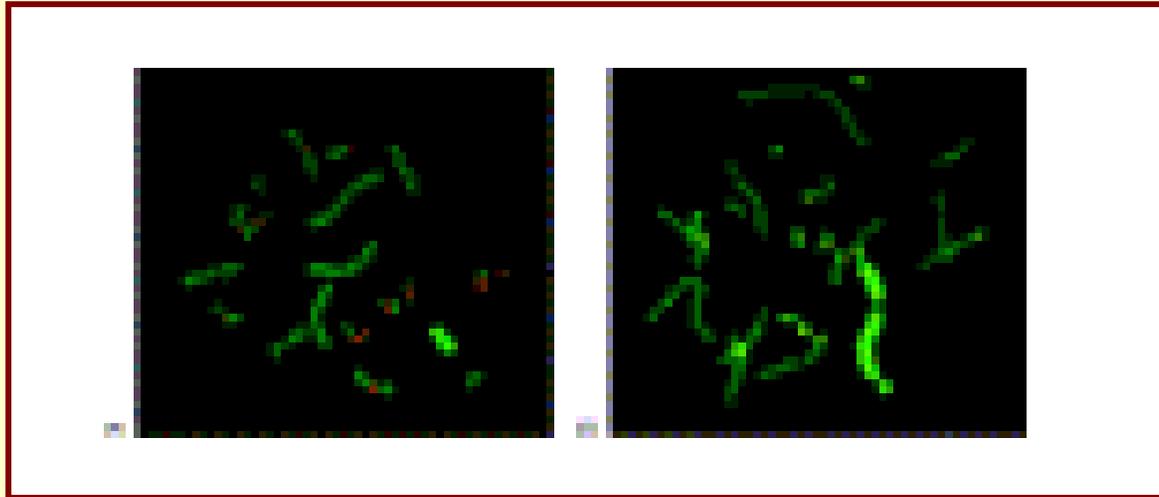
Genomic Instability can be demonstrated in cells of some strains of mice



B. Ponnaiya & R.L. Ullrich, 1998

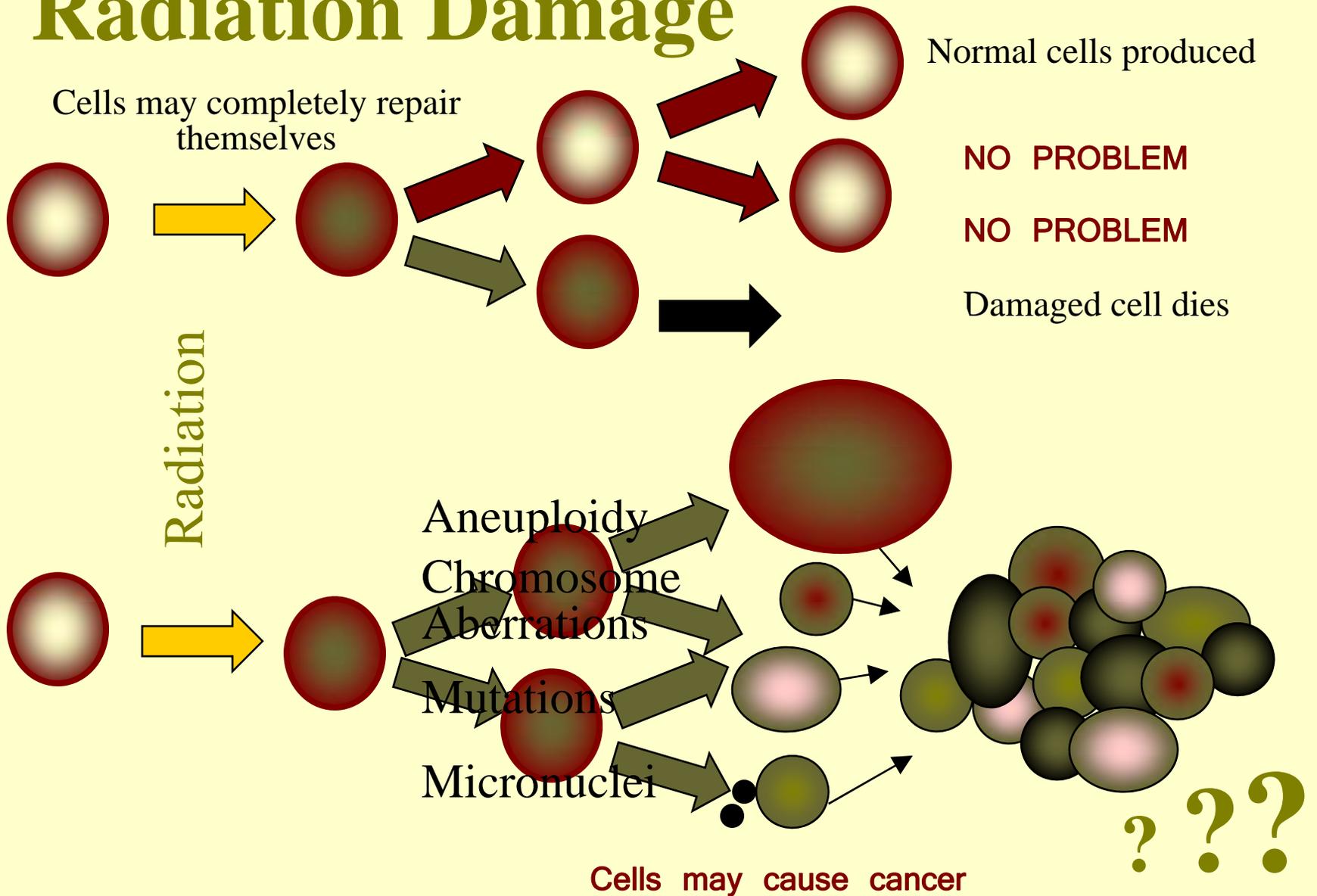
Chromosome damage

Examples of damaged chromosomes from radiation-induced genomic instability



Bill Morgan

Possible Outcomes of Radiation Damage



Impact on Standards



Genomic Instability

- Provides a mechanism to explain how radiation can produce the multiple steps needed to transform a normal cell to a malignant cell
- Supports the LNTH if cellular genomic instability can be shown to increase cancer frequency

Summary



- Radiation-induced genomic instability is defined as detrimental effects that occur several cell generations after radiation exposure.
- This may be due to factors produced by inflammatory response or a failure of genes to turn on or off properly.
- Signaling factors involved in genomic instability may be similar to those involved in bystander effects.
- Increased Reactive Oxygen Species (ROS) may also interfere with normal cellular processes and produce genomic instability.