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Cellular Defense Mechanisms Against the Biological Effects of Ionizing Radiation

Eye-Opener E0-10

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Modern Radiation Biology

Understanding Mechanisms - Cellular Responses and Risk

Genetics and Environment - Role in Responses and Risk

Biological Dosimetry - Detecting Damage and Risk

Dosimetry and Microdosimetry

Biological ***Defense*** Mechanisms Against the Effects of ***High Doses*** of Ionizing Radiation

Biological ***Response*** Mechanisms Against the Effects of ***Low Doses*** of Ionizing Radiation

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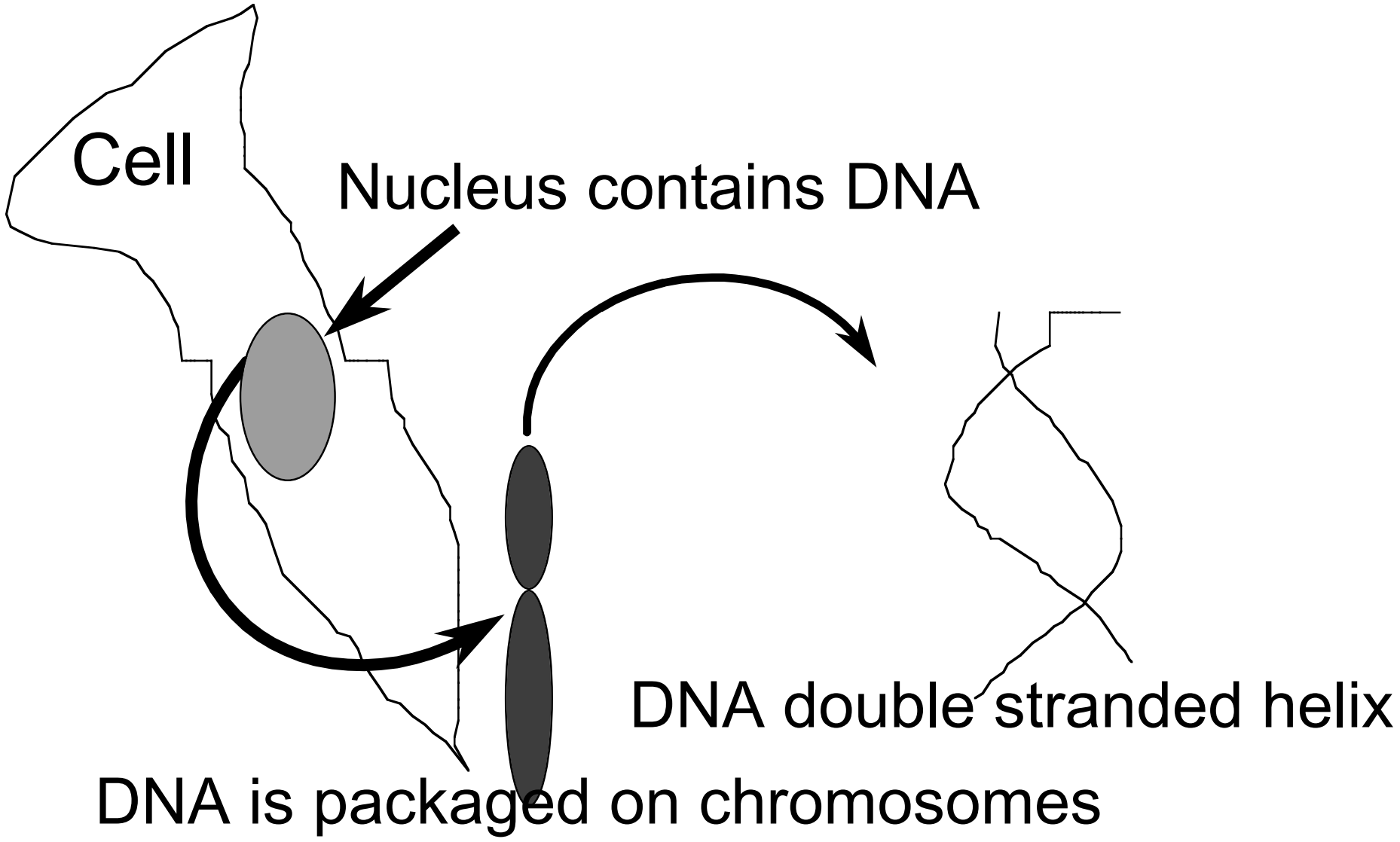
What are the biological risks?

- cell death
- genetic changes
- cancer

Critical Target is DNA



Critical Target is DNA

1. Alpha particles through nucleus are lethal but particles through cytoplasm are not lethal.

2. Cells with nucleus removed are not killed by radiation but if an irradiated nucleus is put into a cell the cell will die.

3. Microbeams can kill a cell by hitting the nucleus

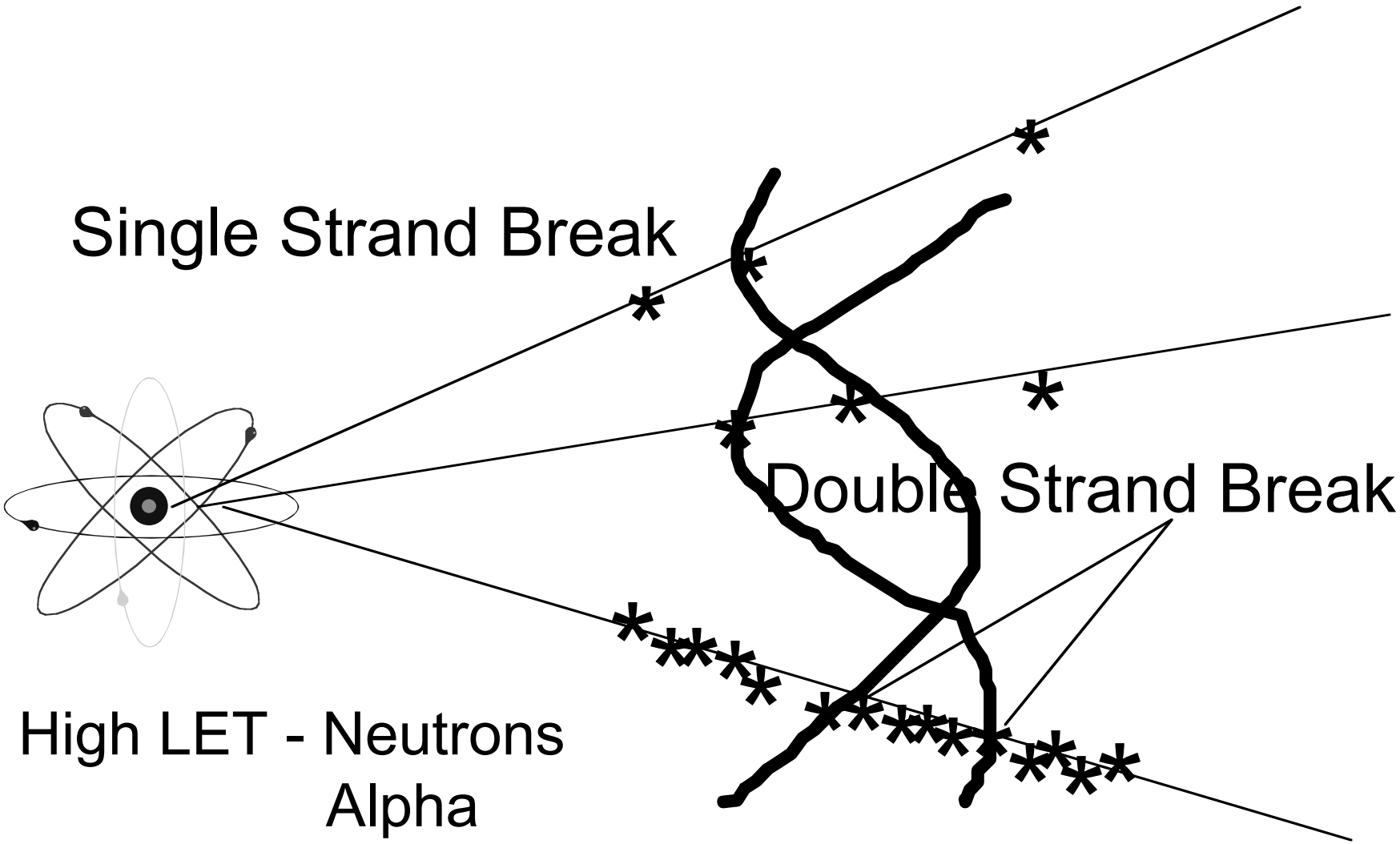
4. There is a bystander effect that indicates that DNA is the target in irradiated cells but the effect may be seen elsewhere.

LET and Damage Distribution

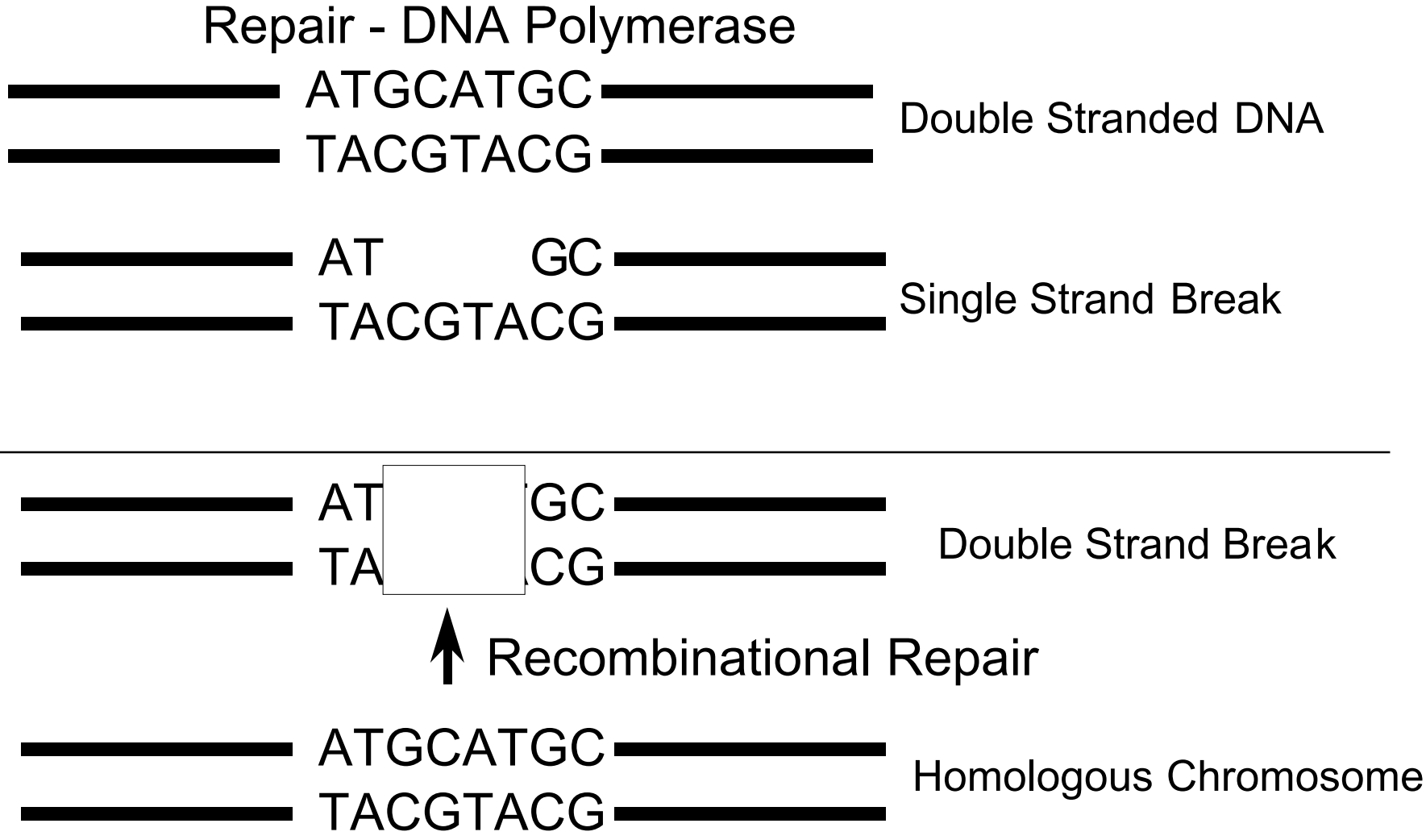
Low LET - Spare ionization tracks that are evenly distributed throughout the nucleus and produce mainly DNA single strand breaks

High LET - Dense ionization tracks that are clustered throughout the nucleus and produce mainly DNA double strand breaks

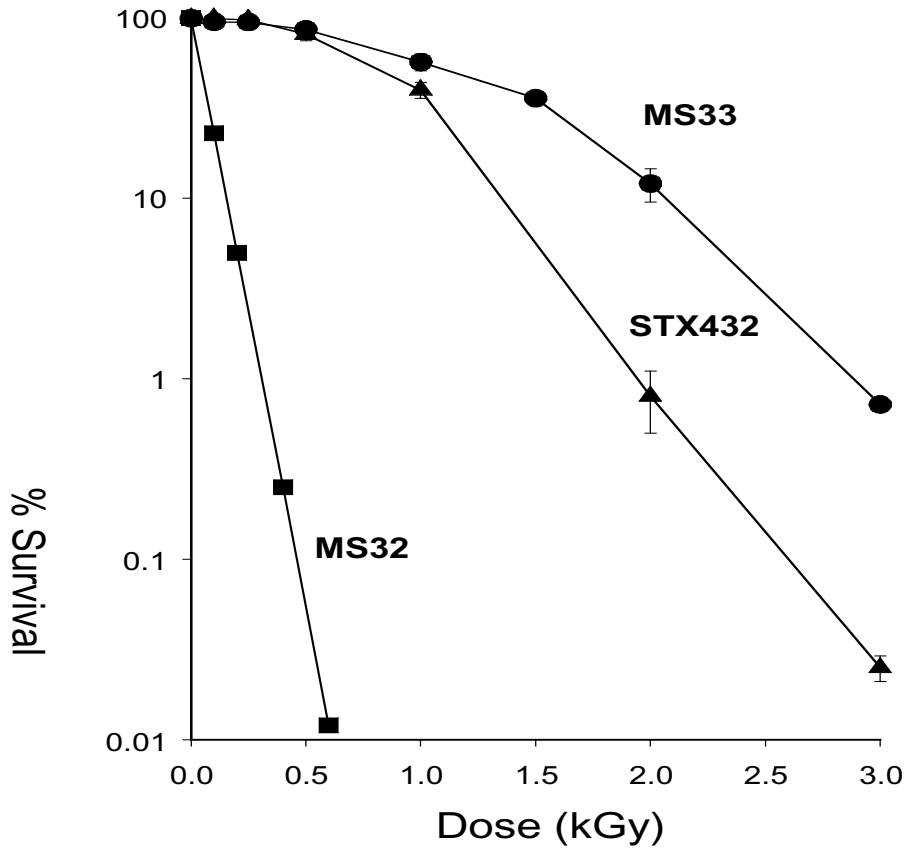
Types of DNA Damage



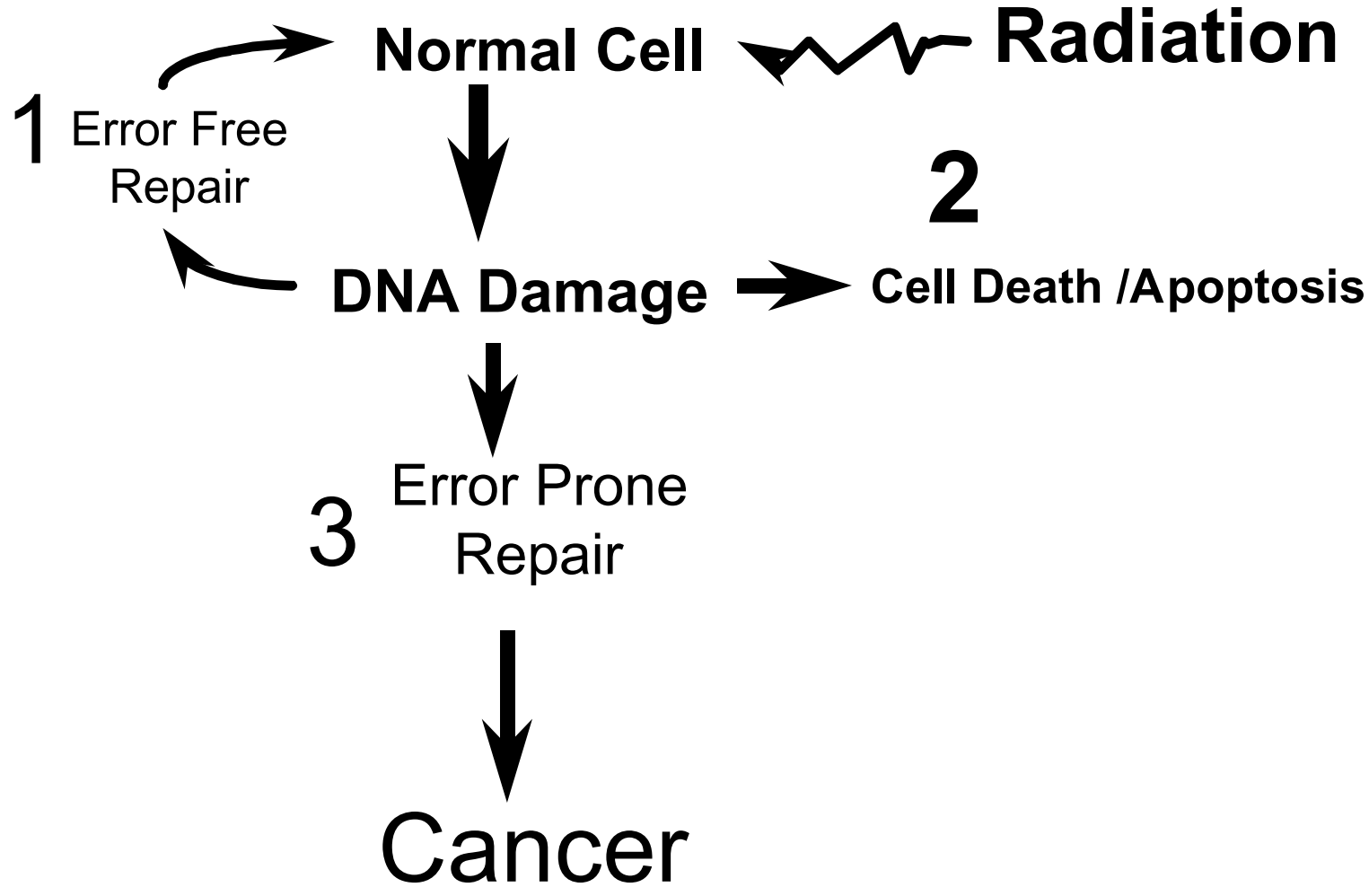
DNA Strand Break Repair



Survival of yeast cells after exposure to gamma radiation



DNA Damage and Risk
MUTATION AND CANCER



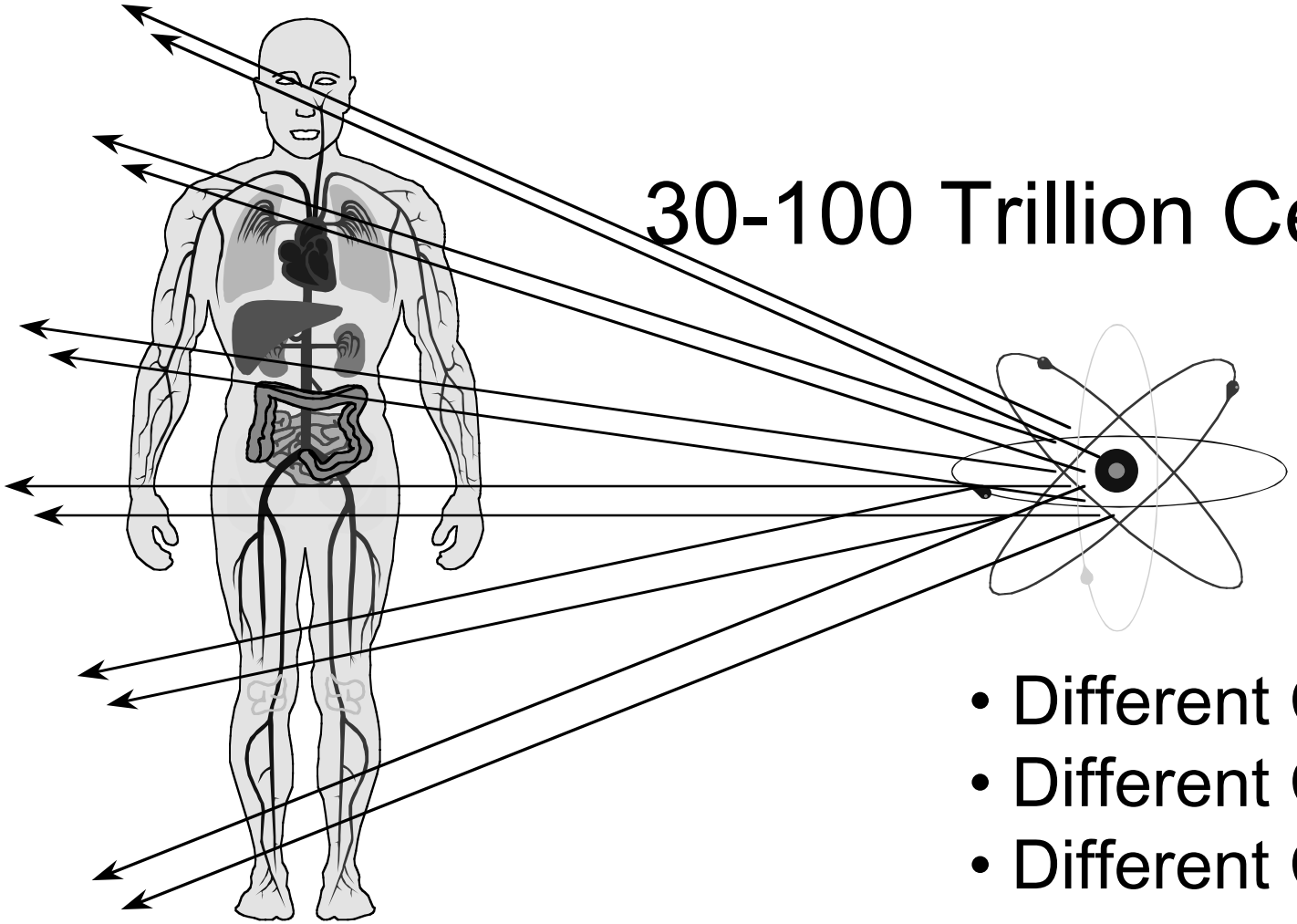
Adaptive Response - The induction of DNA error free repair by prior sublethal low priming dose of radiation.

Micronucleus formation - reduced micronucleus formation when acute priming exposure is followed by incubation time.

Micronucleus formation - reduced micronucleus formation immediately following a chronic exposure.

Radiation Biology

1 mGy = 1 year of background radiation



30-100 Trillion Cells at Risk

- Different Cell Types
- Different Cell Cycle
- Different Cell Targets

Transformation Frequency in C3H/10T1/2 Cells

Dose (mGy)	Frequency (x10-4)
0 (control)	18
1.0	6.2
10	3.9
100	4.9

Bystander Effects

% Cells Hit	Exact # Alpha	Transformed Cells/10-4
0	0	0.99
10	8	10.6
100	8	13.2

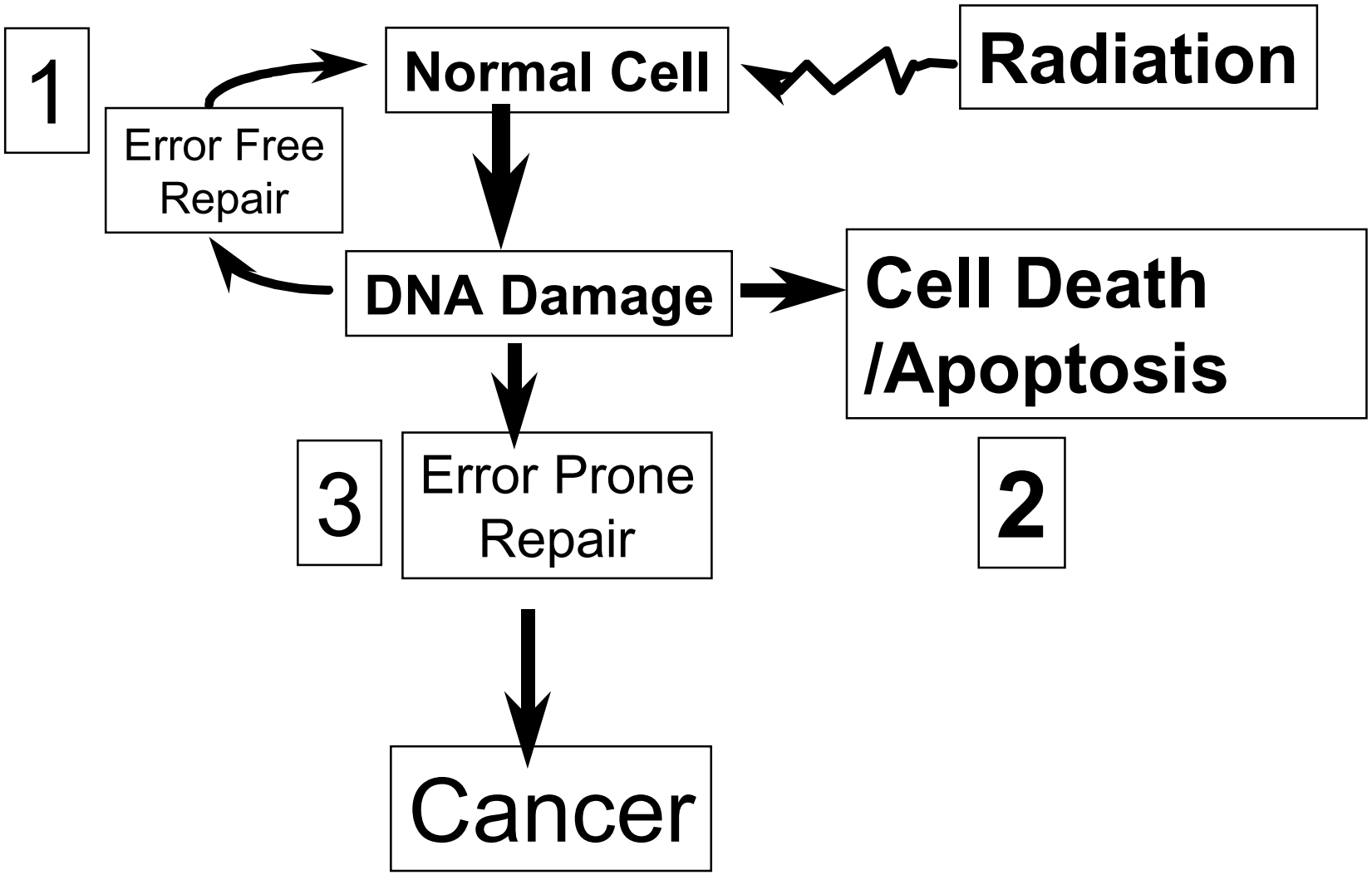
Heat Shock Response/Stress Response

Heat Shock Induces Thermal Tolerance and Radiation Resistance in Yeast

Heat Shock Induces Radiation Resistance in Mice (40 degrees Celsius for 60 minutes 24 hours prior to a lethal 9 Gy dose confers 100% survival)

Heat Shock Protects Skin Cells from Chemical Carcinogens

Cell Death / Apoptosis



Apoptosis/Programmed Cell Death (Cell Suicide)

- Normal process in development
- About 0.1% of cells in body die every day from apoptosis
- Defects in apoptosis increases cancer risk

Apoptosis

- cell suicide, programmed cell death
- genetically controlled
- regulatory / protective mechanism
- cells go apoptotic when DNA is defective

Understanding radiation-induced apoptosis will help us understand risk

Apoptosis

Individual Variability

Potential as Biological Dosimeter

May be Useful to Assess Individual Radiation Response

Adaptive Response Enhances Apoptosis

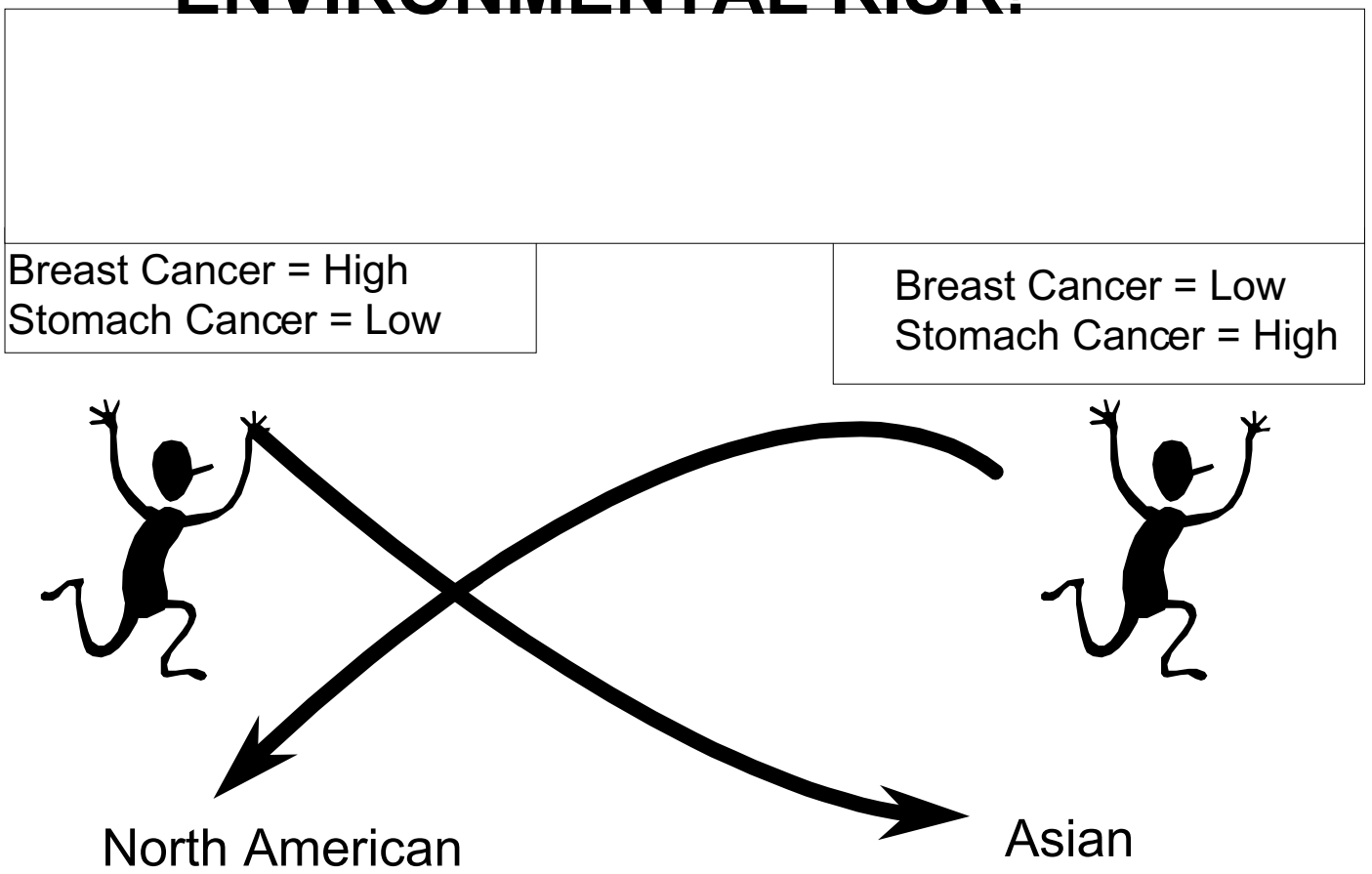
IAP - **Inhibitor of Apoptosis Proteins** are Differentially Induced by Chronic and Acute Doses

Radiation Cancer Risk Genes

Prediction
Relative Risk - Genetics Vs Environment

- **Identification of Radiogenic Cancer Risk Genes**
- **Assays to Detect Radiogenic Cancer Risk Genes**
- **Animal Models with Knockout Genes**

ENVIRONMENTAL RISK!



Risk of getting cancer = 35%

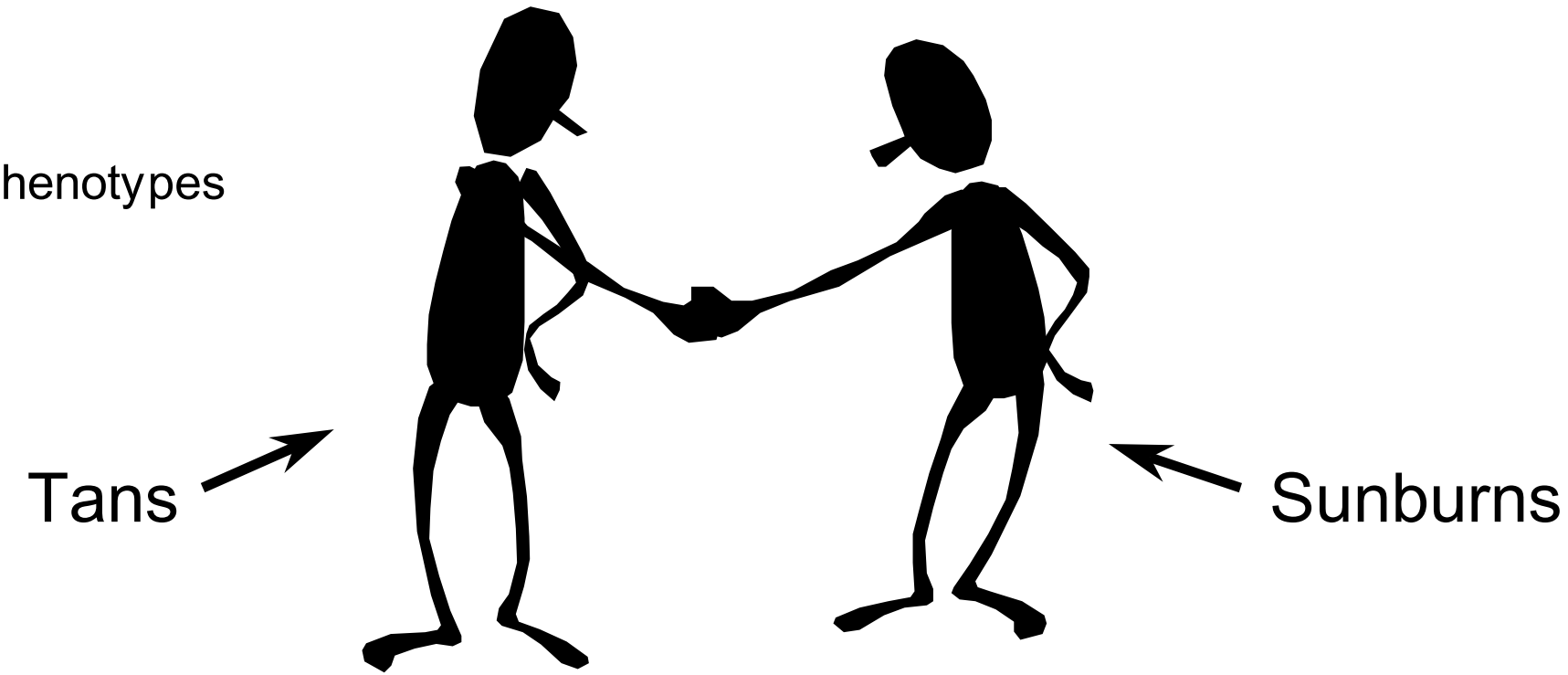
Risk of dying from cancer = 20%

Cancer risk from exposure to radiation = 5% / Sv

Cancer Risk and Radiation

Risk of UV-Induced Cancer

Phenotypes



Genetic Predisposition!

Genes and Cancer Risk

Xeroderma pigmentosum

XP

HOMOZYGOUS - Cancer Prone
HETEROZYGOUS - ?

Children of the Moon

www.xps.org

Cancer Genes - Rad51, p53

- **p53 is the "guardian of the genome" protein and controls apoptosis**
- p53 protein plays a major role in cancer risk
  - Human Papillomavirus (HPV) causes cervical cancer (Sexually Transmitted Cancer)
    HPV makes E6 oncoprotein which attacks and inactivates p53, preventing apoptosis and causing cancer
  - When p53 is genetically inactivated "Knocked Out" in the cells of a mouse, the mouse has a higher spontaneous cancer risk and is also more prone to radiation-induced cancer

p53 “Knockout” Mice

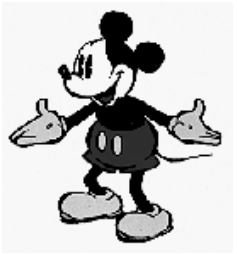
Kemp et al. Nature Genetics 8:66-69, 1994

Normal p53
Two good copies
Homozygous

> 100 Weeks
no tumours

4 Gy

> 100 Weeks
no tumours

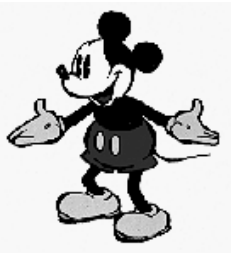


One bad p53 copy
One good copy
Heterozygous

70 weeks
tumours

4 Gy

40 Weeks
tumours



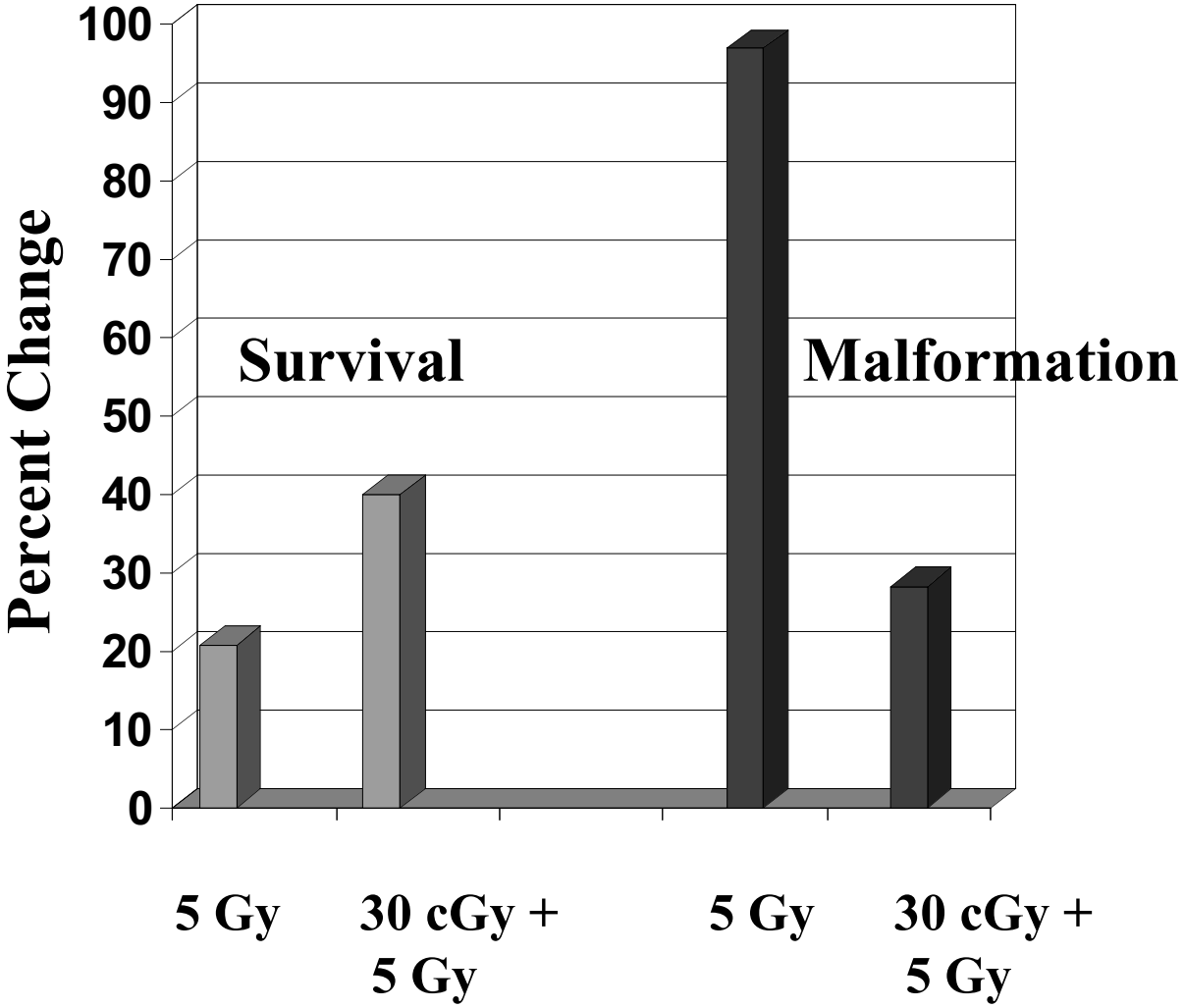
No p53
Two Bad Copies
Knockout

21 weeks
tumors

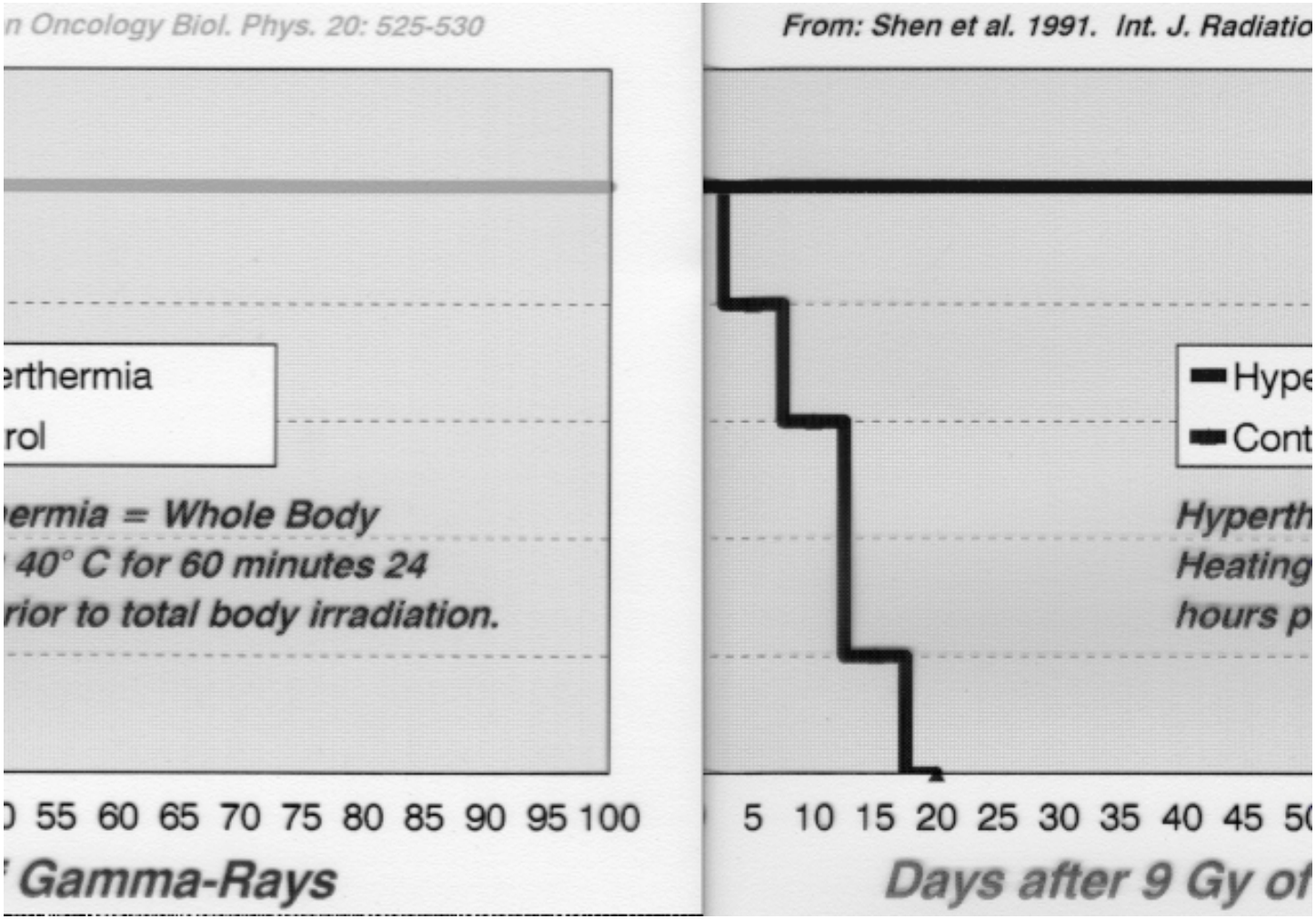
1 Gy

14 Weeks
tumours

Effect of *In Utero* Irradiation in Fetal Mice



Wang *et al*. 1998 *Rad. Res*. **150**, 120-122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Gamma-Rays
Days after 9 Gy of