Fallout and its Effects
Biological Response

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What I am not going to talk about

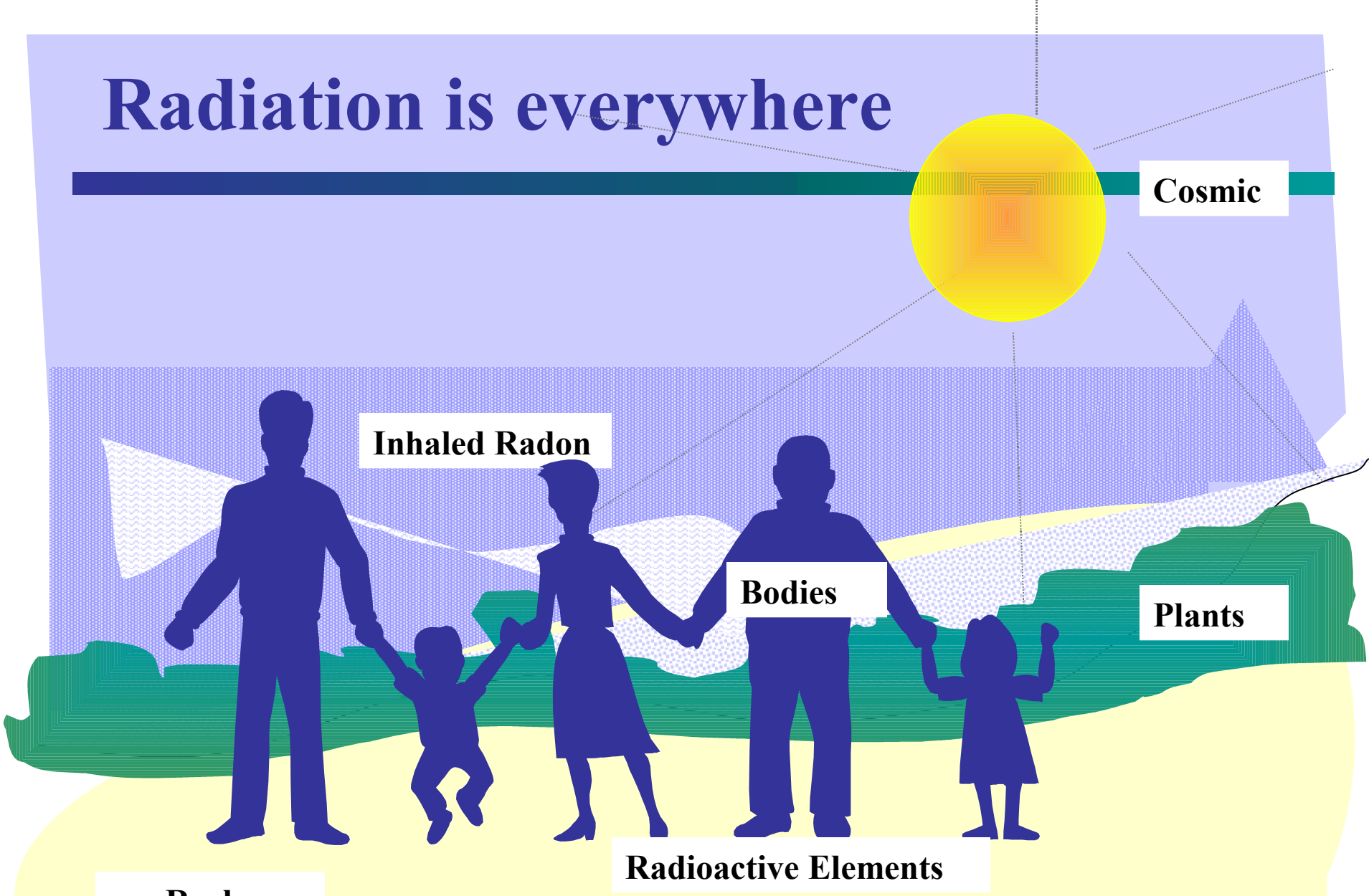
- Politics
- Church
- Reinbursement

What I am going to talk about

- Background radiation
- Background cancer
- Problems in detection of radiation-induced cancer
- New molecular biology
- Impact on risk

Background Radiation

Radiation is everywhere



We live in a sea of radiation…

Normal annual exposure from natural radiation

About 240 mrem/yr

Radon gas	140 mrem
Human body	40 mrem
Rocks, soil	30 mrem
Cosmic rays	30 mrem

Normal annual exposure from man-made radiation

About 165 mrem/yr

Medical procedures	150 mrems
Consumer products	10 mrems
One coast to coast airplane flight	2 mrems
Watching color TV	1 mrem
Sleeping with another person	1 mrem
Weapons test fallout	less that 1 mrem
Nuclear industry	less than 1 mrem

Medical Radiation Exposures

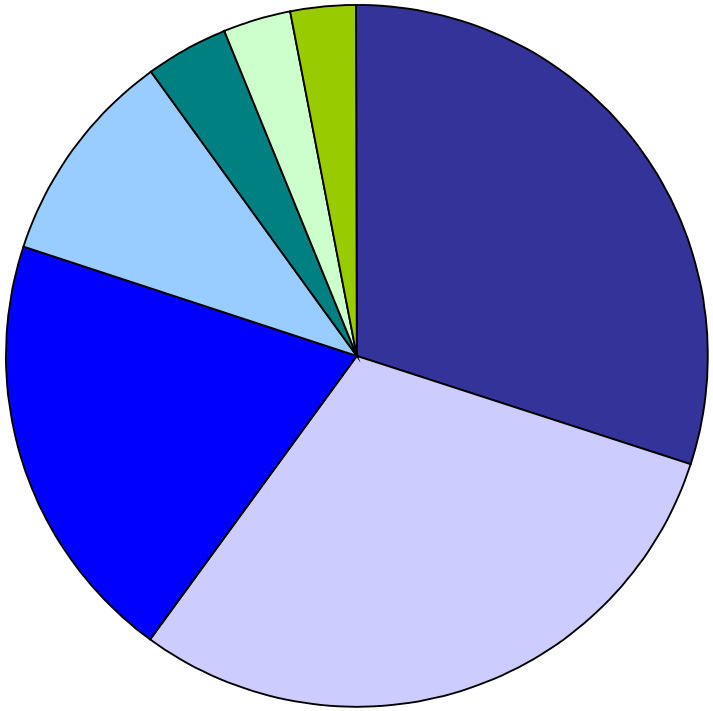
- 200 million medical x-rays/year
  - X-ray 1 mGy
- 100 million dental x-rays/year
  - Dental 0.6 mGy
- 10 million doses of radiopharmaceuticals/yr
- 67 million CT scans/year
  - Head scan 40-60 mGy/scan
  - Body scan 10-40 mGy/scan
- 8 million radiation cancer therapy/yr
  - 1000-5000 mGy/treatment

Dose Ranges

DOSE (mrems)	CATEGORY	EXAMPLE
1,000,000-10,000,000	Cancer radiotherapy	Total tumor dose
100,000-1,000,000	Experimental radiobiology	A-bomb survivors
10,000-100,000	Cancer epidemiology	Cancer detectable Space station mission
1000-10,000	Low Dose Program	Occupational limit Utah fallout
100-1000	Medical diagnostics	Natural background Airline flight
10-100	Regulatory standards	Dental, chest X-rays Occupational limits
1-10	Negligible doses	Three mile island

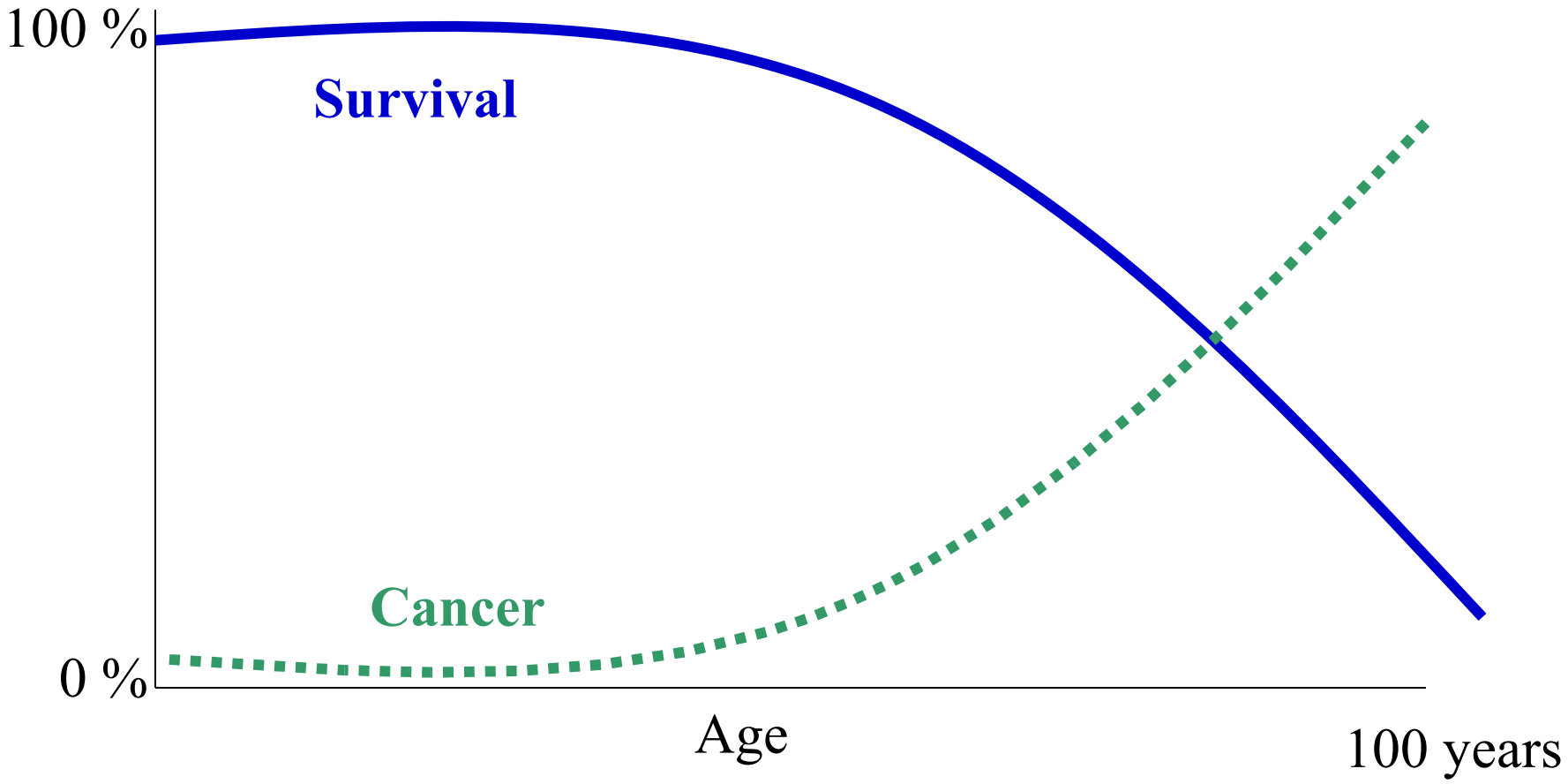
Background Cancer

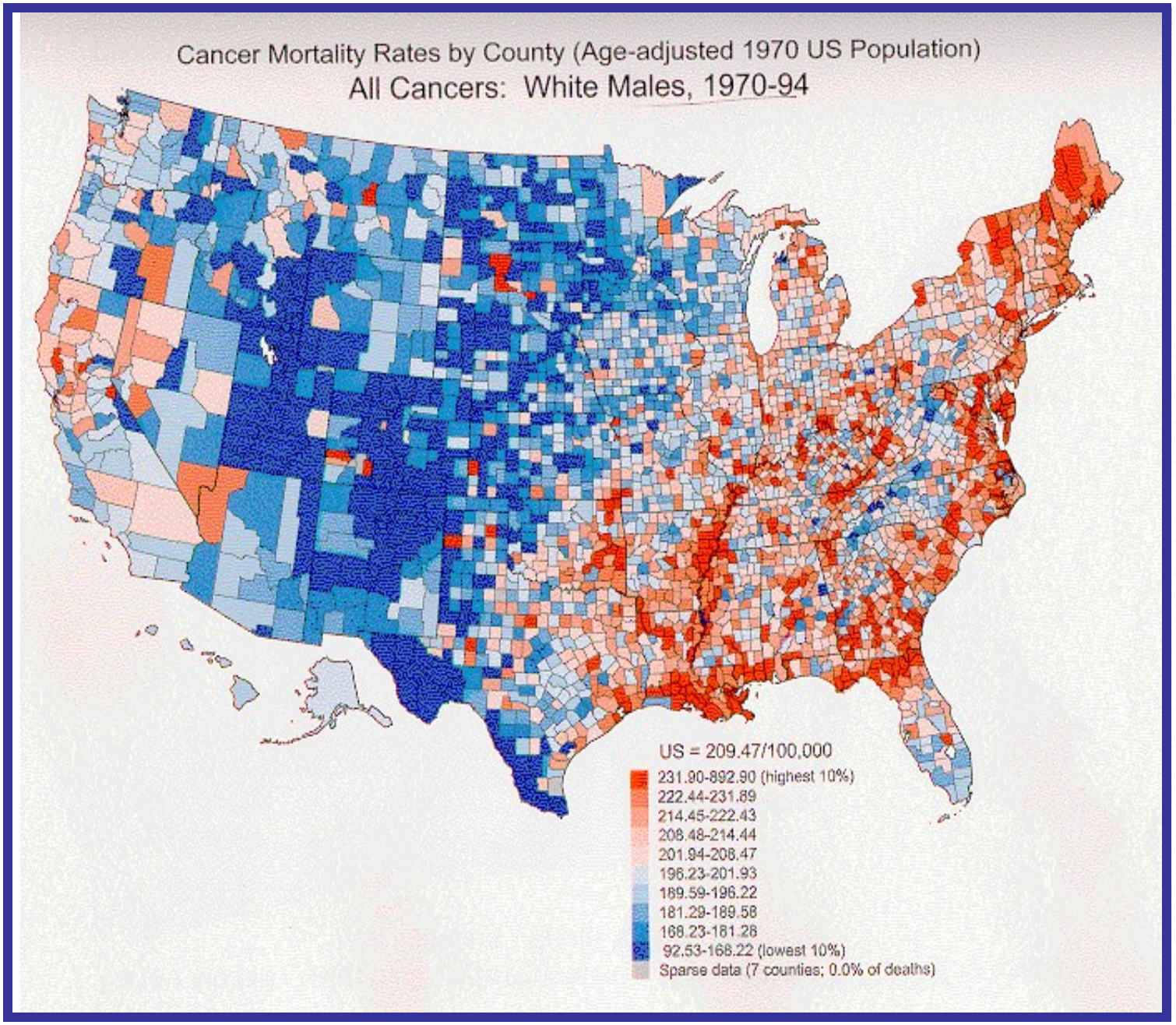
What Causes Cancer?



- Cigarette smoke
- Diet & Nutrition
- Chronic infection
- Occupational exposure
- Genetic
- Alcohol Drinking
- Environmental Pollution

The Influence of Age on Cancer and Survival




Cancer Mortality Rates by County (Age-adjusted 1970 US Population)
All Cancers: White Males, 1970-94
US = 209.47/100,000
231.90-892.90 (highest 10%)
222.44-231.89
214.45-222.43
208.48-214.44
201.94-208.47
196.23-201.93
189.59-196.22
181.29-189.58
168.23-181.28
92.53-168.22 (lowest 10%)
Sparse data (7 counties; 0.0% of deaths)

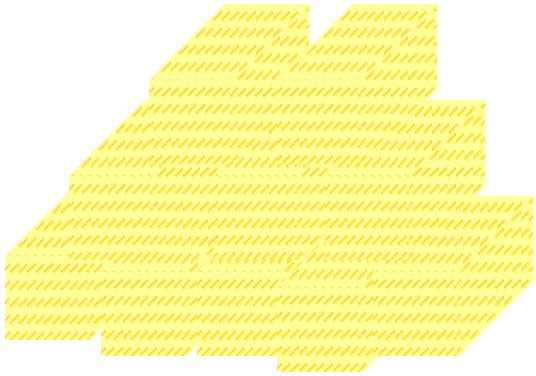
Is there a radiation-induced cancer epidemic?

- Life span well above the national average
- Cancer incidence lowest in the country
- The data suggests, “No!!”
- Why the concern?
  - Fallout did exist.
  - Everyone was exposed.
  - There is a pay off for those that develop the “proper” disease.

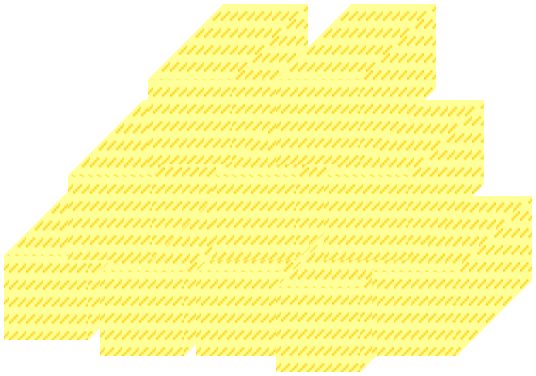
Problems with Low Dose Epidemiology

- Background radiation

- Background cancer



Background



Low

High

Why isn't there more radiation- induced cancer?

Radiation is a poor mutagen and a poor carcinogen, but a very good cell killer.

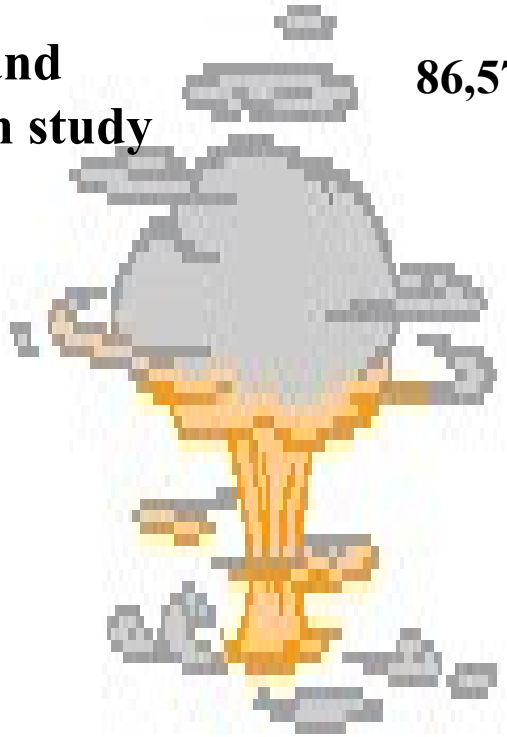
- High doses kill many cells
  - Radiation sickness
  - Cancer therapy
- Low doses kill a few cells
  - Dead cells do not cause cancer.
  - Damaged cells are often repaired.

Linking radiation to cancer

- A-bomb
- Medical exposures
- Chornobyl
- Utah fallout
- Three Mile Island

Effects of Atomic Bomb

- **Killed outright by the bomb or acute radiation effects.** — **100,000 people**
- **Survived acute effects and followed for the lifespan study** — **86,572 people**



Atomic Bomb Survivor Excess Cancer

Population of Survivors Studied **86,572**

Total Cancers observed after the Bomb	8,180
Total Cancers Expected without Bomb	7,743
Total Cancer Excess	**437**

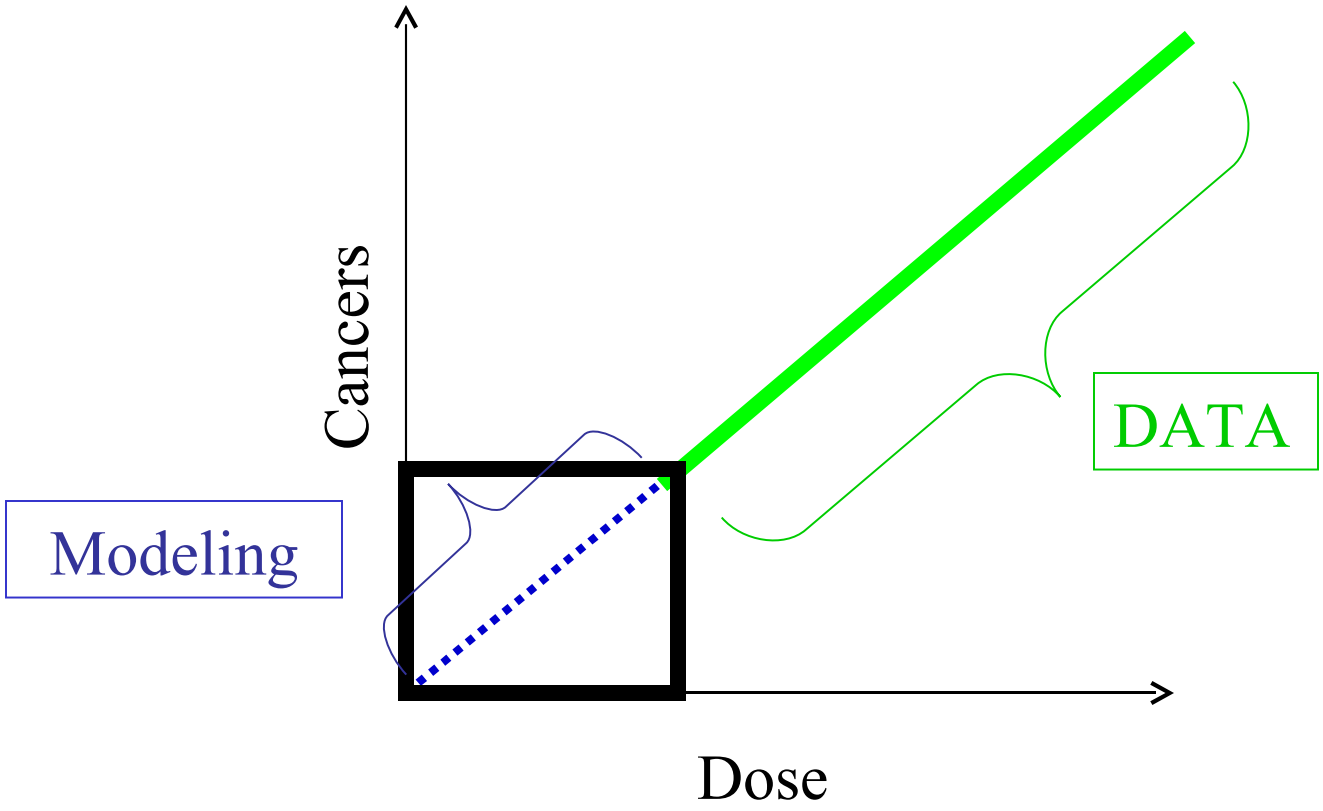
Excess Tumor		Excess Leukemia		
334	+	104	=	437

Why now?

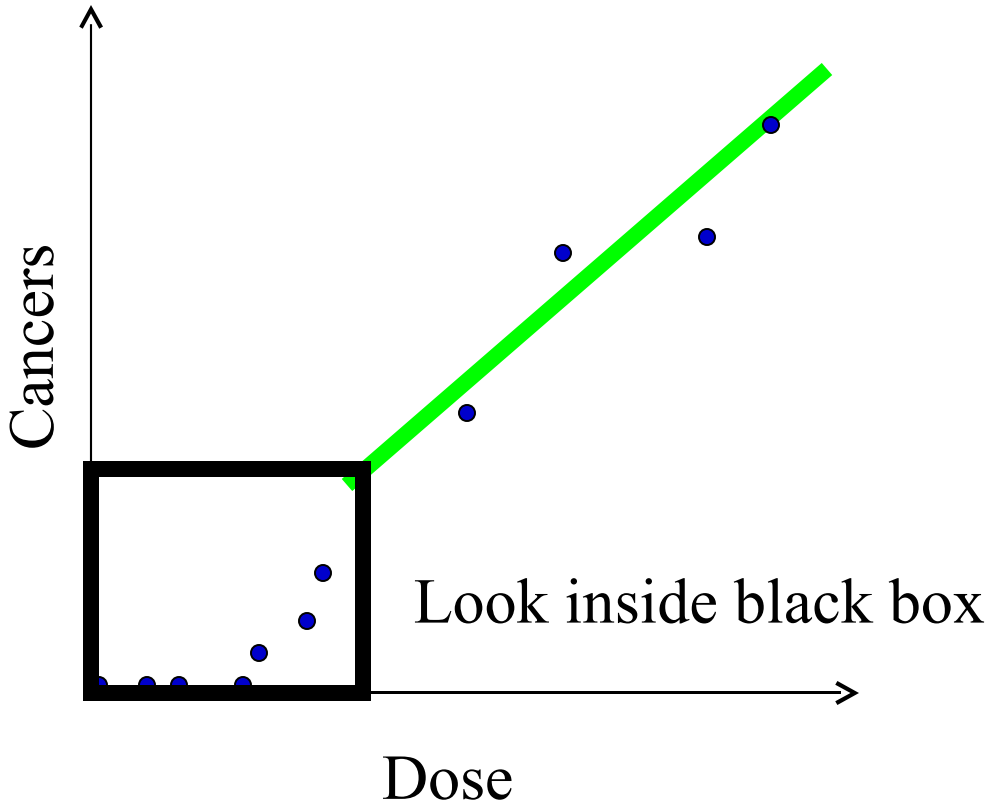
- Standards set from high dose effects, but low dose effects have not been measurable until now

- New technological developments and biological discoveries have made it possible for mechanistic studies of low dose effects

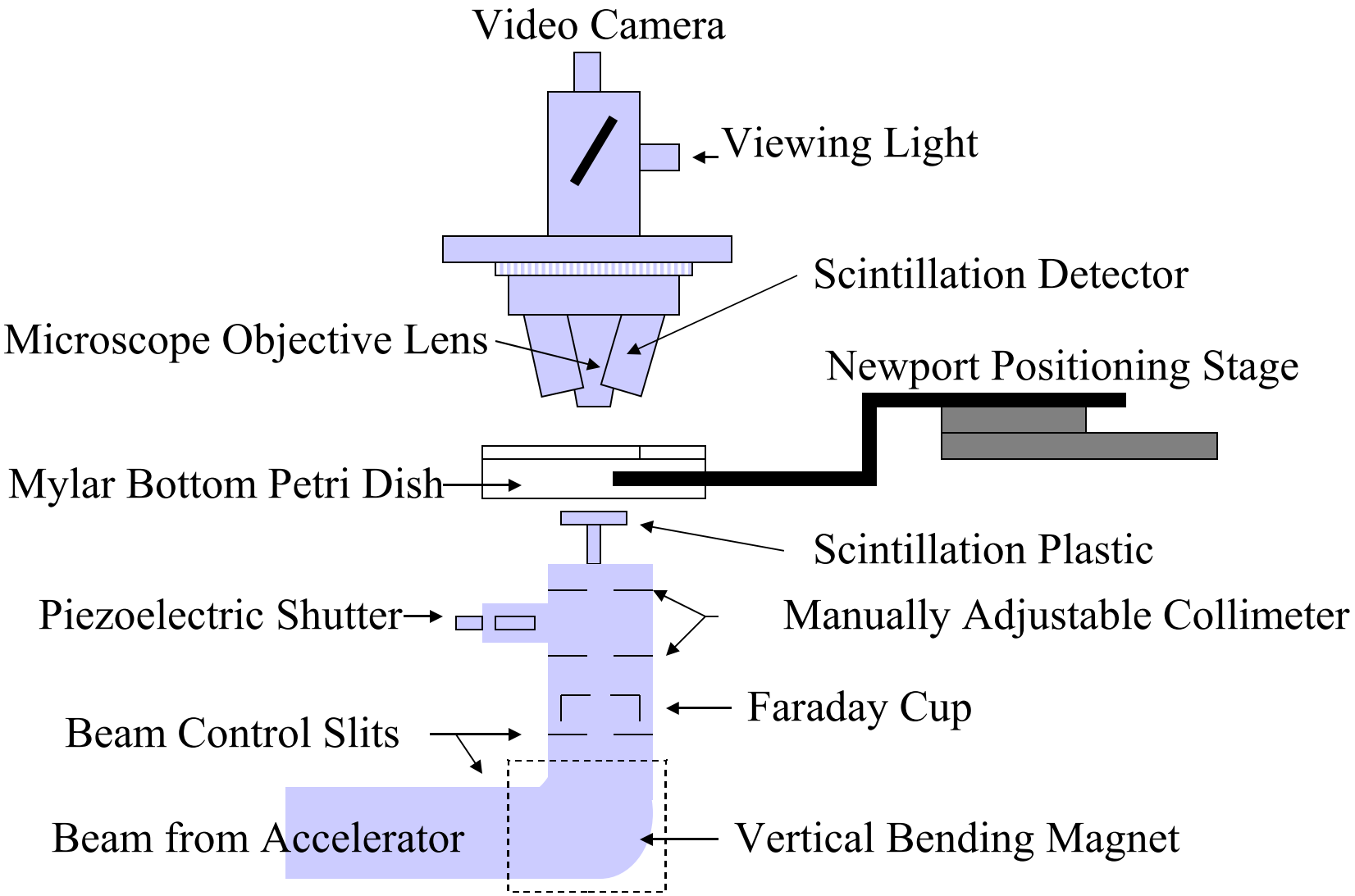
Linking radiation to human cancer studies



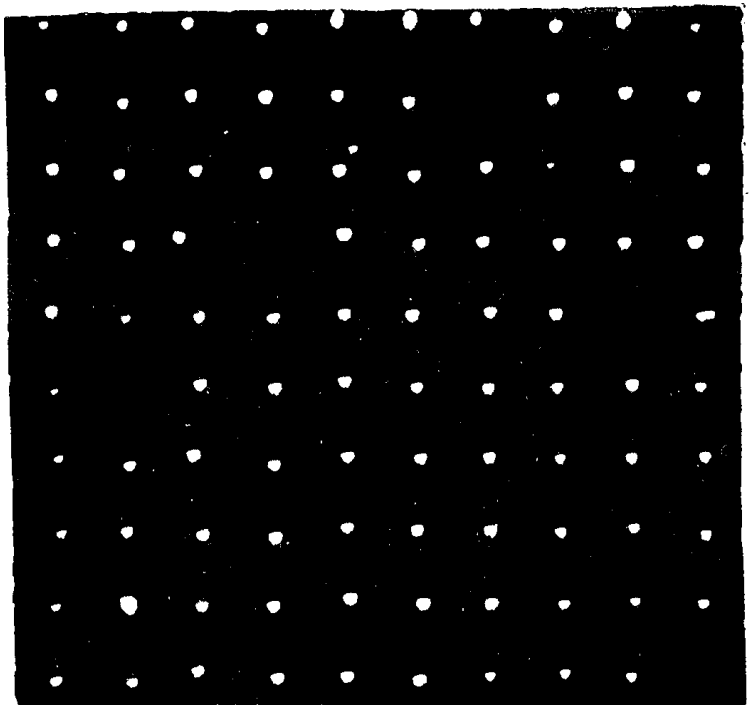
Linking cancer to cell and molecular radiation studies

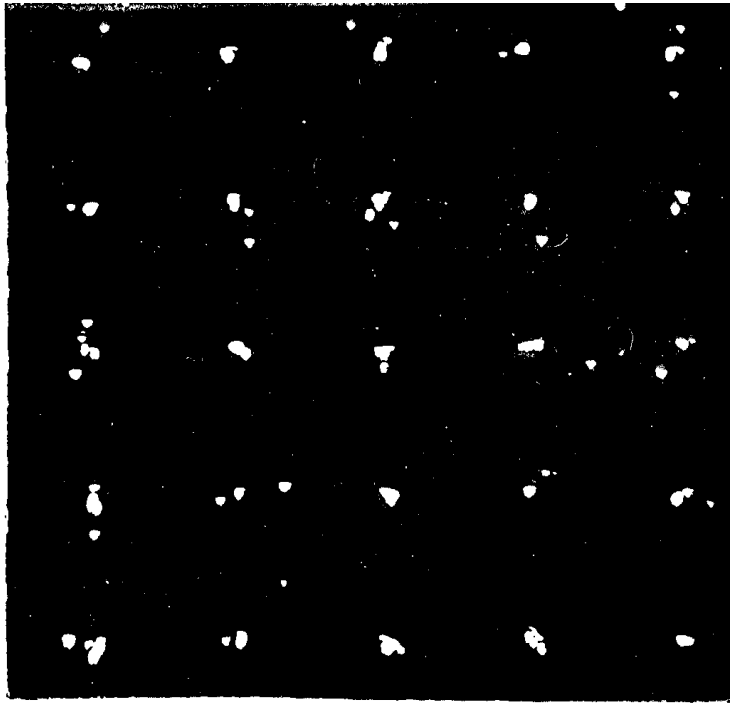


Alpha-Particle Radiation System



Microbeam Hit Accuracy

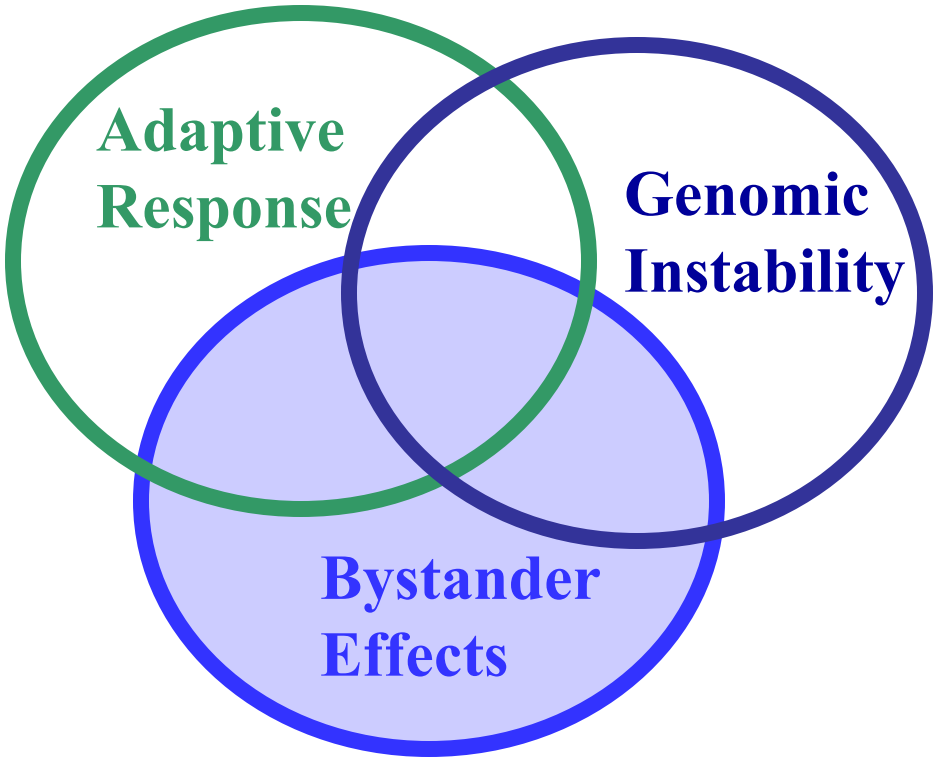




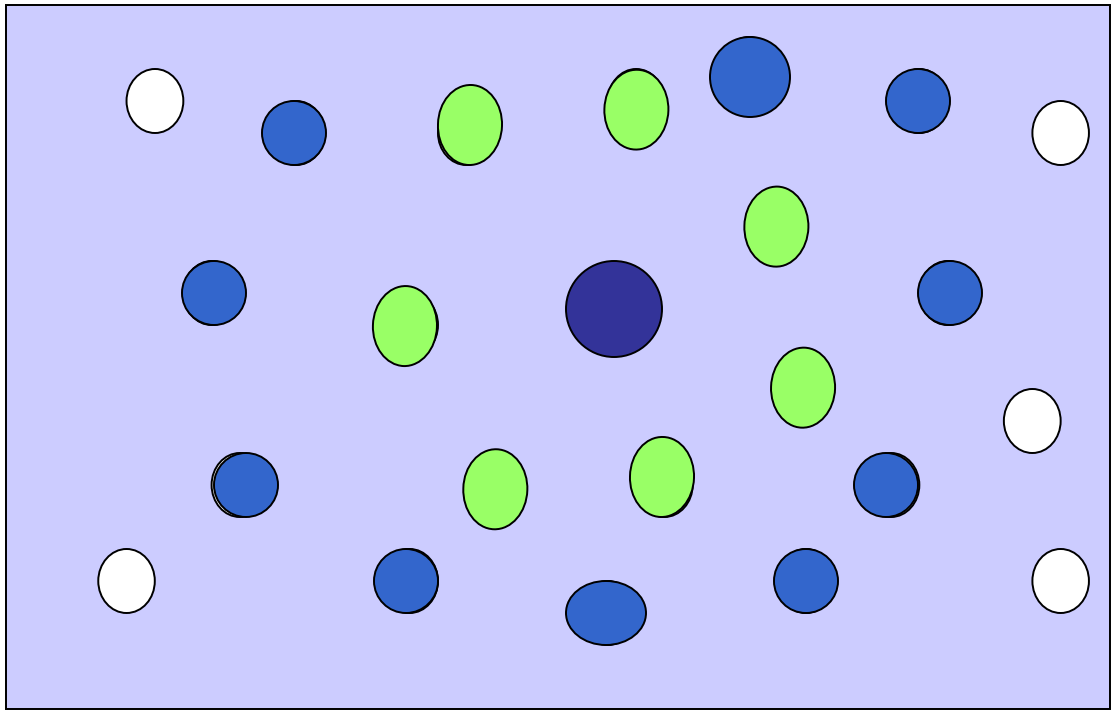
Cell to molecular changes

- **Bystander Effects**
  - Cells respond without energy deposition
  - Cell-cell communication
  - Materials into the media
- **Adaptive Response**
  - Small dose alters response to large dose
  - Small dose decreases spontaneous damage
- **Genomic Instability**
  - Loss of genetic control many cell generations after the radiation exposure

Relationship between biological responses to radiation

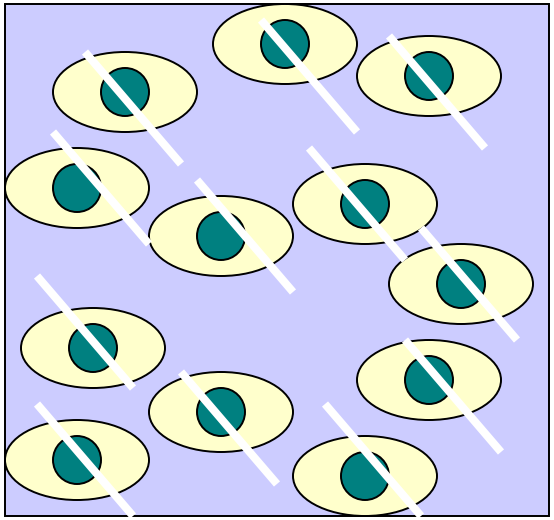


Bystander Effects *in vitro*

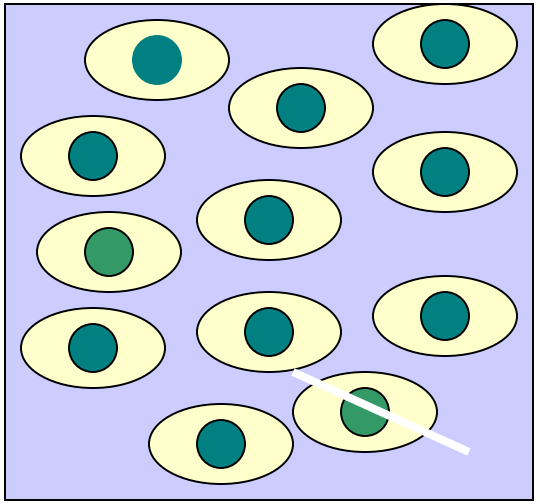


Microbeam

Each cell hit by one particle

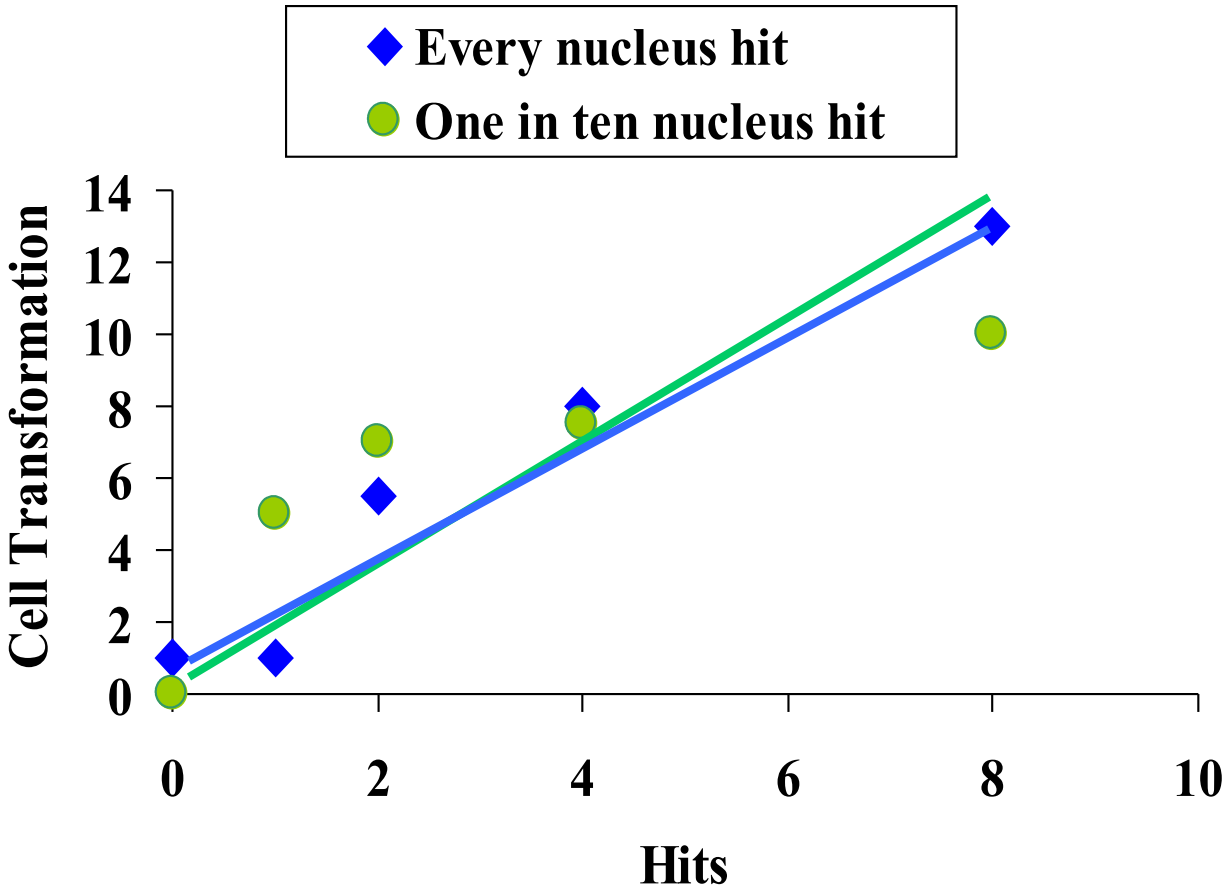


10 % of cells hit with 1 alpha particles



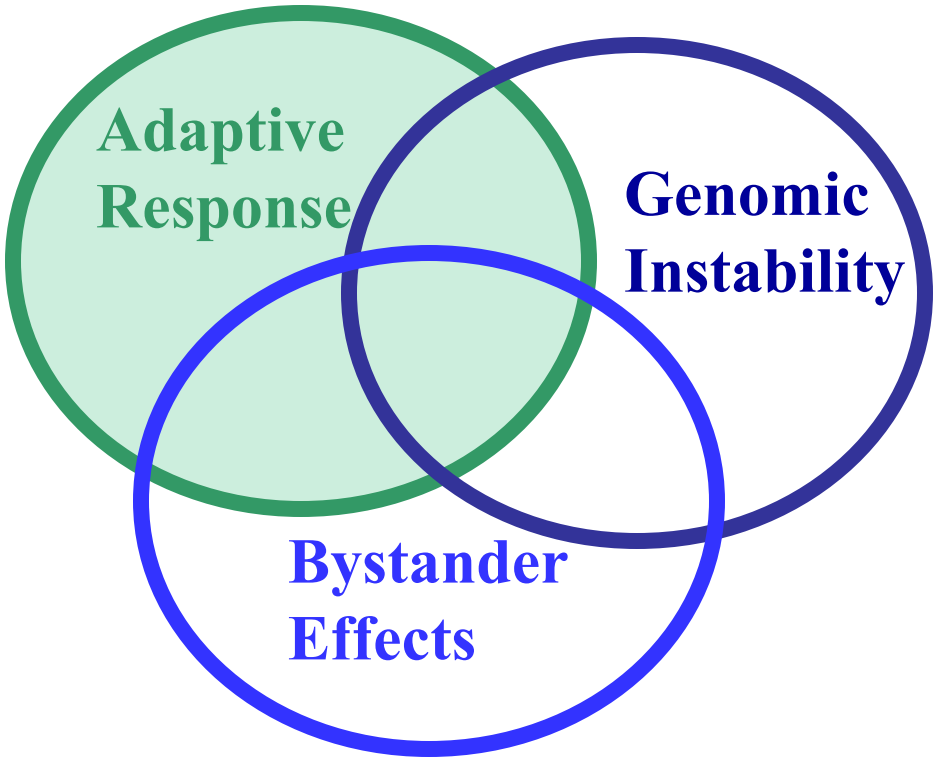
Sawant et al. 2000

Cell Transformation

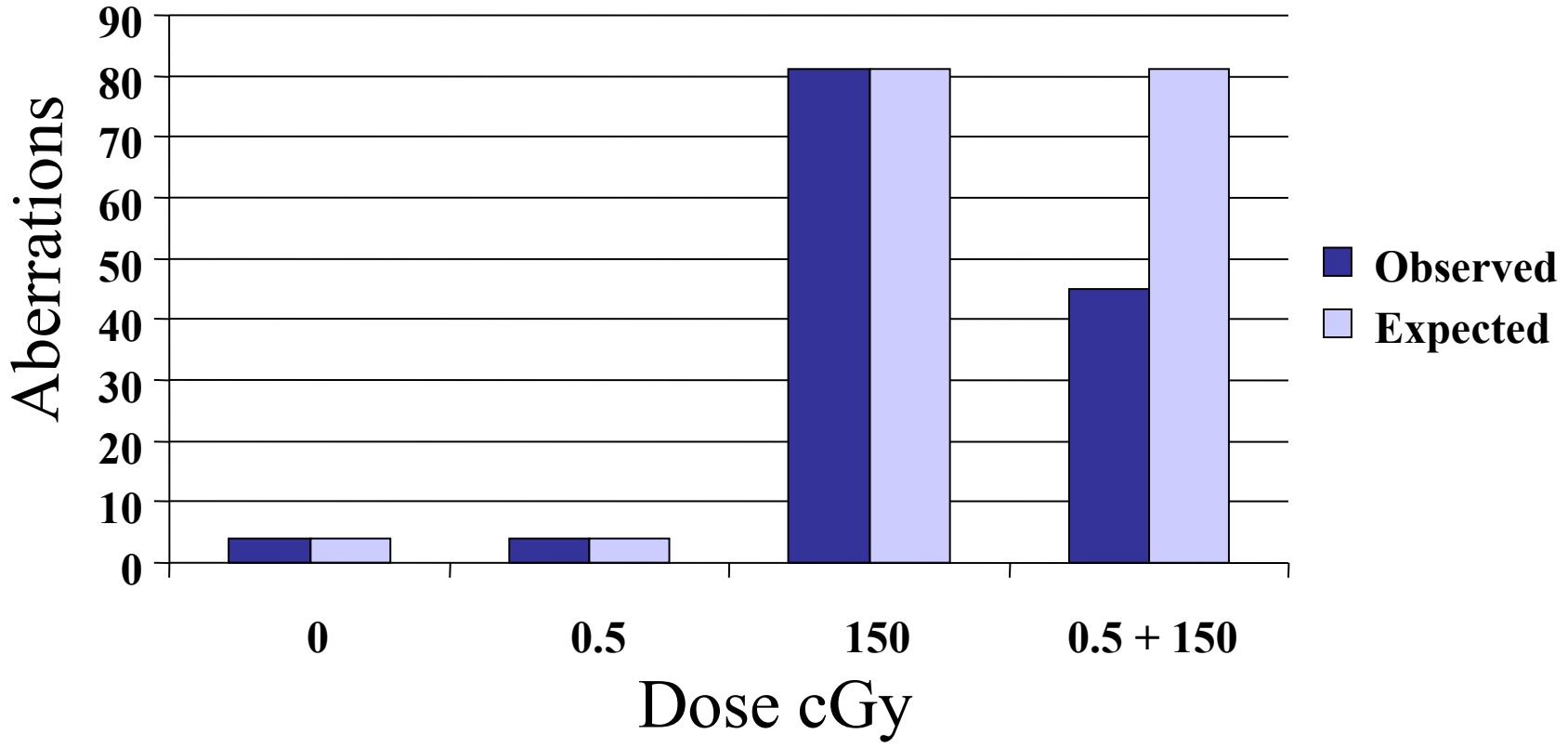


Sawant et al.2000

Relationship between biological responses to radiation

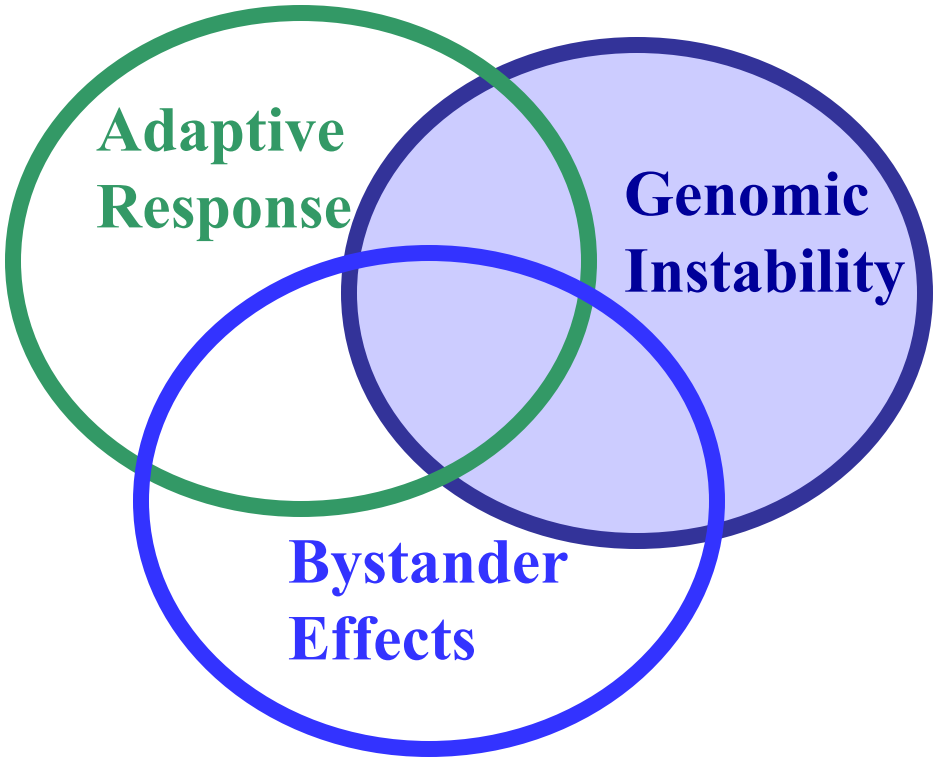


What Genes are Responsible for the Adaptive Response ?



Shadley and Wolff 1987

Relationship between biological responses to radiation

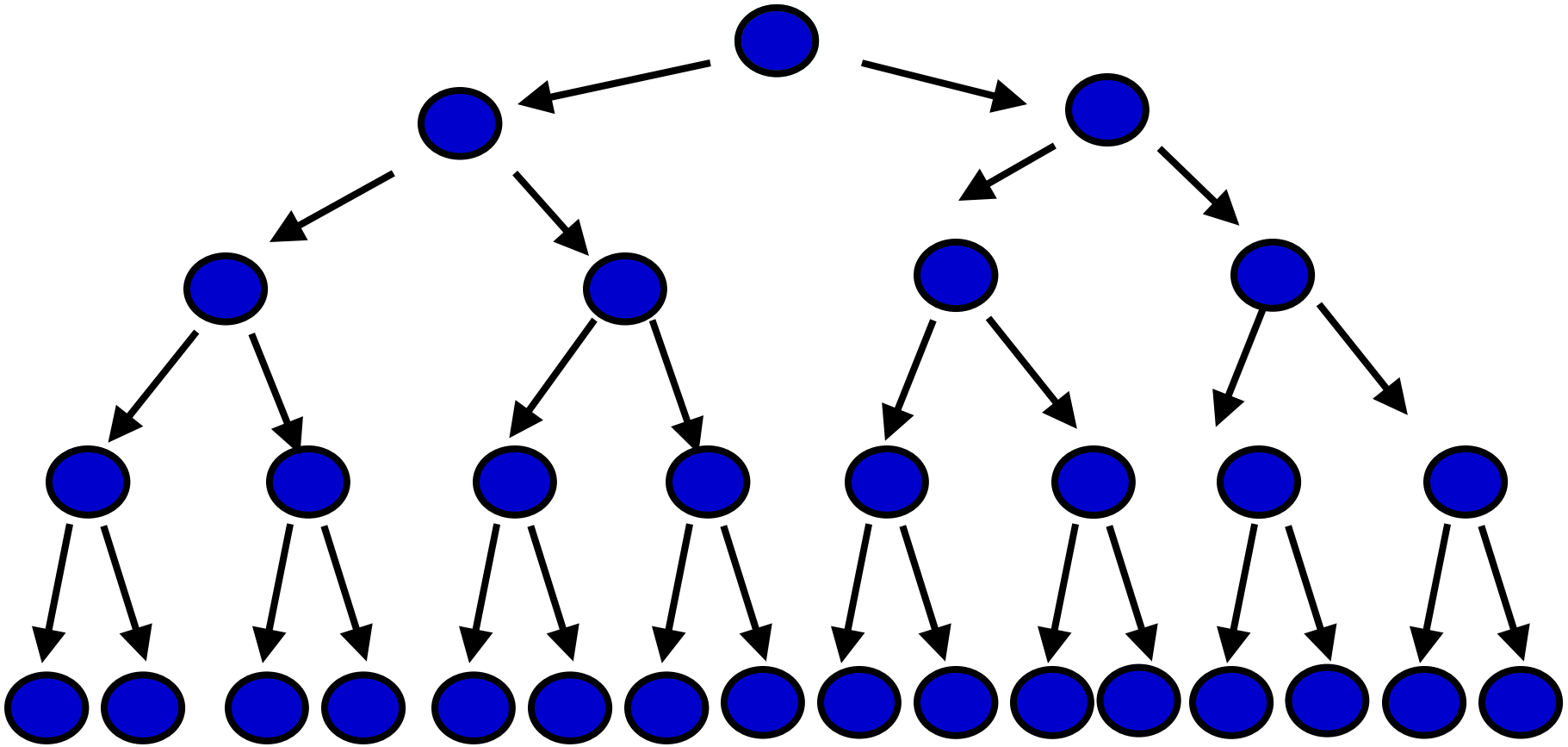


Radiation-induced Genetic Damage

Old Paradigm

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

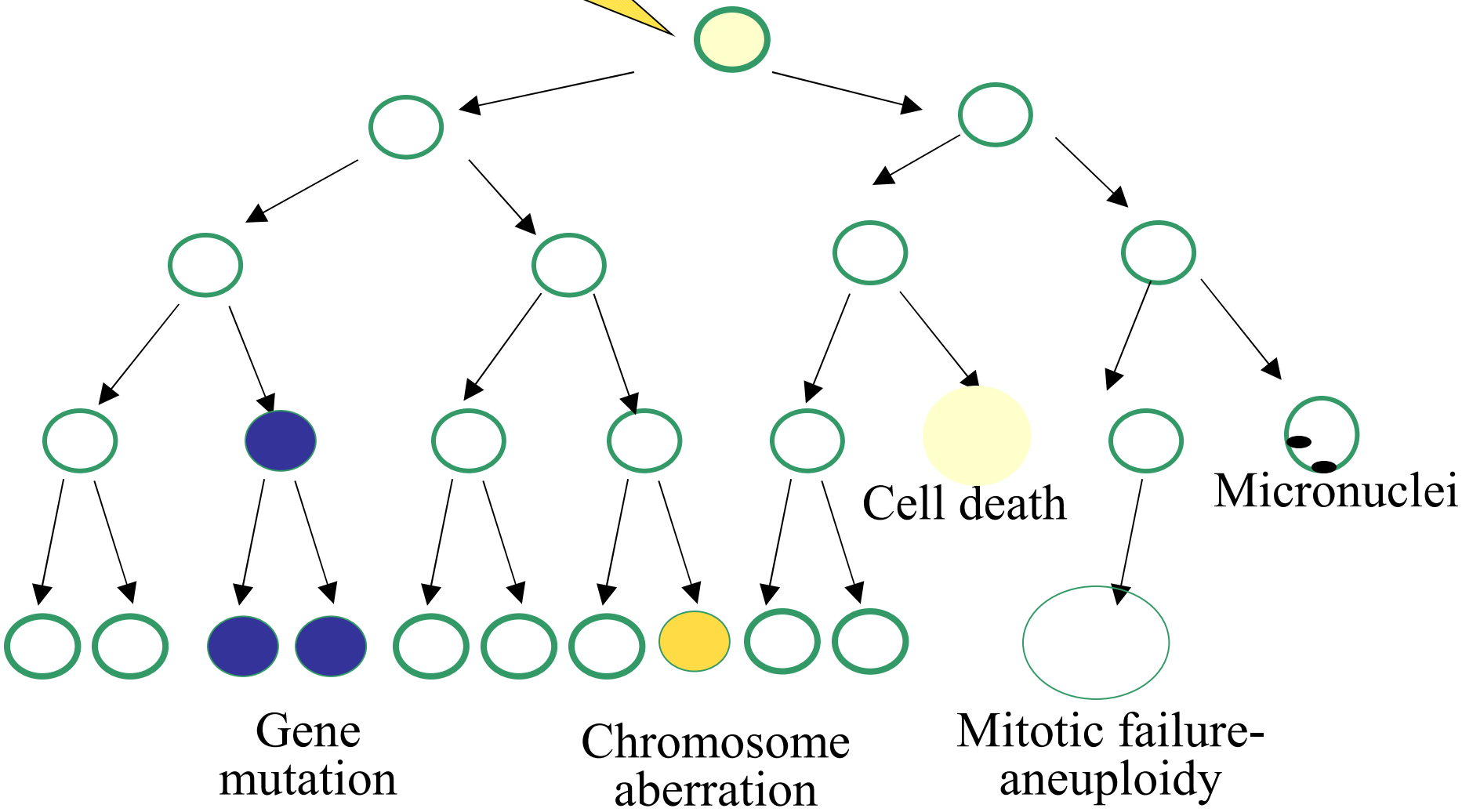
Mutation is a rare event



Genomic Instability

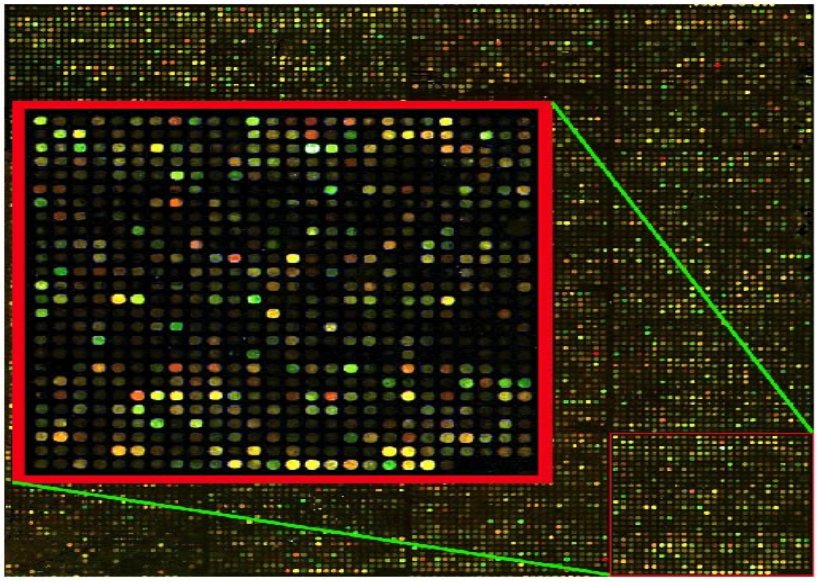
New Paradigm

After a cell is exposed to radiation, different things can happen …sometimes after many cell divisions. This is a frequent event.



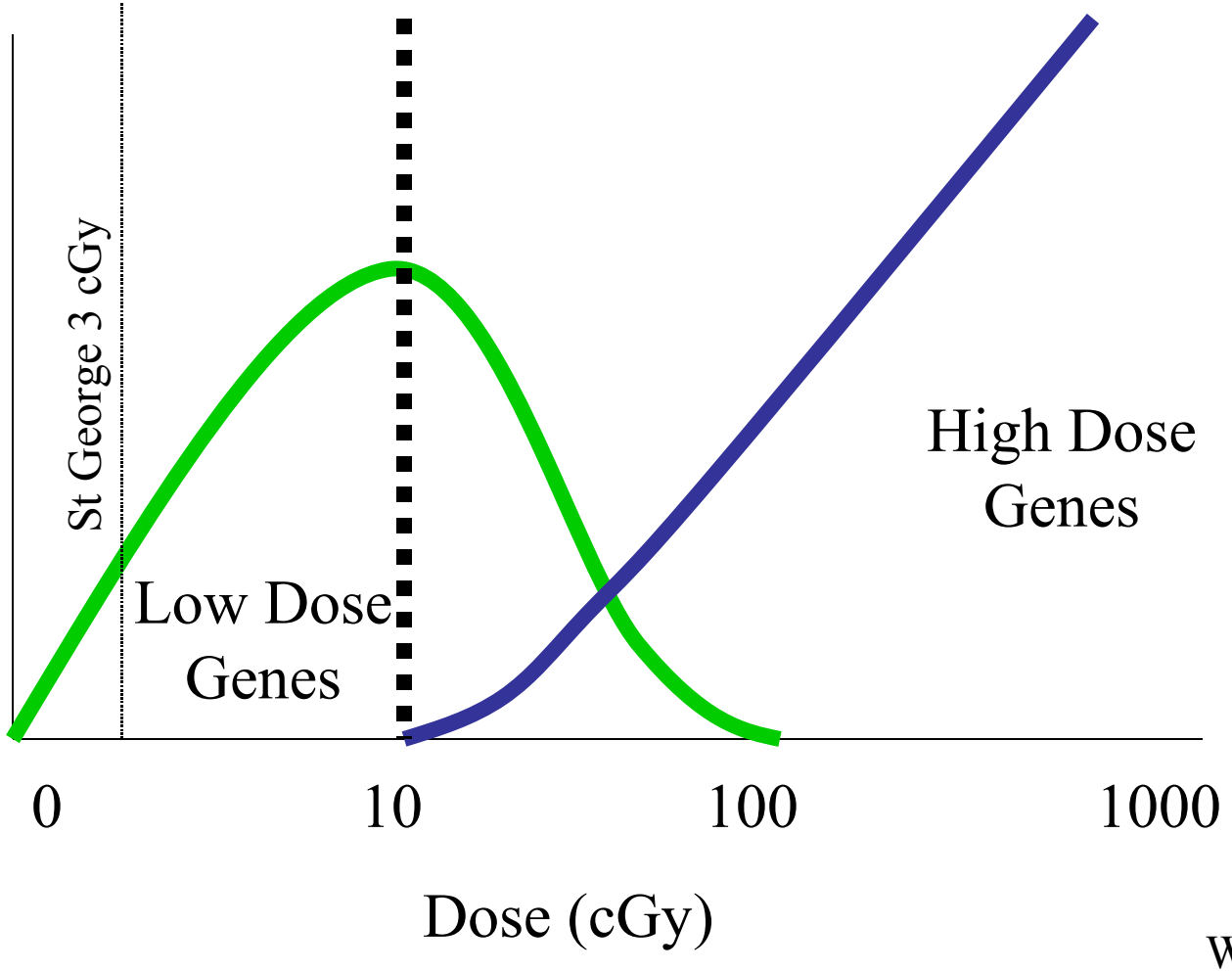
Measuring changes in gene expression

HeLa vs normal human skin fibroblast
20K human chip



Gene Chips

Radiation-induced changes in gene expression



Wyrobek

Protective Response

It was found that low-dose IR exposures modulated genes involved in stress response, synaptic signaling, cell-cycle control and DNA synthesis/repair, suggesting that low-dose IR may activate protective and reparative mechanisms as well as depressing signaling activity.

Yin 2003

Observations on radiation effects

- Adaptive response vs additive effects
- Hit theory vs bystander effects
- Mutation vs genomic instability

Summary

- High radiation doses are a real and serious danger.
- Radiation is a very good cell killer but a poor cancer producing agent.
- Scientific advances say that low doses of radiation produce very different biological responses than high doses.
- Medical uses of radiation are beneficial.
- Environmental radiation levels are not a major cause of cancer.

HEALTH EFFECTS FROM FALLOUT

Ethel Gilbert

Radiation Epidemiology Branch

National Cancer Institute

Case-Control Study of Leukemia from NTS Fallout in Utah

- **1177 persons who died from leukemia (cases)**
- **3550 persons who died of other causes (controls)**

- **Residential histories and fallout deposition rates used to estimate external doses**

- **Mean dose to bone marrow**
  - **3.2 mGy for all subjects**

Case-Control Study of Leukemia from NTS Fallout in Utah

- **Suggestive association for all leukemia excluding CLL (p = .094)**
- **Similar association for CLL (not significant)**
- **Significant associations for**
  - **ALL (p = .01)**
  - **Leukemia before age 20 (p = .02)**
  - **Leukemia 1952-57 (p = .04)**

Cohort Study of Thyroid Disease from NTS Fallout

- **Several thousand school children in Utah, Nevada, and Arizona clinically evaluated for thyroid disease in 1965-70**
- **Re-evaluated in 1985-86**
- **Extensive efforts to estimate thyroid doses from I-131 for each subject**

  Mean dose = 0.1 Gy

  Maximum dose = 4.6 Gy

Correlation Study of Thyroid Doses from NTS Fallout and Thyroid Cancer Rates

- **Associations suggested for dose received under one year of age**
  - **Both mortality and incidence data even though little overlap**

- **No evidence of associations for total dose or dose received between 1 and 15 year of age**

Limitations

- **Errors in dose estimates likely to have diluted effects.**

  -- Migration

  -- Errors in estimated county-specific doses

- **Data on dose and thyroid cancer not available for individuals (ecologic study).**

- **Can't capture variation of dose within**

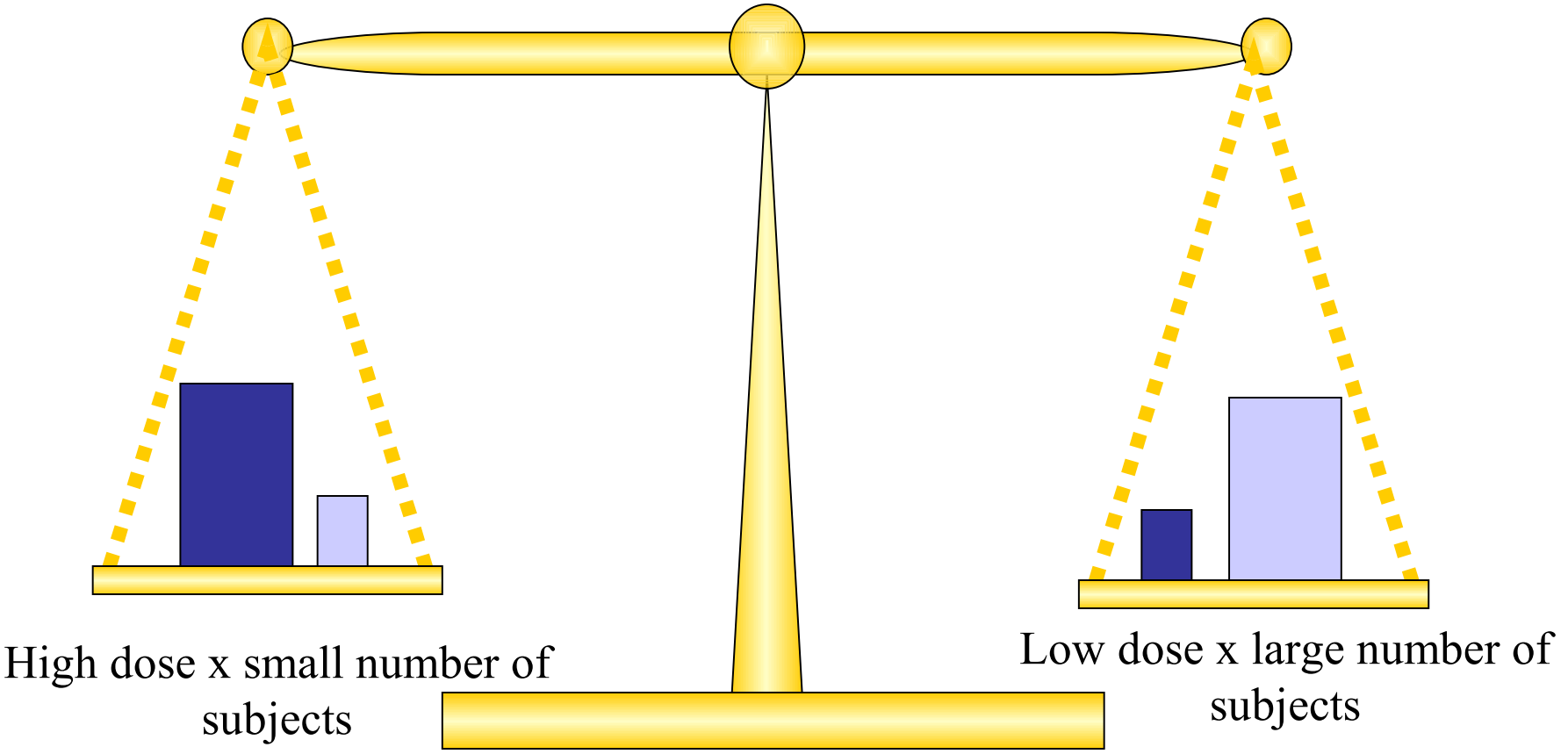
Correlation Study of Thyroid Doses from NTS Fallout and Thyroid Cancer Rates

Because of several limitations:

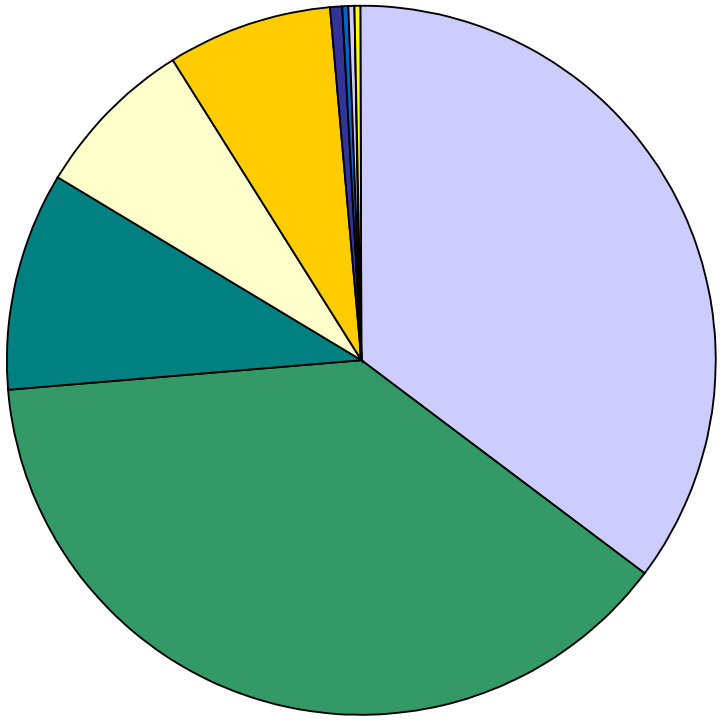
- **The study should <u>not</u> be interpreted as indicating that no thyroid cancers have occurred as a result of exposure to I-131 from atmospheric tests in Nevada**

- **The study is not helpful in quantifying the risks from I-131**

LNTH Assumption with Dose



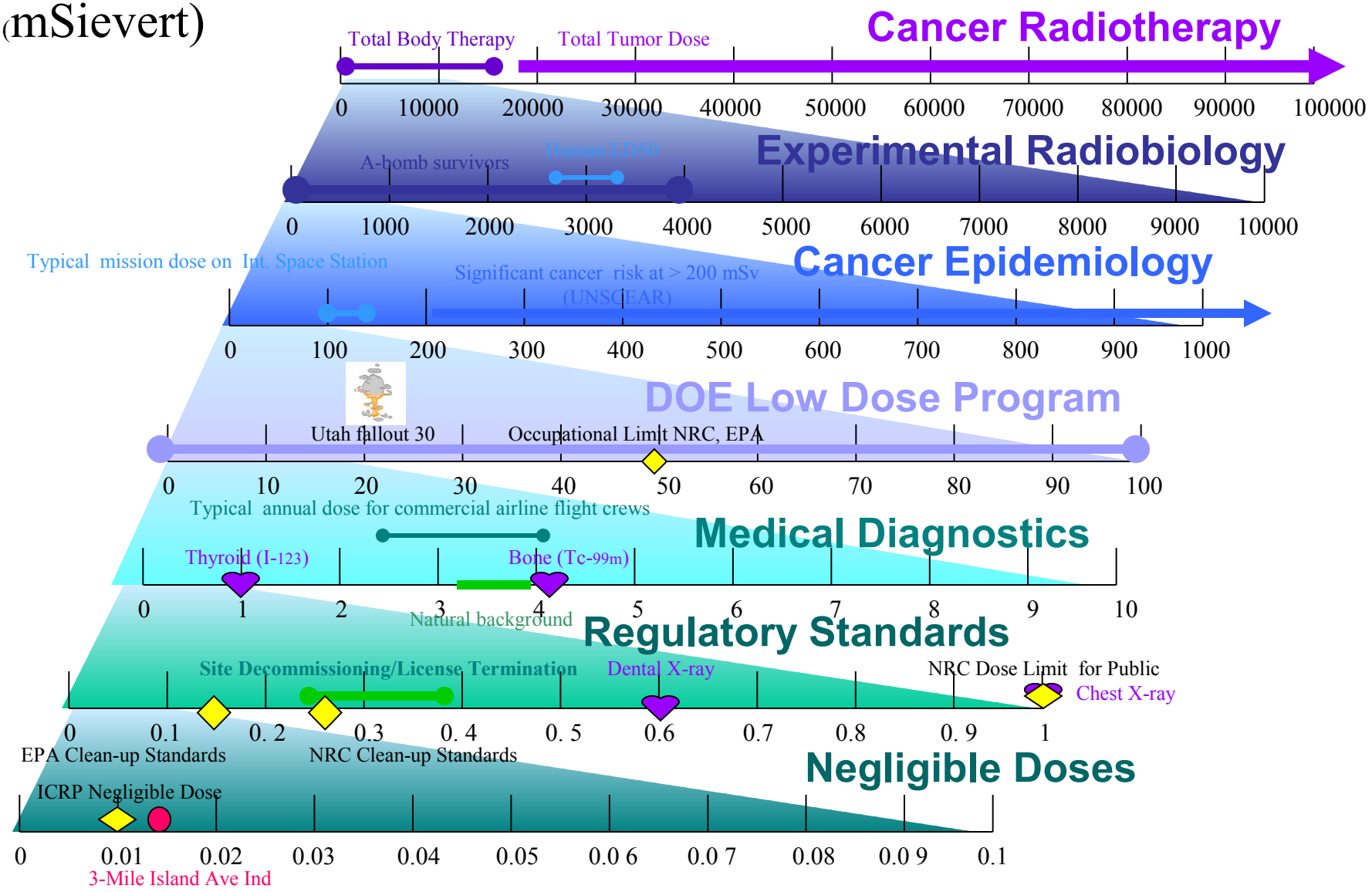
Pie Chart of Doses/WHO



- Radon
- Medicine
- Terrestrial
- Cosmic
- Ingestion
- Chornobyl
- Use
- Occupational Exposure

Dose Ranges

(mSievert)

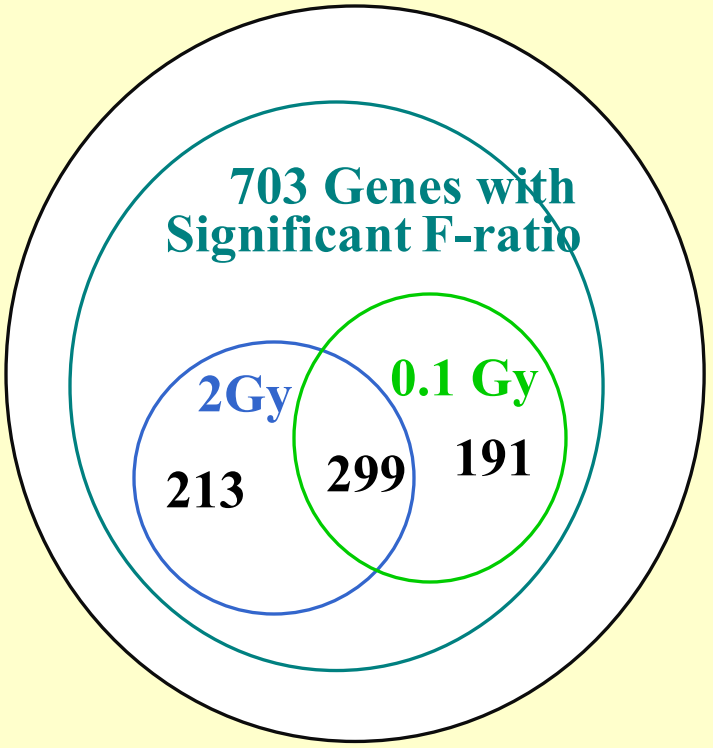


DOE Low-Dose Radiation Research Program

- A 10 year program
- Focused on biological mechanisms of low-dose (< 0.1 Gy) and low dose-rate (< 0.1 Gy / Yr) radiation
- International in scope (currently 70 projects)
- To develop a scientific basis for radiation standards

http://lowdose.tricity.wsu.edu

DIFFERENCES IN TRANSCRIPTION PROFILES BETWEEN LOW AND HIGH DOSE IRRADIATION IN MURINE BRAIN CELLS



Total gene set contains nearly 10,000 genes

Numbers of Genes Differentially Regulated in HLB Cells 4 hr after IR

Up-regulated at 2Gy	245
Down-regulated at 2Gy	135
Up-regulated at 0.1Gy	182
Down-regulated at 0.1Gy	187

Yin 2003