Radiation Risk A Realistic View: Impact of Cellular and Molecular Research

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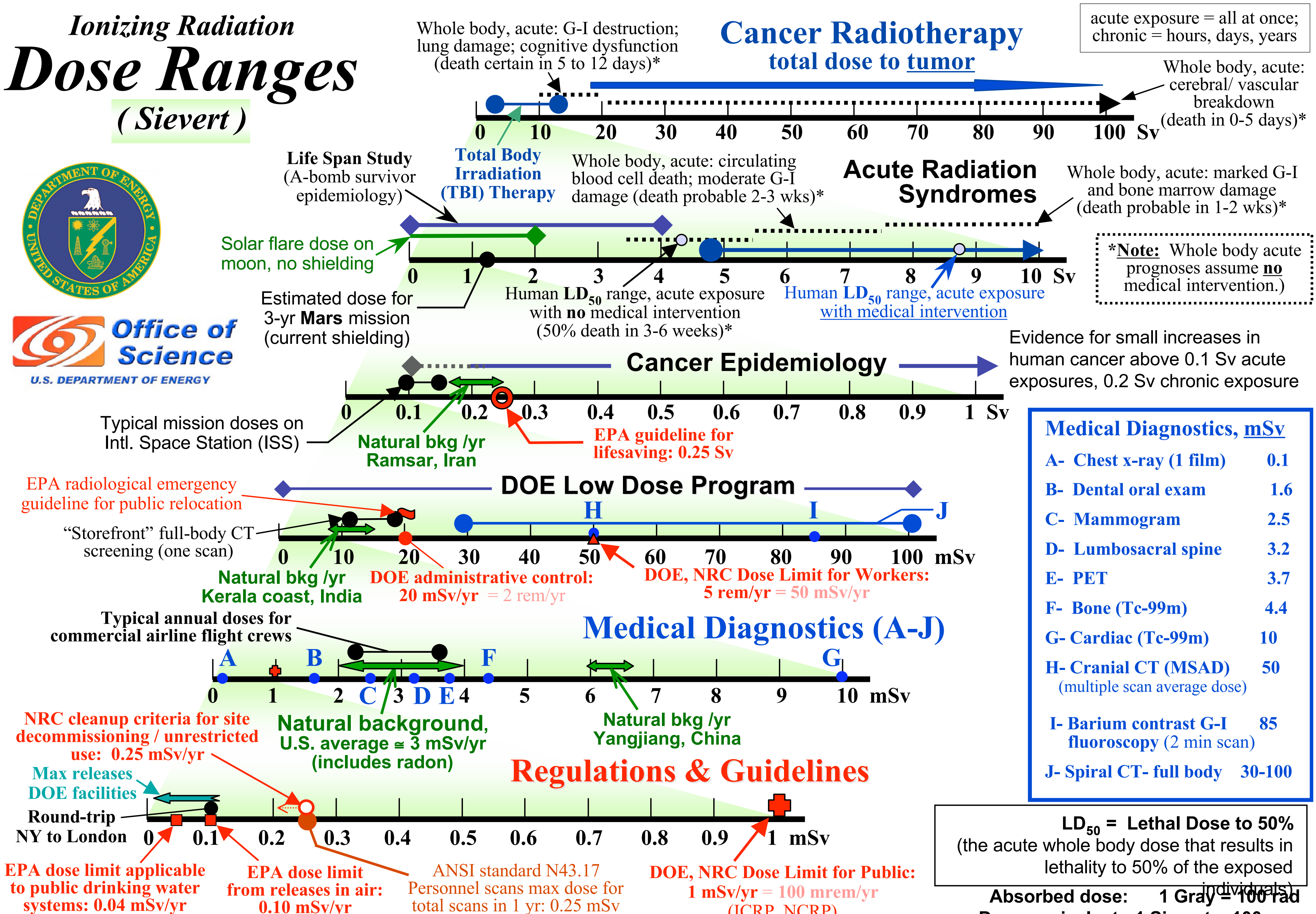
CEMP Meeting July 25, 2006
Mt. Charleston, Nevada



Absorbed dose: 1 Gray = 100 rad
Dose equivalent: 1 Sievert = 100 rem
1 mSv = 100 mrem
(1 Sv = 1 Gy for x- and gamma-rays)

Note: This chart was constructed with the intention of providing a simple, user-friendly, "order-of-magnitude" reference for radiation quantities of interest to scientists, managers, and the general public. In that spirit, most quantities were expressed in the more commonly used radiation protection unit, the rem (or Sievert, 2nd page), and medical doses are not in "effective" dose. It is acknowledged that the decision to use one set of units does not address everyone's needs. (NRC—US Nuclear Regulatory Commission; EPA—US Environmental Protection Agency)
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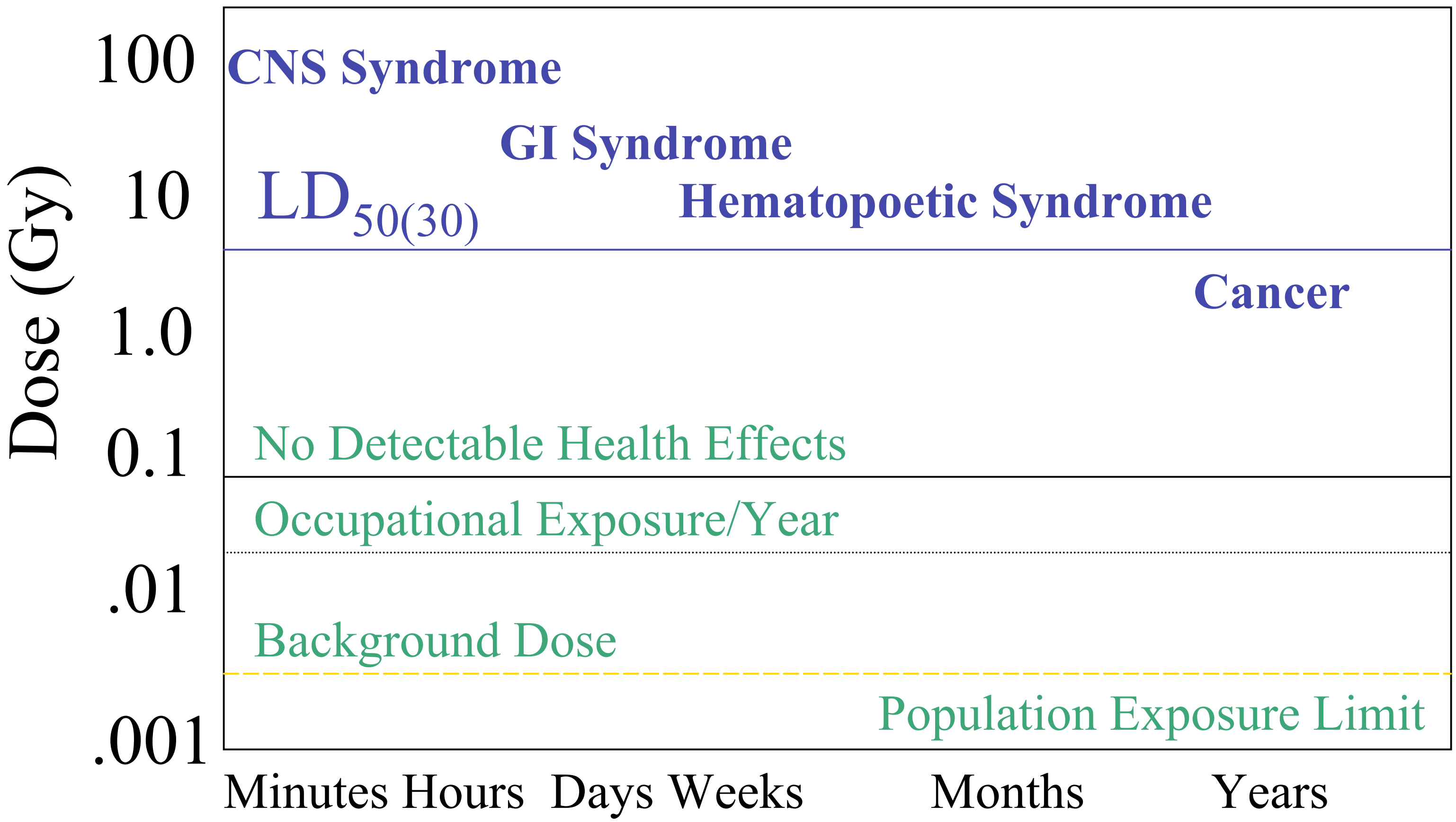
Chart compiled by NF Metting, Office of Science, DOE/BER "Orders of Magnitude" revised **March 2006**

Acute Effects of Radiation



Cerebrovascular Syndrome

- Total body dose of 100 Gy or 10,000 rad of gamma rays (or less of neutrons) results in death in a matter of hours.
- All organ systems are also seriously damaged
- Gastrointestinal and hematopoietic systems would fail quickly at this level, but cerebral much faster

Gastrointestinal Syndrome

- Death is caused by more than 10 Gy of gamma rays or neutrons. **There is no record of any human surviving over 10 Gy acute dose.**

- Symptoms and death are due to depopulation of epithelial lining of the gastrointestinal tract by radiation. Compartments of stem-cells.., differentiating compartment and mature functioning cells.

- 10 Gy doesn’t kill mature cells,but sterilizes dividing cells. As good cells are sloughed off and rubbed away, there are no replacement cells.

Bone Marrow Syndrome

- Death from hematopoietic system failure can occur between 3-8 Gy…
- Mitotically active precursor cells are sterilized, therefore red cells, white cells and platelets are diminished.
- Immune impairment, bleeding and anemia from platelets because of depression of blood elements.
- Red blood cell anemia doesn’t occur.

Summary of High Dose Effects

- No one has survived a dose of 10 Gy or 1,000 Rads without medical intervention
- Doses between 2 and 8 Gy kill dividing cells. If organs cannot replace these cells death occurs. Gut and Bone Marrow and the target organs.
- Doses below 1 Gy, 100 rads, 100,000 mrads produce little life shortening increase in cancer "risk".

Health Effects of Low Doses of Radiation?

- Cancer primary concern for Low doses of radiation
- Genetic Effects
- Birth Defects

Calculation of Genetic Risk

Disease Class	Baseline Frequency/106	Risk/Gy/106 progeny 1st Generation	Risk/Gy/106 progeny 2nd Generation
Mendelian			
Autosomal dominant and X-linked	16,500	~750-1,500	~1,300-2,500
• Autosomal recessive		0	0
• Chromosomal	4,000	b	b
• Milti-factoral			
• Chronic Multi-factorial	650,000c	~250-1,200	~250-1,200
• Congenital abnormalities		~2,000[d]	~2,400-3,000[d]
• Total	738,000	~3,000- 4,700	~3,940 to 6,700

- Total Risk/Gy expressed as a percent of baseline **~0.41-0.64** **~0.53-0.91**

Radiation Induced Cytogenetic Damage

- Dose, Dose-rate and LET dependent
- Different types of aberrations and risk
  - Un-Stable Aberrations
  - Stable Aberrations
  - Chromosome type and Chromatid type
- Complex Aberrations

Complex Chromosome Aberrations

Late Non-Cancer Effects of Radiation

- Fetal Malformation
  - Spontaneous abortions
  - Birth defects
  - Developmental abnormalities
- Mental Retardation
  - Change in head size
  - Loss of I.Q.
- Cataracts
- Fibrosis

Embryology of the developmental stages during pregnancy

Preimplantation
Cell proliferation & differentiation

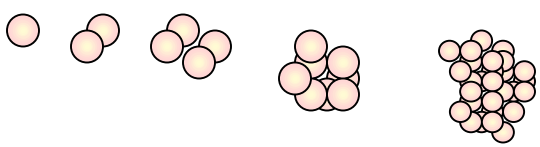
Embryo
Differentiation & organogenesis

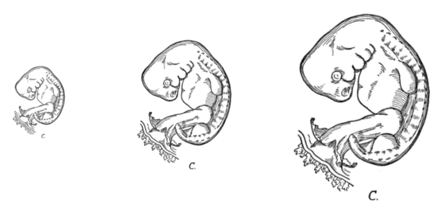
Fetus
Growth

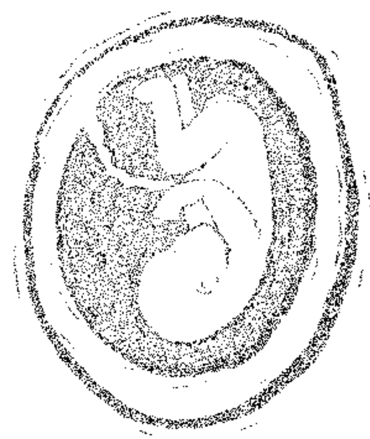
Birth

0 10 20 30 40 ⟶ 270

Time (Days)







Endoderm, Mesoderm, Ectoderm

Induction of abnormalities by 200 R (2.0Gy) after acute exposure

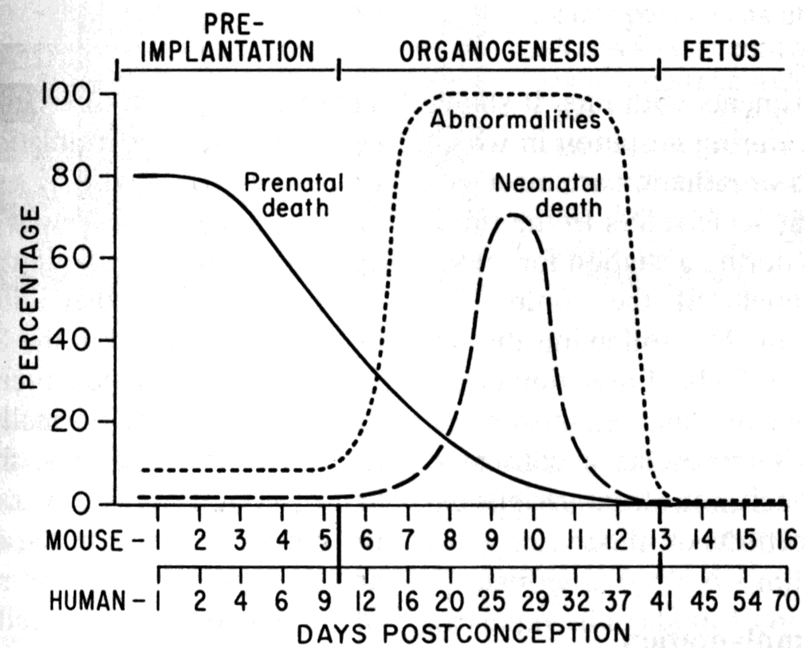


Figure 12.1. Incidence of abnormalities and of prenatal and neonatal death in mice given a dose of 200 R at various times after fertilization. The lower scale consists of Rugh's estimates of the equivalent stages for the human embryo. (Data from Russell LB, Russell WL: An analysis of the changing radiation response of the developing mouse embryo. J Cell Physiol 43[suppl 1]:1030–149, 1954.)

Hall

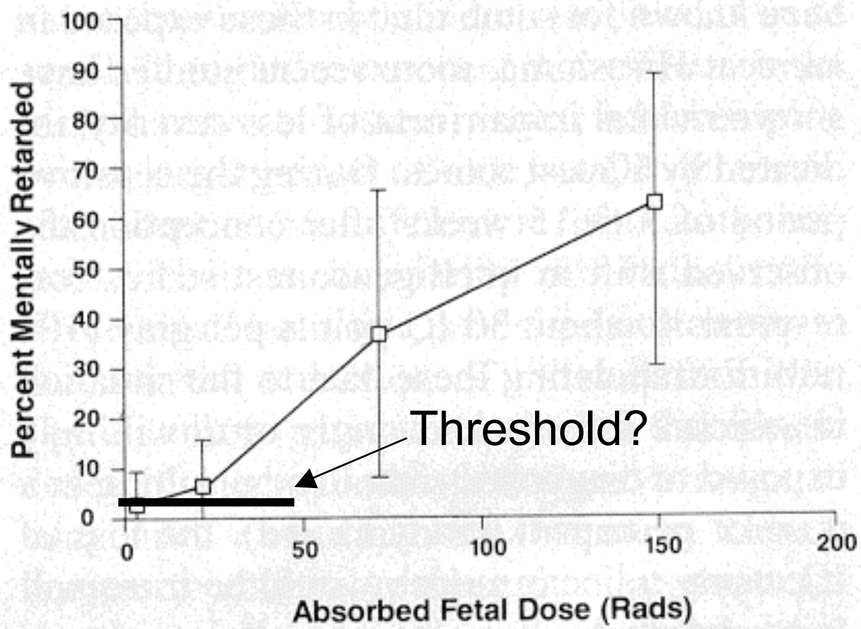
The influence of Time of Exposure on the production of malformation

- There is a window of time when the fetus is in a stage that is sensitive to radiation
- This is related to the organs and tissues being formed at the time.
- High dose radiation exposure during this time window is very effective in producing congenital malformations.

Calculation of Risk using Real World Assumptions.

- 3.5 Radiation induced Cases in the population of 100,000 people followed over 10 years (Worst Case)
- 3.5 x 0.018 fraction of time in sensitive stage= 0.063
- 0.063 x 0.01 fraction of population receiving Maximal Dose =0.0063
- 0.0063 x 0.5 for dose rate effectiveness= 0.0032
- 0.0032 x the LNTH assumption=????
- Relate 0.0032 radiation induced malformations to the 2,800 "normal" cases.
- At what dose do you recommend an abortion????

Radiation induced Mental Retardation



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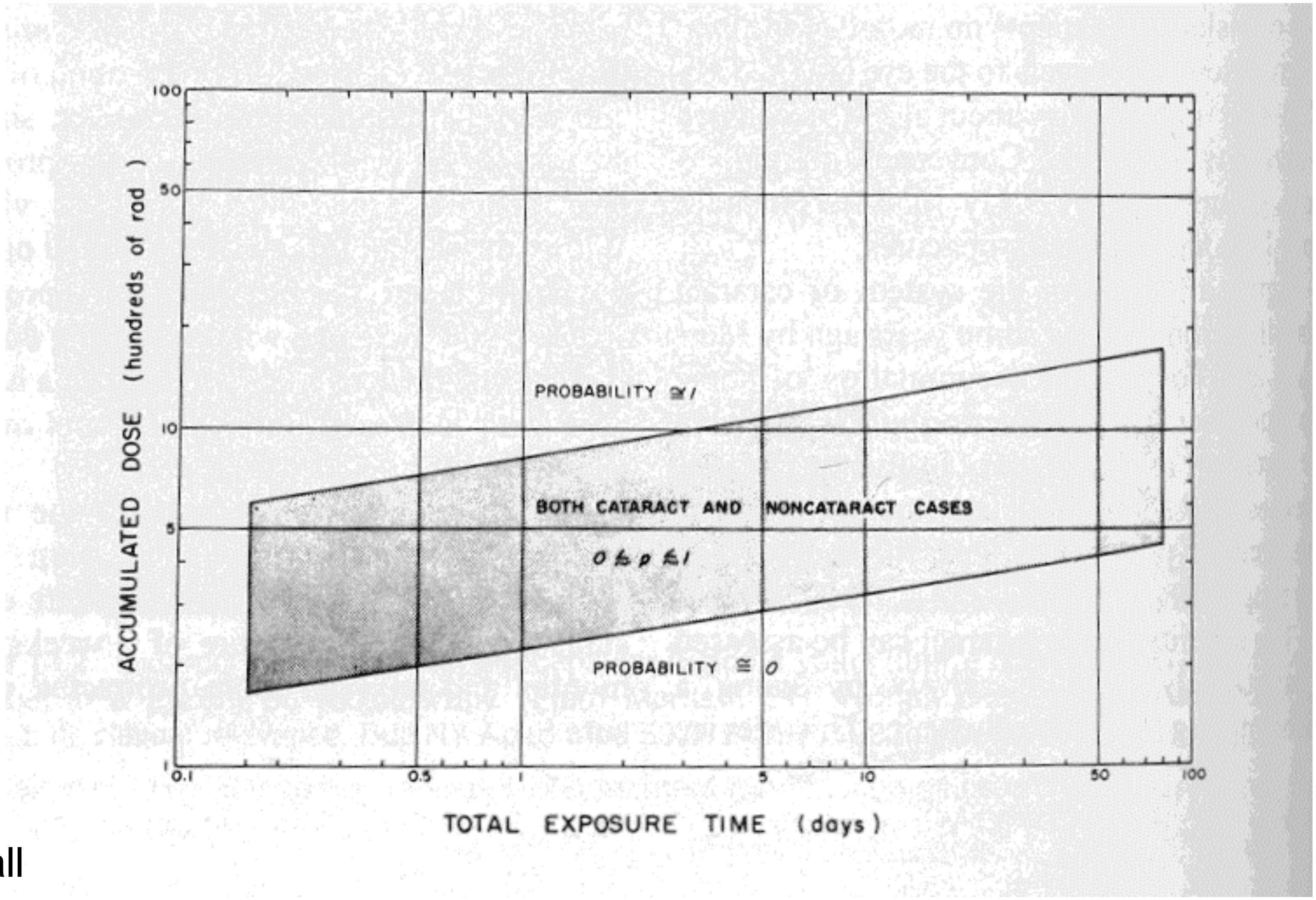
"Dose and time Response" for induction of cataracts



Hall

Overview of Radiation Exposure of Tissues and Organs

403 accidents worldwide from 1944-1999

120 Acute deaths from these accidents

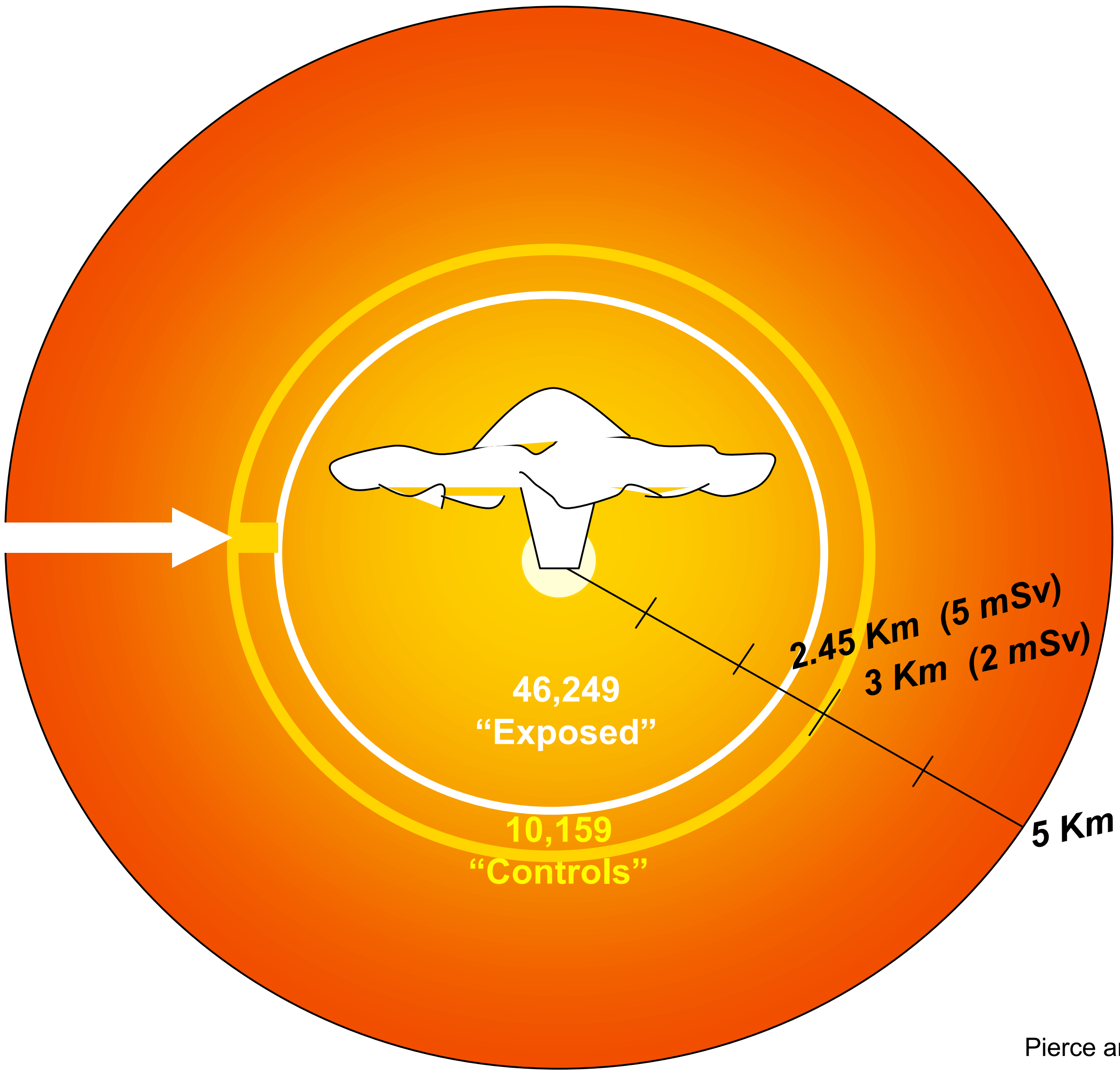
- 19 reactors
- 303 involved radiation devices, sealed sources or x-ray machines
- 81 radioisotopes

Effects of Atomic Bomb

- **Killed outright by the bomb or acute radiation effects.** — **About 200,000 people**
- **Survived for lifespan study** — **86,572 people**

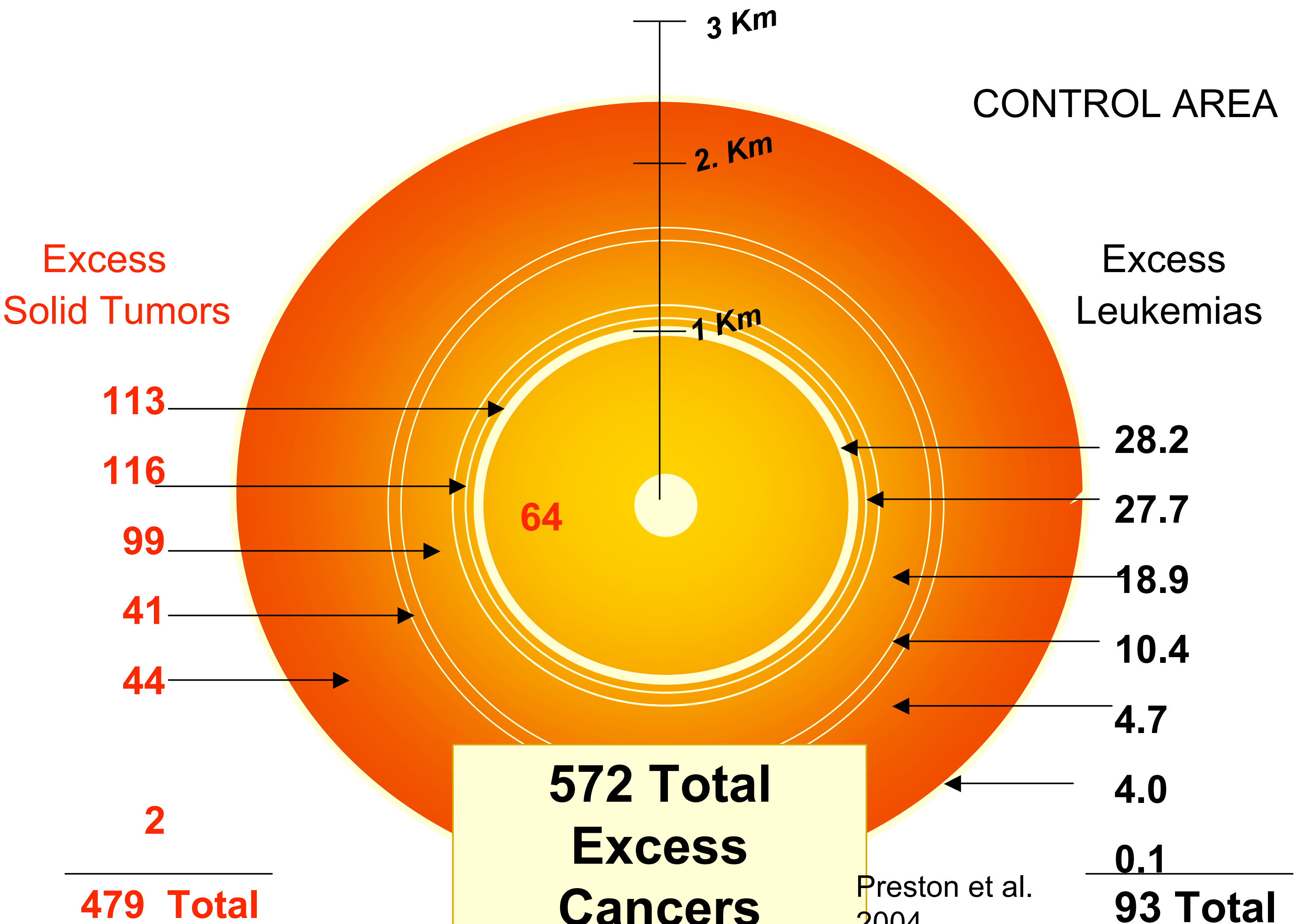
A-BOMB SURVIVOR STUDIES

5% less cancer than total controls



Pierce and Preston 2000

A-BOMB SURVIVOR STUDIES



572 Total Excess Cancers

Preston et al. 2004

Atomic Bomb Survivor Excess Cancer

Population of Survivors Studied **86,572**

40% of these people are still alive 60 years after the bomb

Cancer Mortality observed after the Bomb	10,127
Cancers Mortality Expected without Bomb	9,555
Total Cancer Mortality Excess	**572**

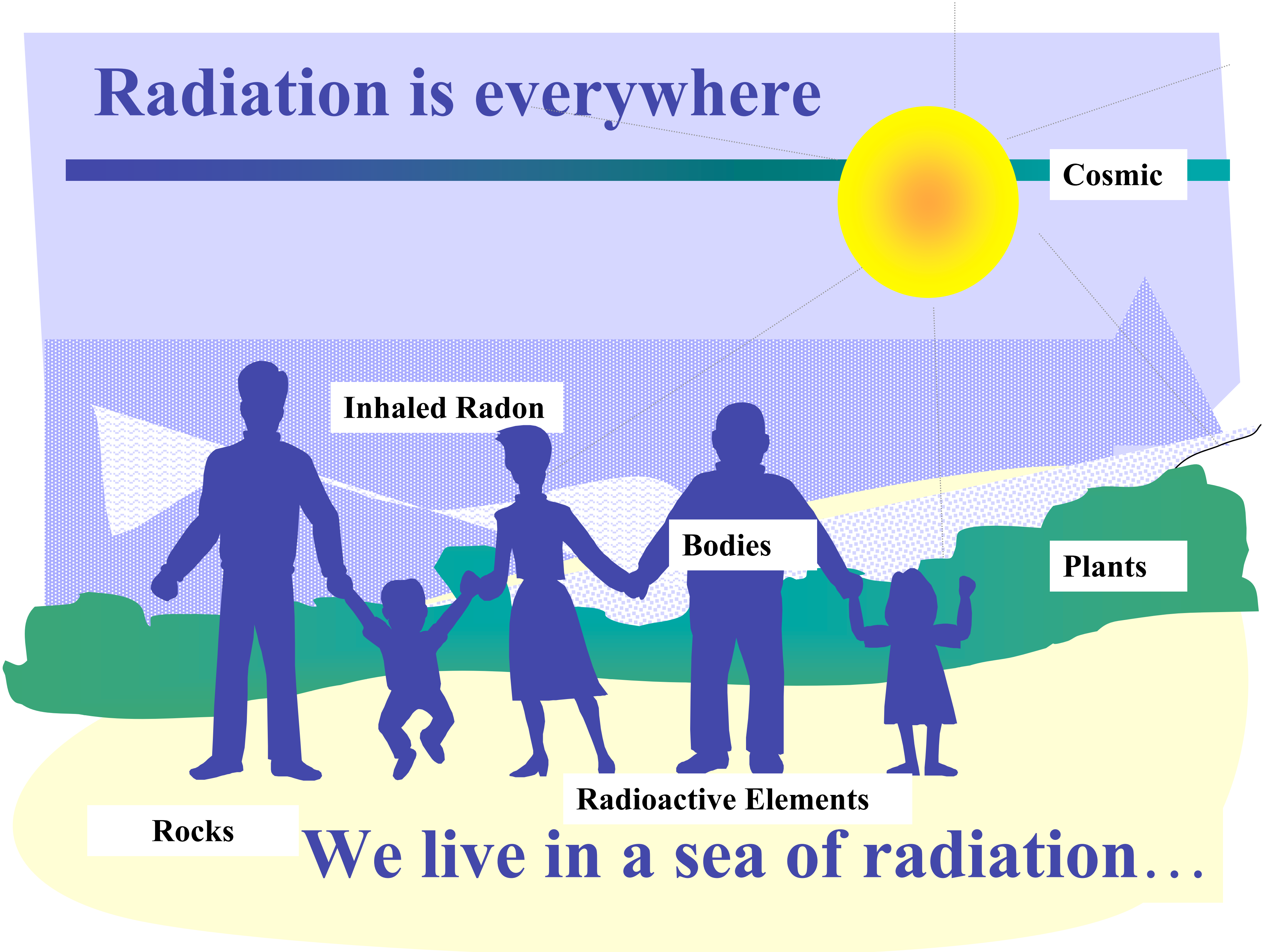
Excess Tumor		Excess Leukemia		
479	+	94	=	572

Problems with Detection of Cancer following Low Doses

- Background radiation
- Background cancer
- High signal to noise ratio

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

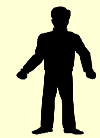
Background Radiation


Radiation is everywhere
Cosmic
Inhaled Radon
Bodies
Plants
Radioactive Elements
Rocks
We live in a sea of radiation…

Normal annual exposure from natural radiation

About 300 mrem/yr


Radon gas	200 mrem
Human body	40 mrem
Rocks, soil	28 mrem
Cosmic rays	27 mrem




Normal annual exposure from man-made radiation

About 70 mrem/yr


Medical procedures	53 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

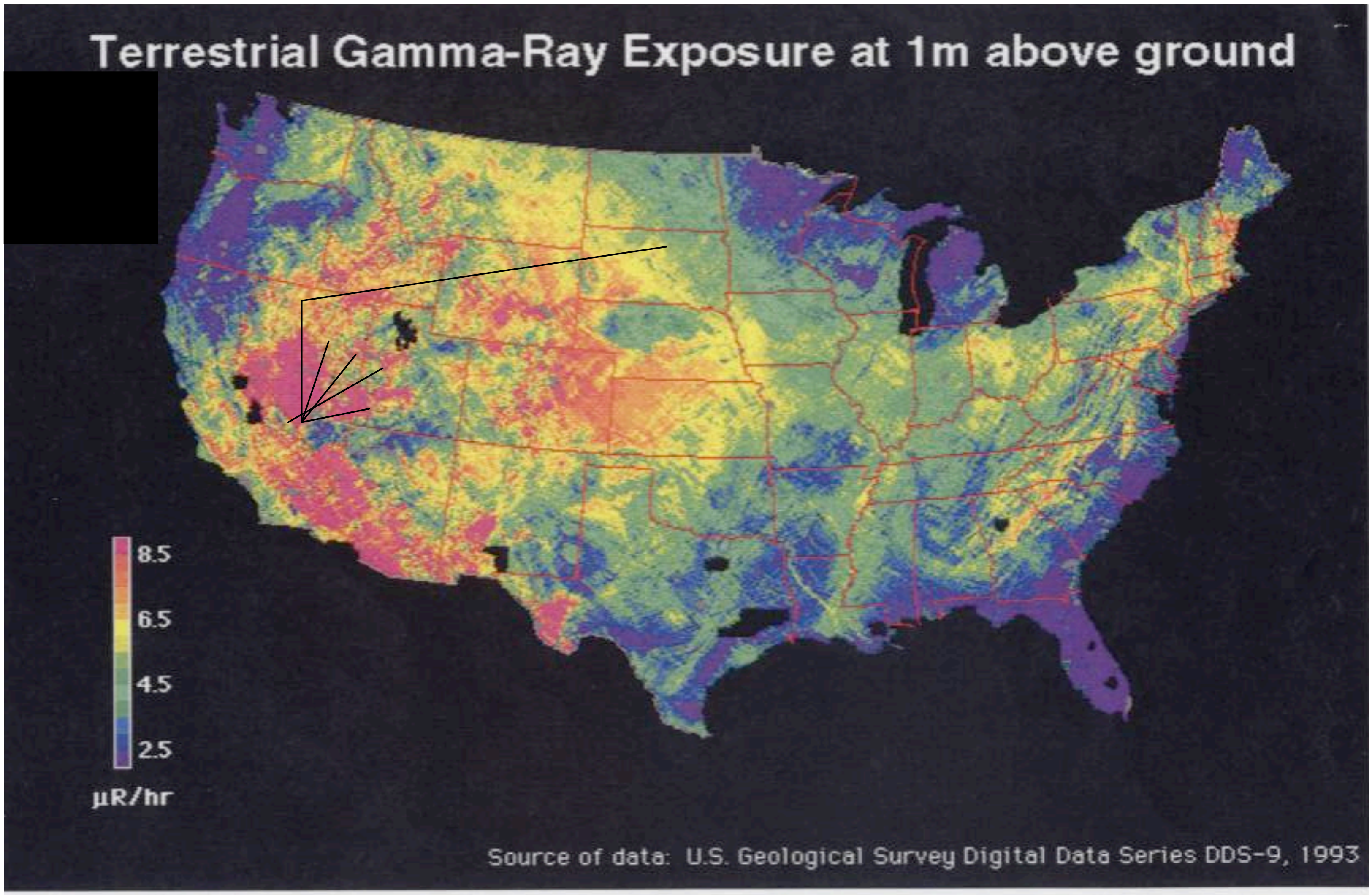


Medical Radiation Exposures

- 300 million medical x-rays/year
  - X-ray 0.1 mGy
- 100 million dental x-rays/year
  - Dental 0.06 mGy
- 10 million doses of radiopharmaceuticals/yr
- 37 million CT scans/year
  - Head scan 4-6 mGy/scan
  - Body scan 40-100 mGy/scan
- Large doses from radiation therapy

Background
Cancer

U.S Dose Rates from Natural Background



Nevada Test Fallout

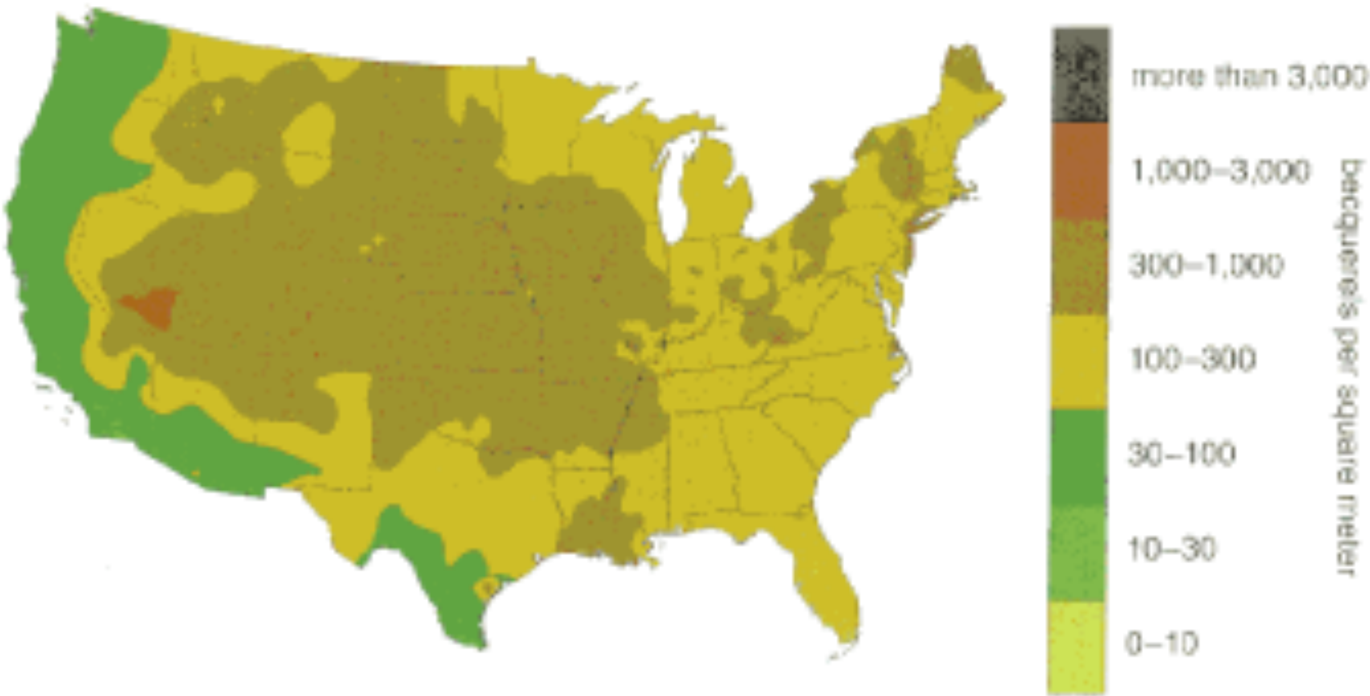
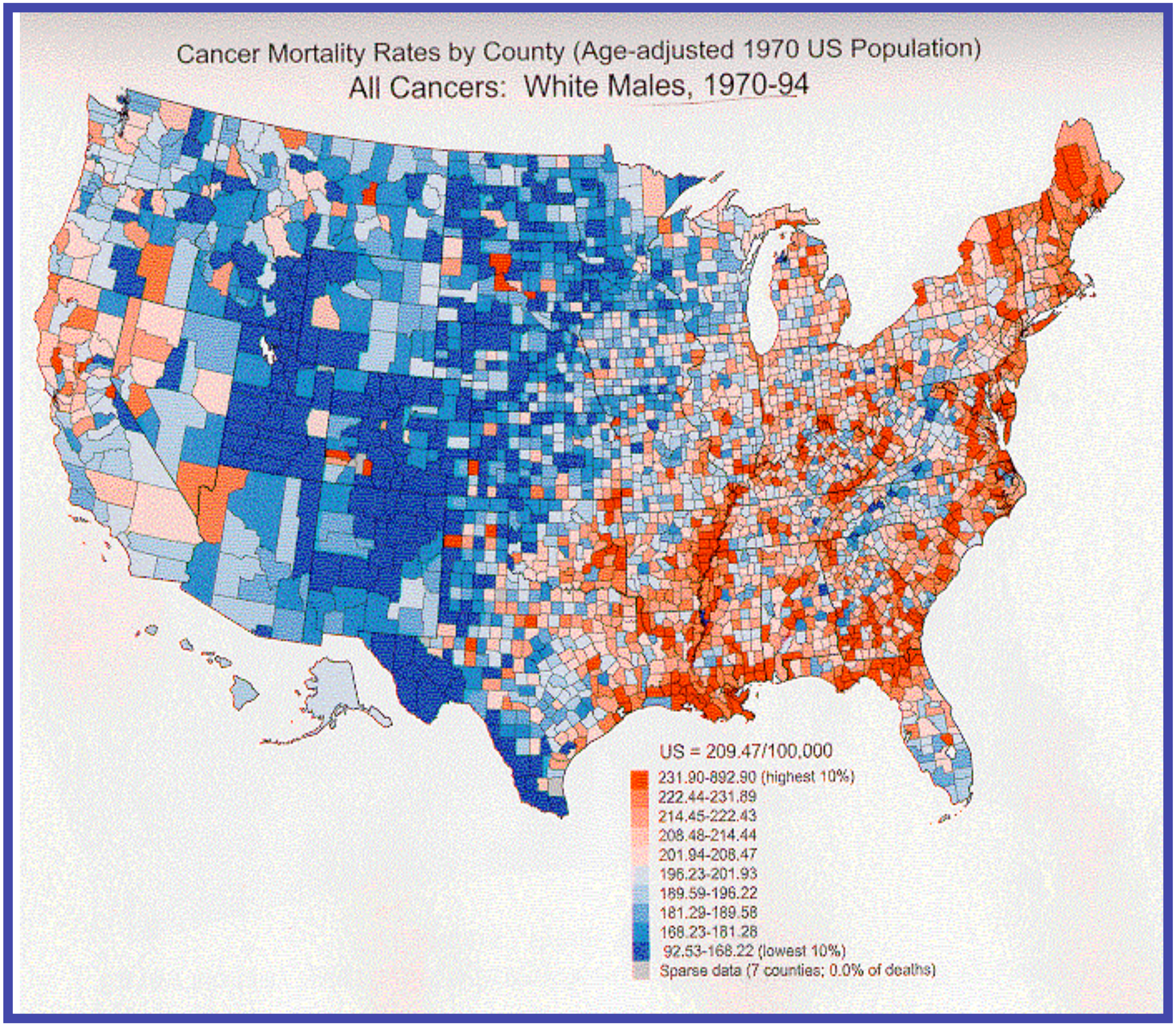
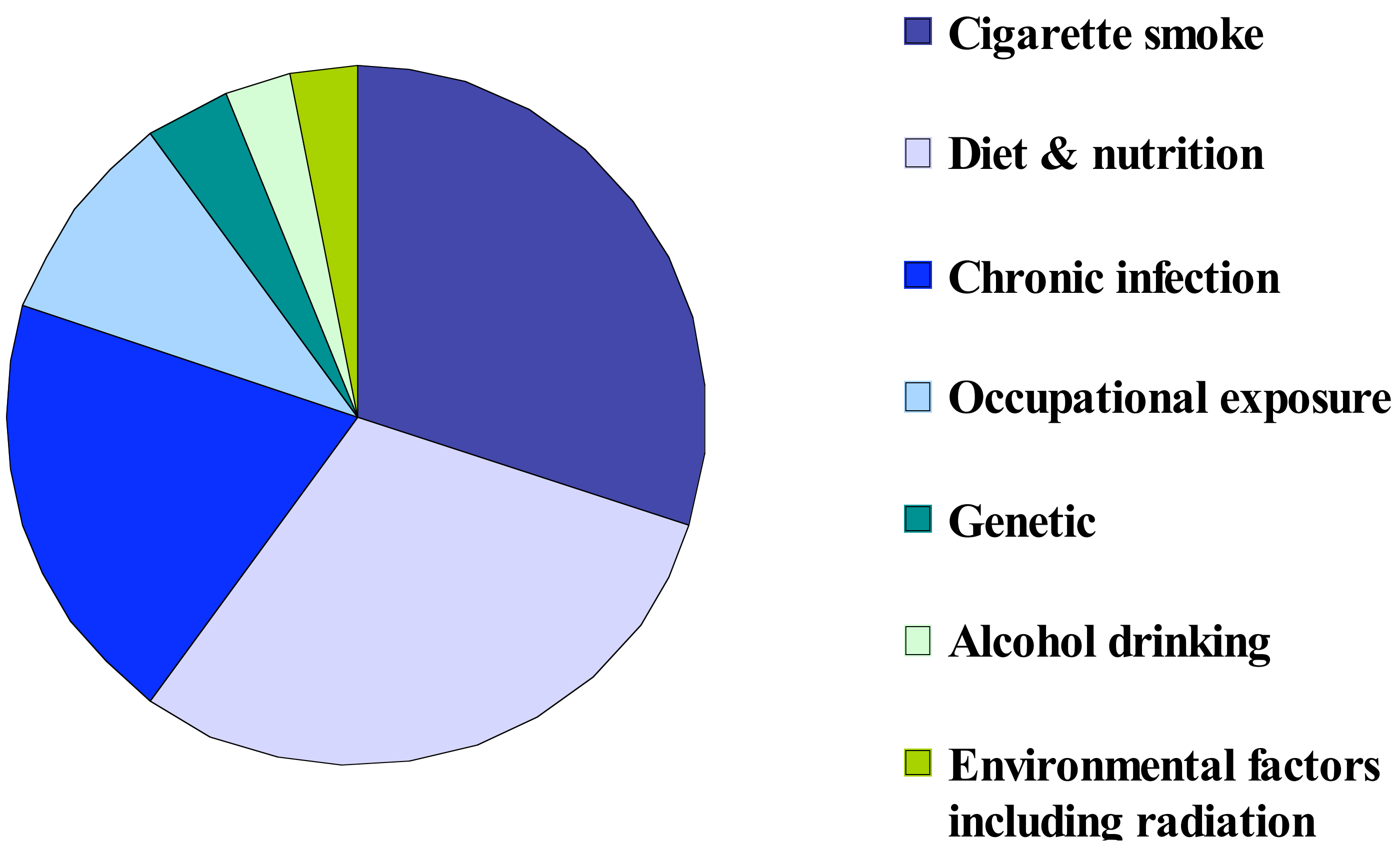


Figure 7. Cesium-137 deposition density resulting from the cumulative effect of the Nevada tests generally decreases with distance from the test site in the direction of the prevailing wind across North America, although isolated locations received significant deposition as a result of rainfall.

Simon et al. 2006


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
206.48-214.44
201.94-206.47
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)

What Causes Cancer?



How Much Radiation?

- It is very difficult to understand units
- Huge range of every day exposures
- How much radiation does it take to significantly increase cancer frequency?

It takes a lot of radiation to produce cancer!!!

Number of people	Dose/Person (Gy)	Amount/ Person (J)	Amount (J)	Background Cancer	Excess Cancer
1	10	*700	700	0.42	0.0
10	1	70	700	4.2	1.0
100	0.1	7	700	42	1.0
1,000	0.01	0.7	700	420	1.0
10,000	**0.001	0.07	700	4,200	1.0
100,000	0.0001	0.007	700	42,000	1.0

*This is a large lethal amount of radiation given to one person. Cancer can never be detected with this quantity of radiation regardless of population size!!!

Background low LET dose/person

It takes a lot of radiation to produce Cancer!!!

Number of people	Dose / Person (Gy)	Quantity/ Person (J)	Quantity (J)	Background Cancer	Excess Cancer
1	0.1	7.0	7.0	0.42	0.01
10	0.1	7.0	70	4.2	0.1
***100**	0.1	7.0	700	42	1.0
1,000	0.1	7.0	7000	420	10
10,000	0.1	7.0	70,000	4,200	100
100,000	0.1	7.0	700,000	42,000	1000
86,611	0.14	10.3	894,557	10,127	**572

Amount per person and the population size is below the level to detect cancer

Cancer is detectable in this range of population, dose, exposure.

**** A-bomb observed response.**

*BEIR VII

Mechanisms for Cancer Induction

High Doses

Cancer

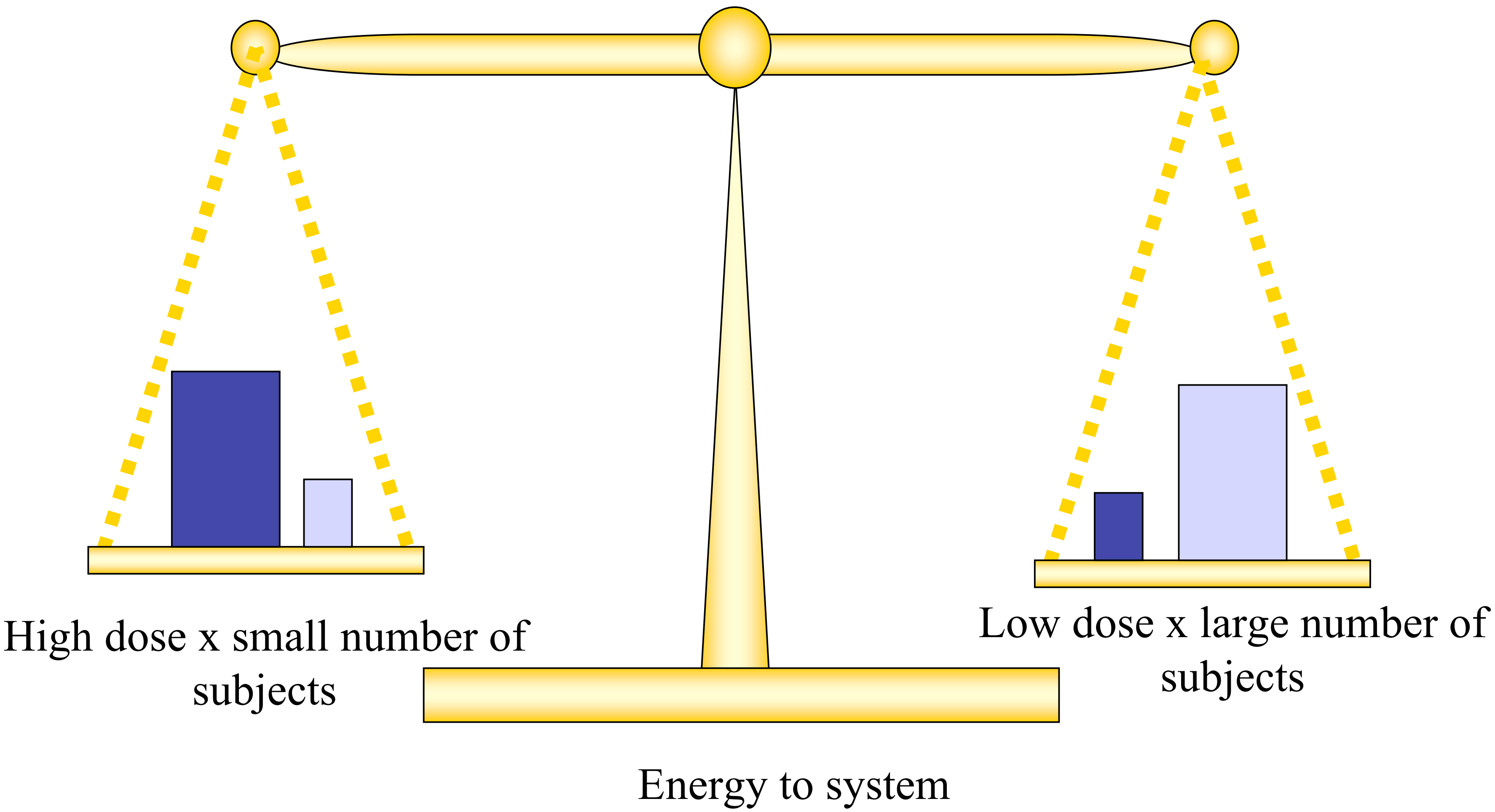
- Changes in gene expression
- Mutations
- Chromosome aberrations
- Genomic instability
- Cell killing
- Stimulate cell proliferation
- Tissue and matrix disruption
- Inflammation

Low Doses

Cancer?

- Changes in gene expression
- Mutations
- Chromosome aberrations
- Adaptive response

LNTH Assumption with Dose



DOE Low-Dose Radiation Research Program

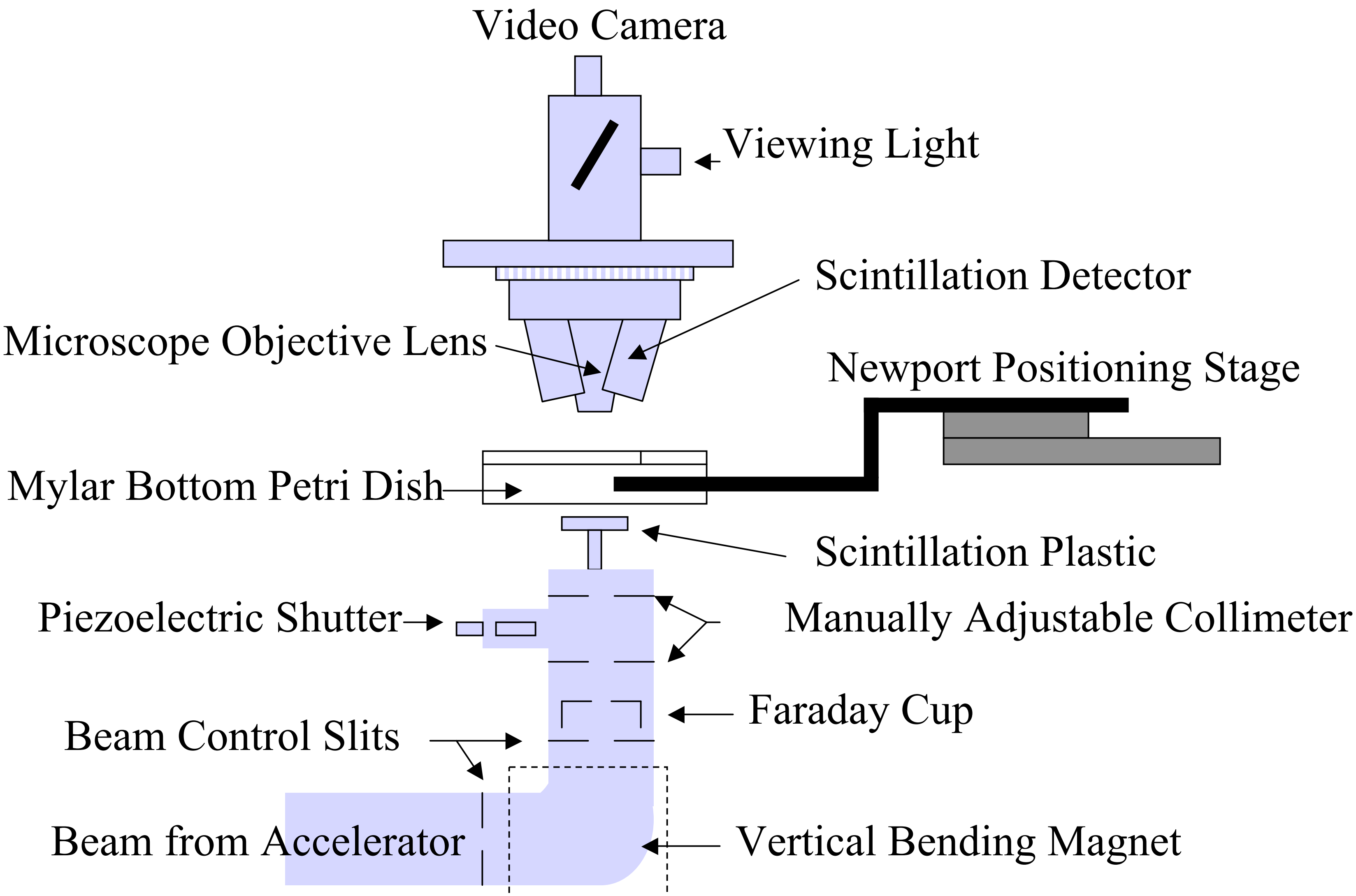
- A 10 year program, running for 7 years.
- Focused on biological mechanisms of low-dose (< 0.1 Gy) and low dose-rate (< 0.1 Gy / Yr) radiation
- International in scope (currently 80 projects)
- To develop a scientific basis for radiation standards

http://lowdose.tricity.wsu.edu

Key Research Areas

- Technological Advances
- Biological Advances

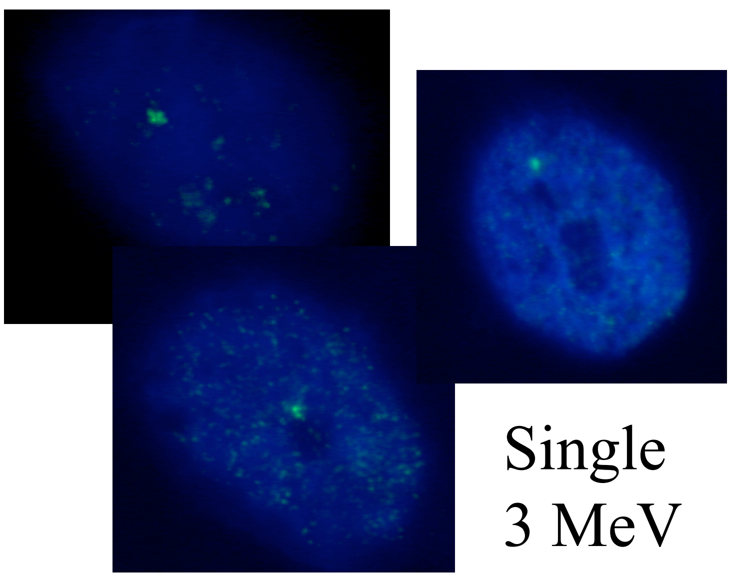
Alpha-Particle Radiation System



Texas A&M

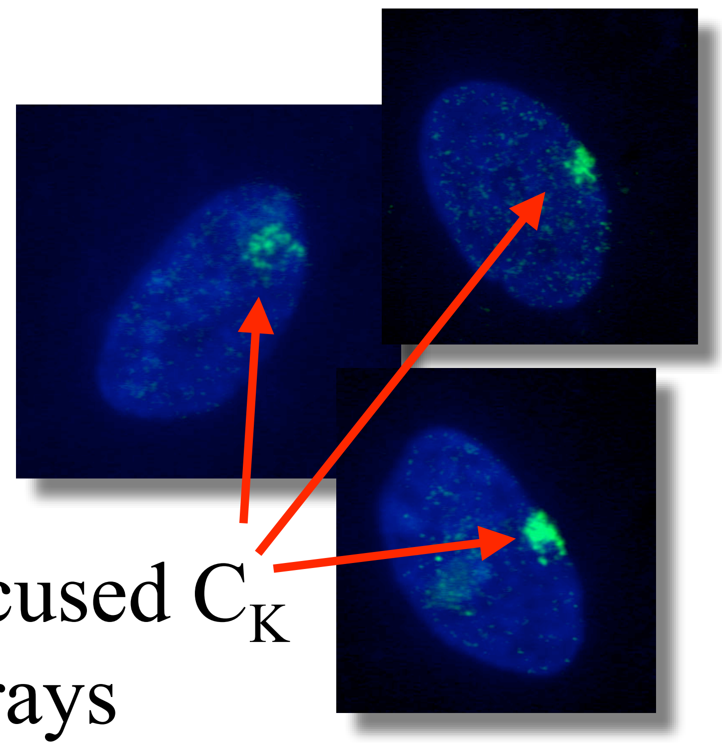
Microbeams recent findings

- Localised DNA damage observed after both focussed soft X-ray production and charged particle induction using γH2AX



5 mm

Single
3 MeV
Helium ion



Focused C_K
X-rays

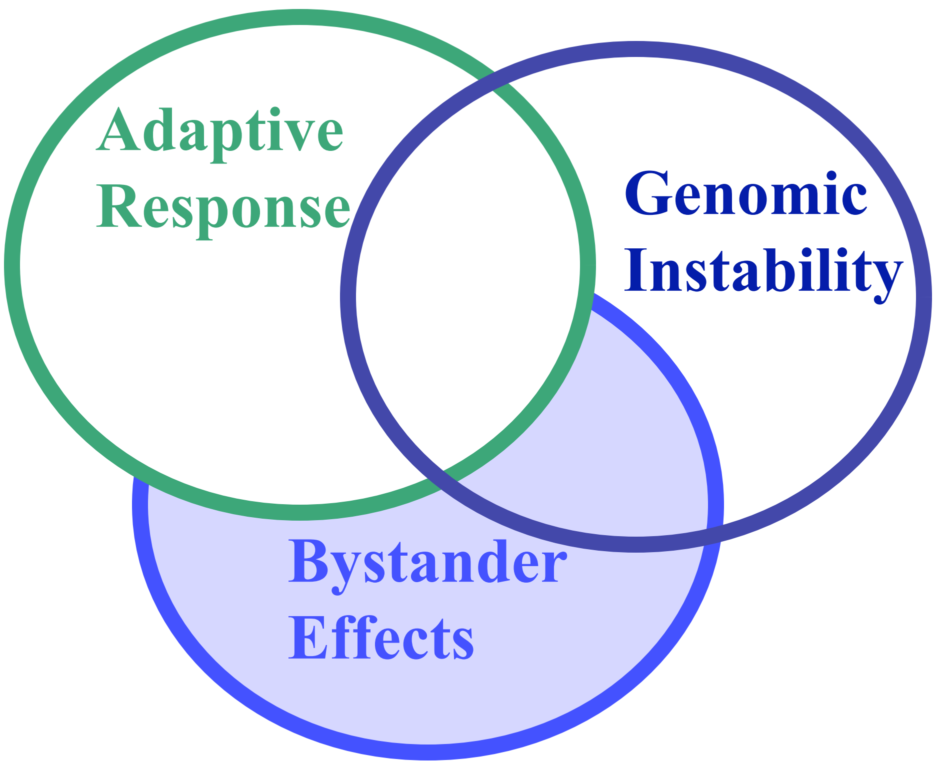
Cellular Changes

- **Bystander Effects**
  - Cells respond without energy deposition
  - Cell-cell communication
  - Materials into the media

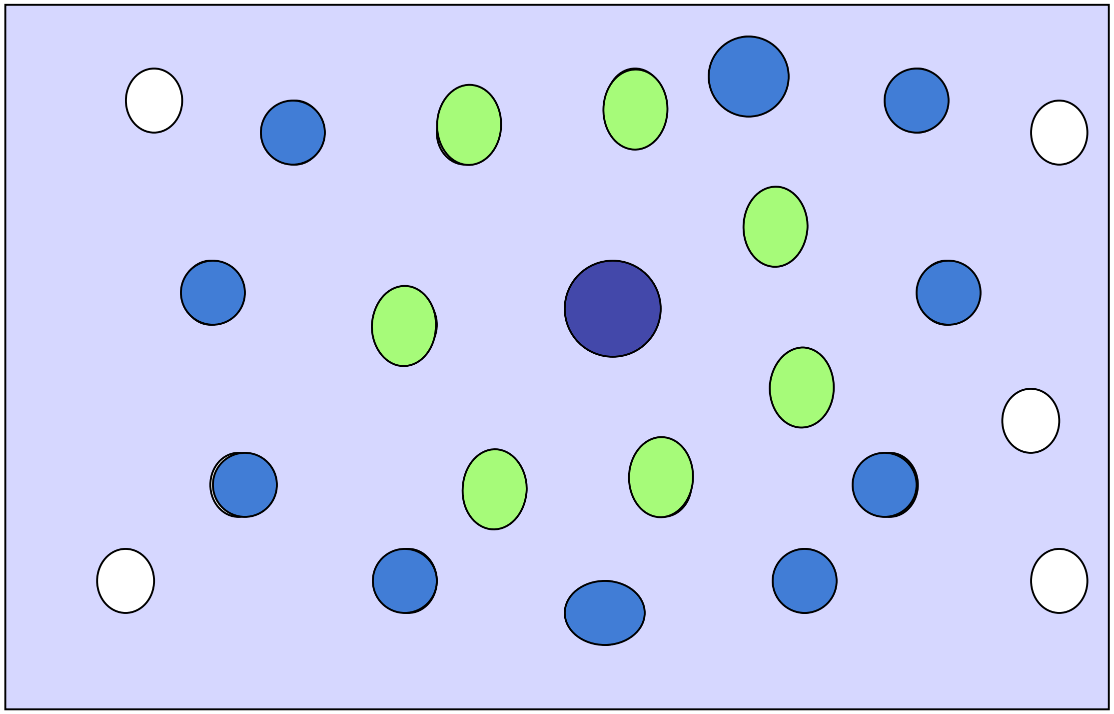
- **Adaptive Response**
  - Small dose alters response to large dose
  - Small dose decreases spontaneous damage

- **Genomic Instability**
  - Loss of genetic control many cell generations after the radiation exposure

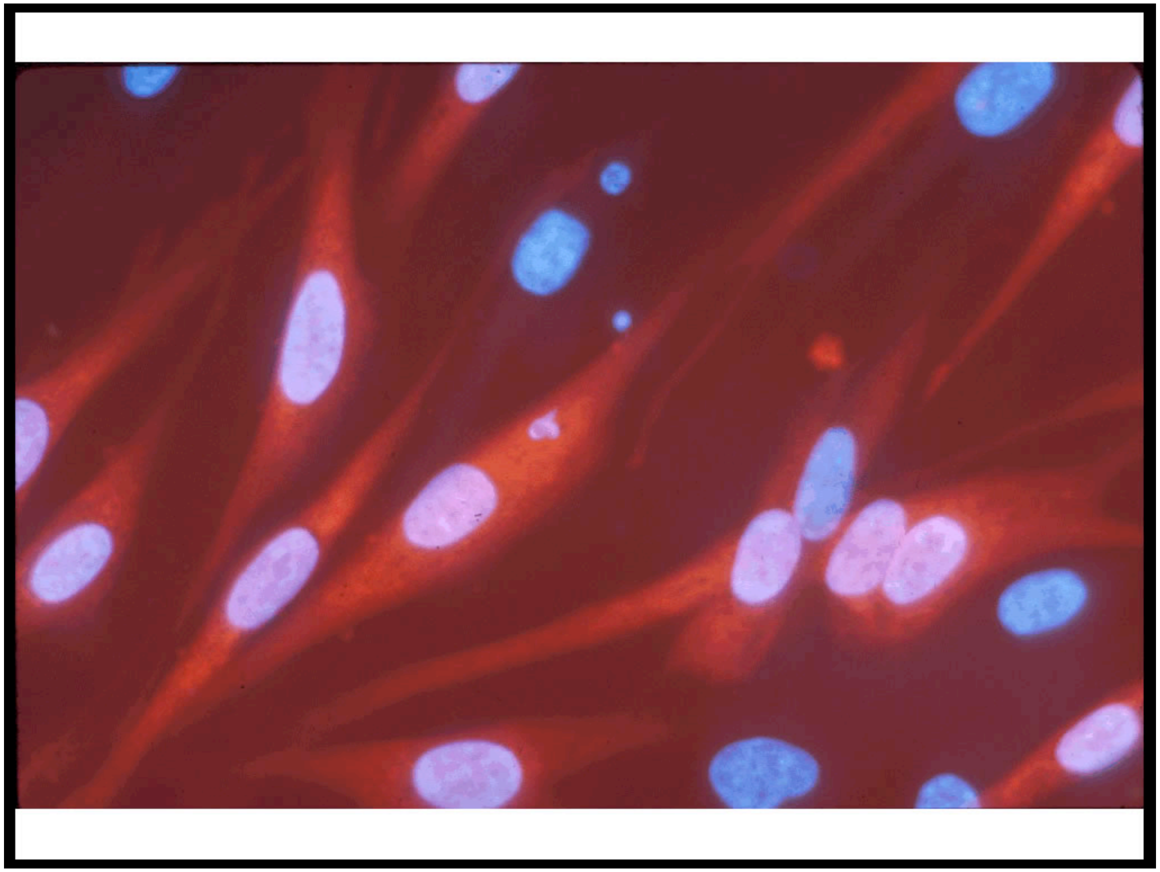
Relationship between biological responses to radiation



Bystander Effects *in vitro*



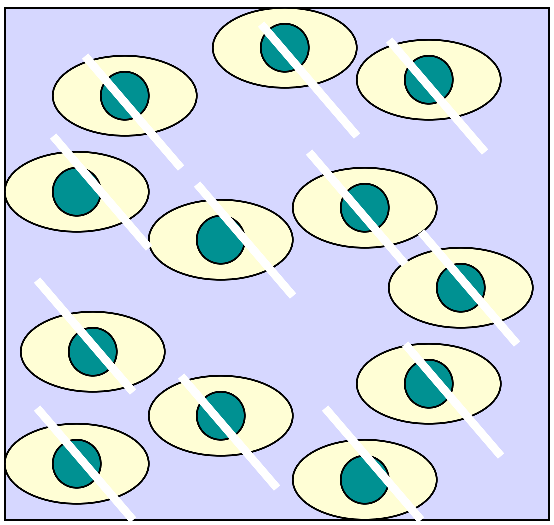
Micronuclei in non-Exposed Cells



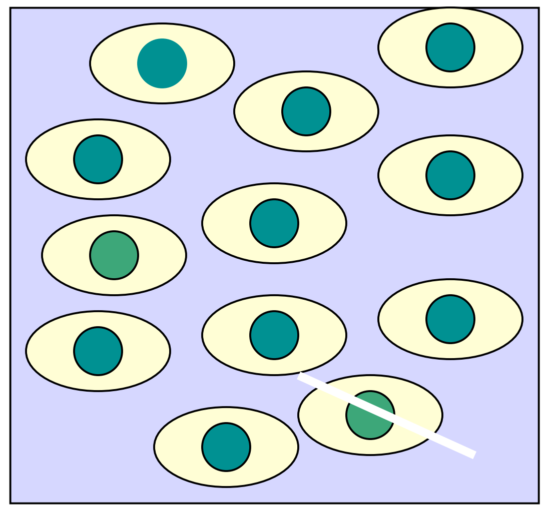
Geard

Microbeam

Each cell hit by one particle

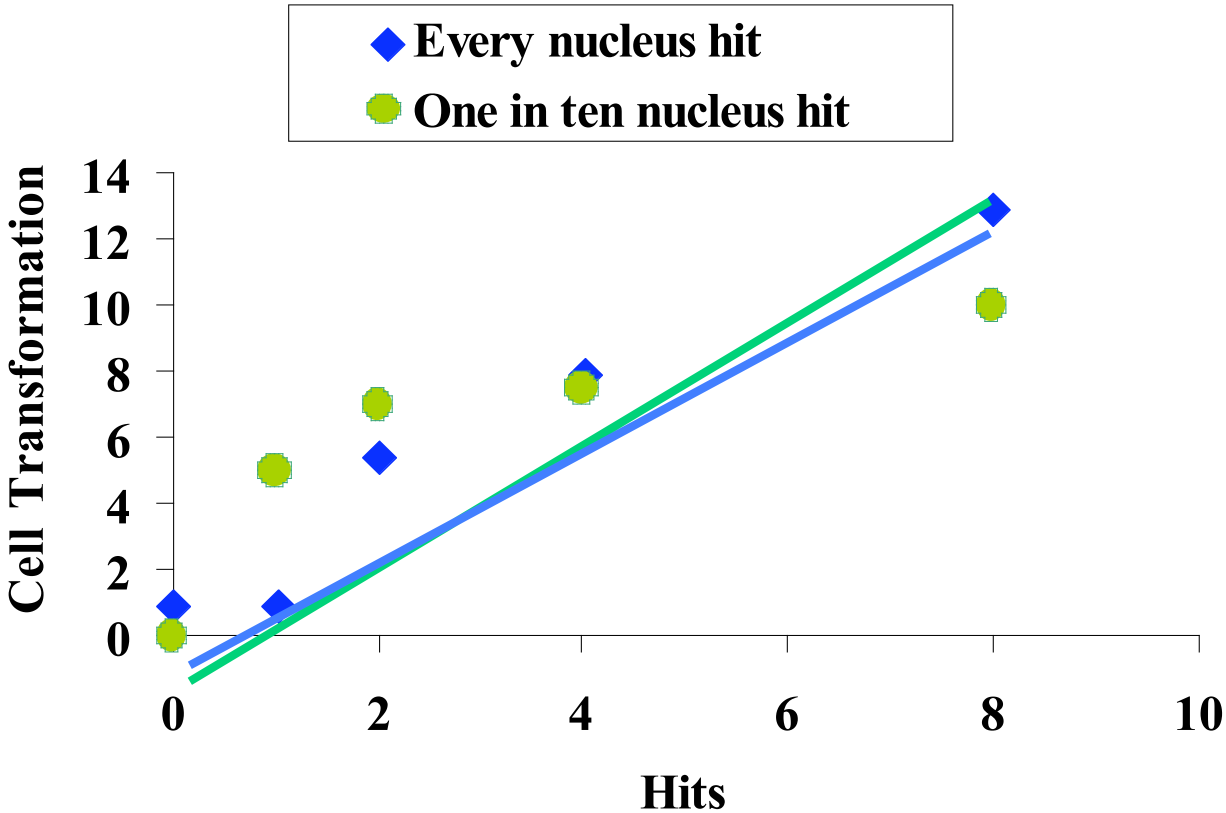


10 % of cells hit with 1 alpha particles



Sawant et al. 2000

Cell Transformation

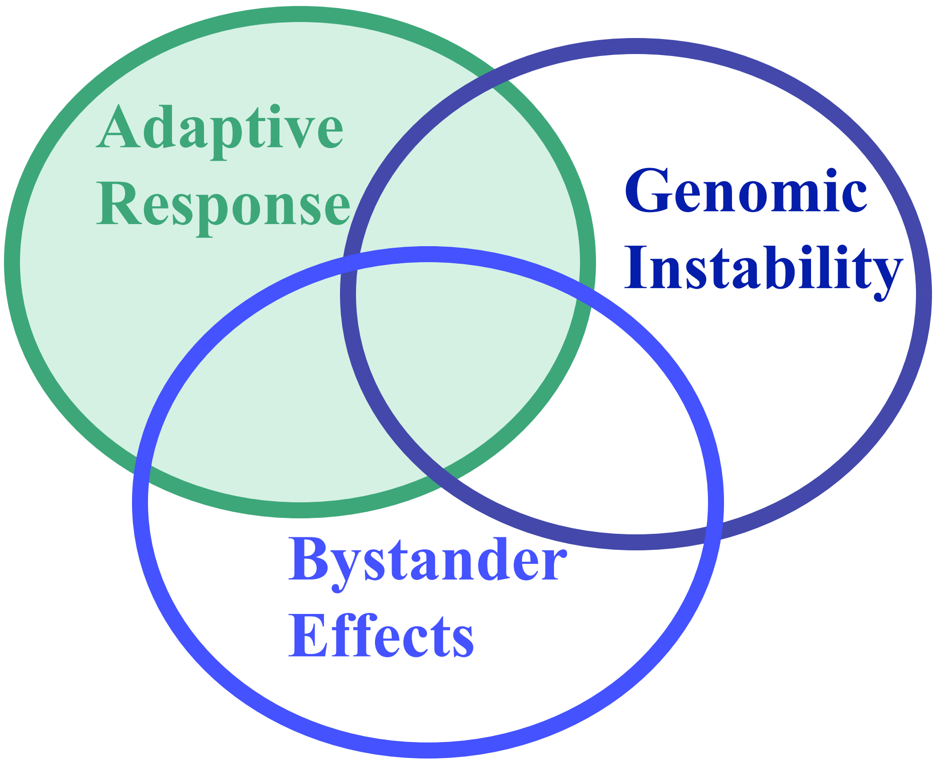


Sawant et al.2000

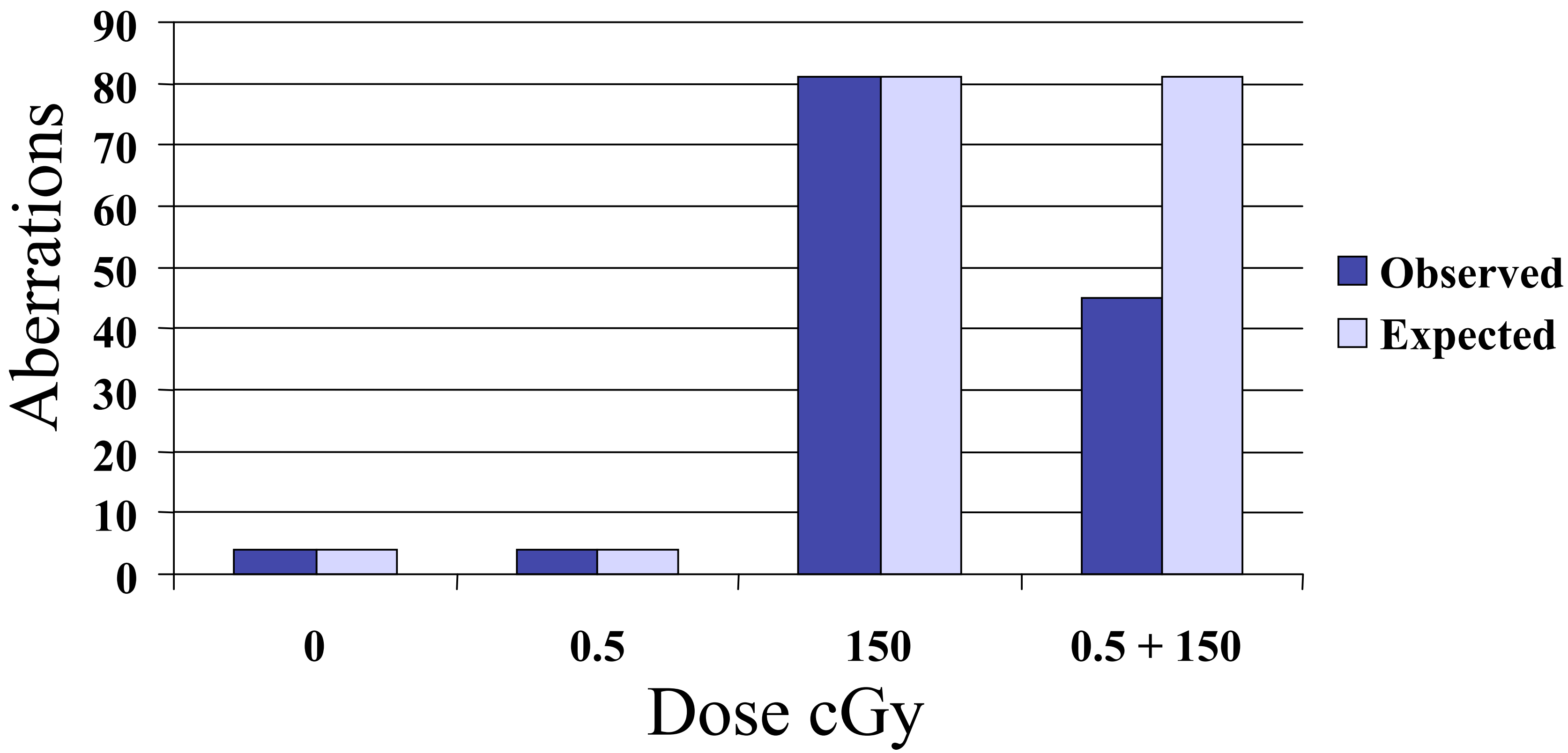
Low Dose Rate exposures: No Bystander Effects in unexposed Tissues or Organs

- Cancer from internal emitters are at the site of radionuclide deposition
- Secondary cancers from radio-therapy located at the exposure site
- At low dose rates there is little evidence for cancer in non-exposed tissues

Relationship between biological responses to radiation



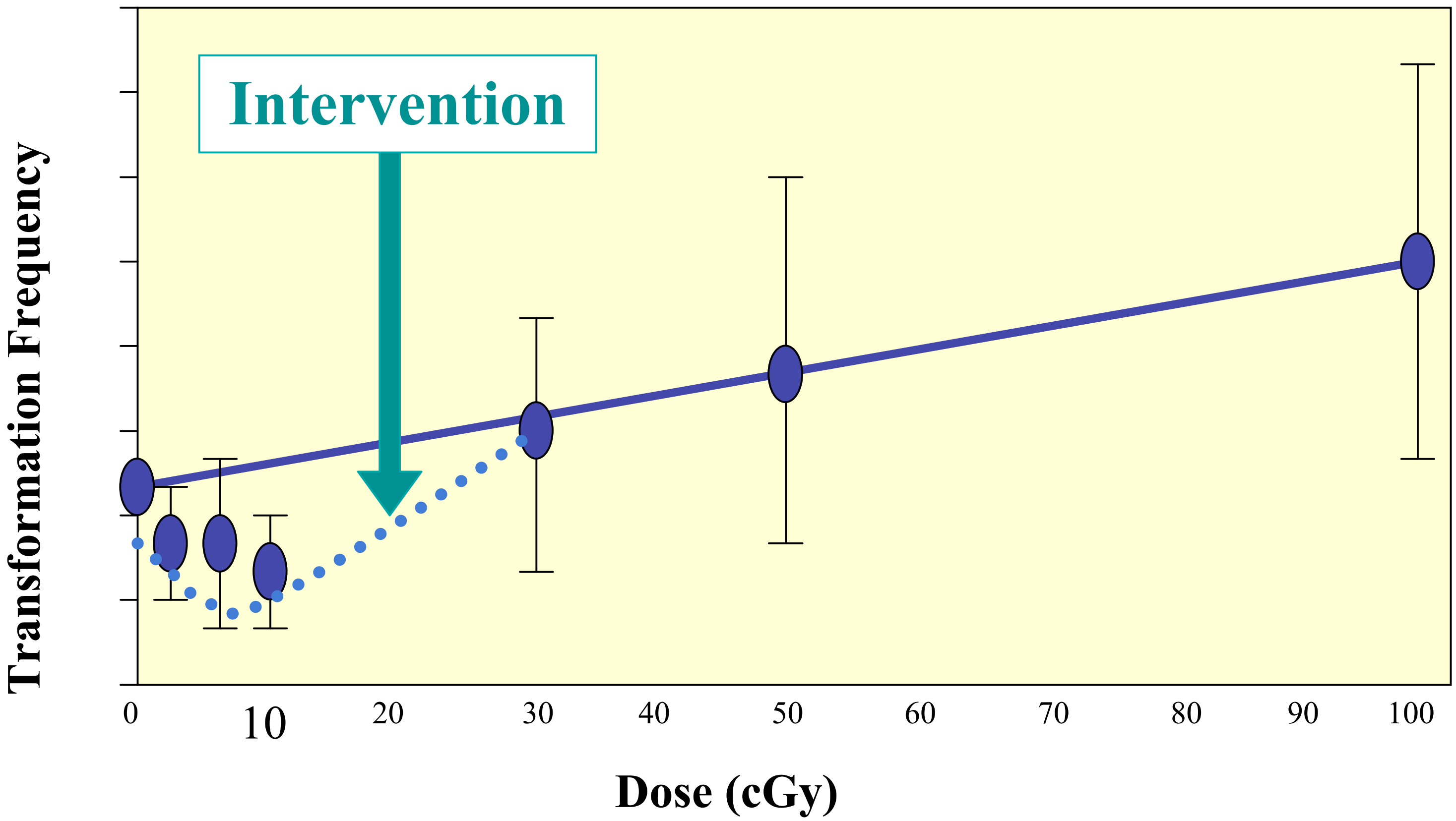
What Genes are Responsible for the Adaptive Response ?



Shadley and Wolff 1987

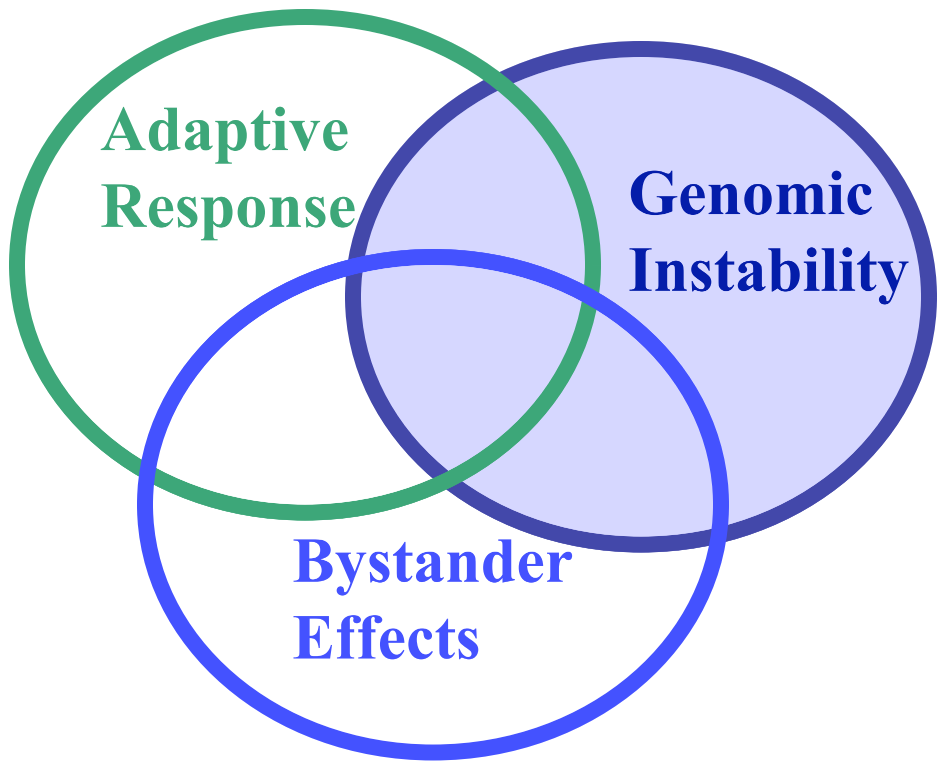
Adaptive Response

Sub-linear dose response



Redpath et al. 2001

Relationship between biological responses to radiation

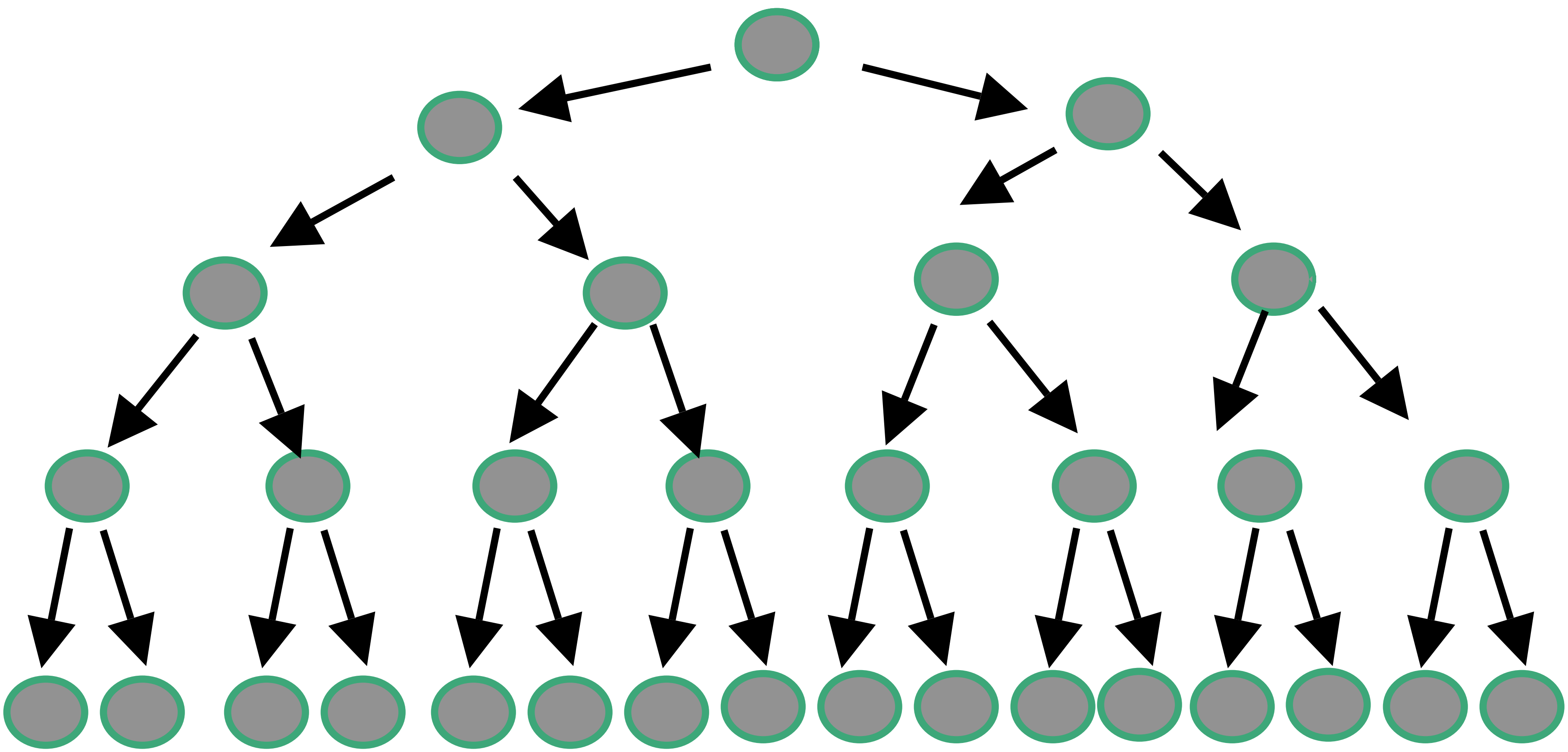


Radiation-induced Genetic Damage

Old Paradigm

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

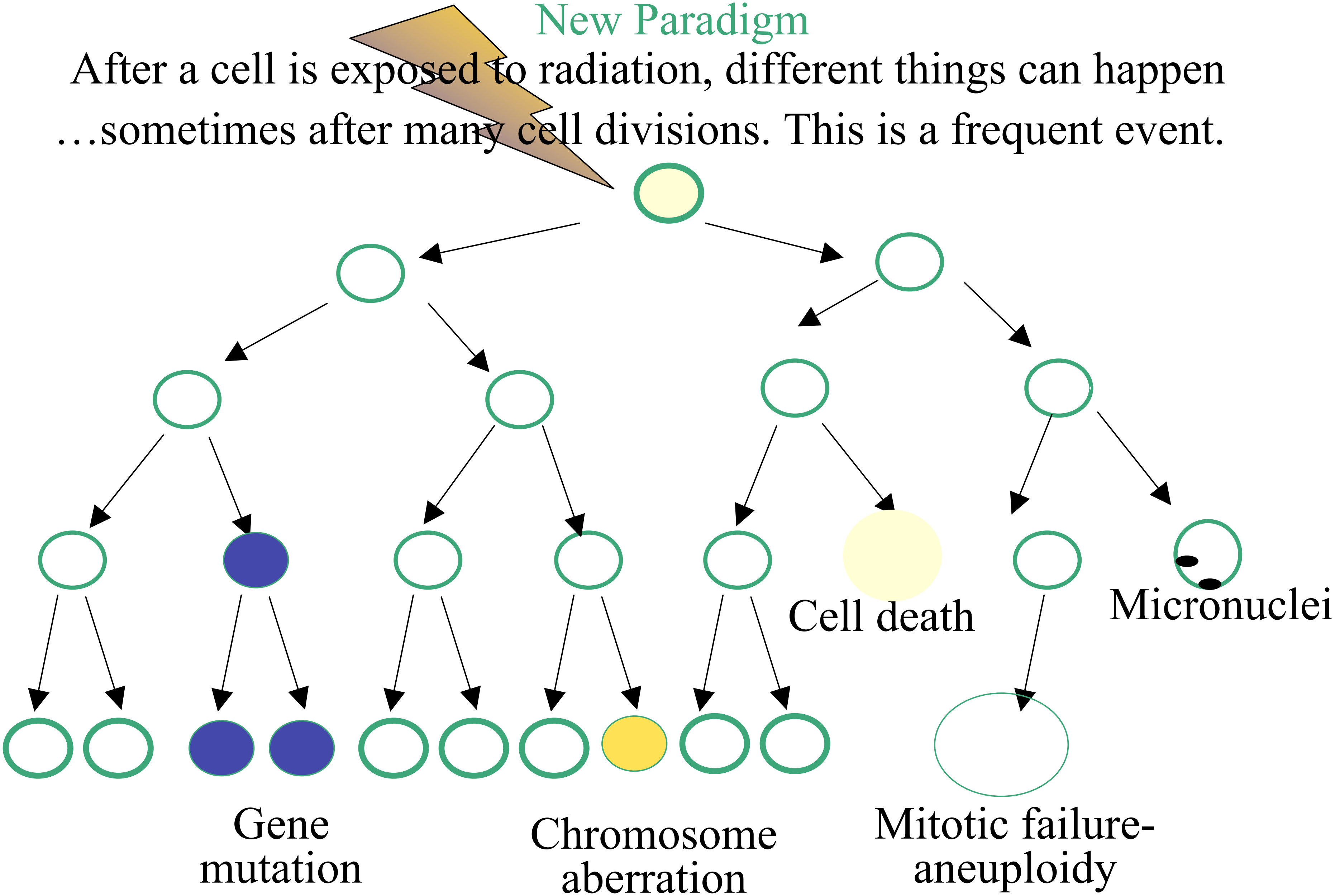
Mutation is a rare event



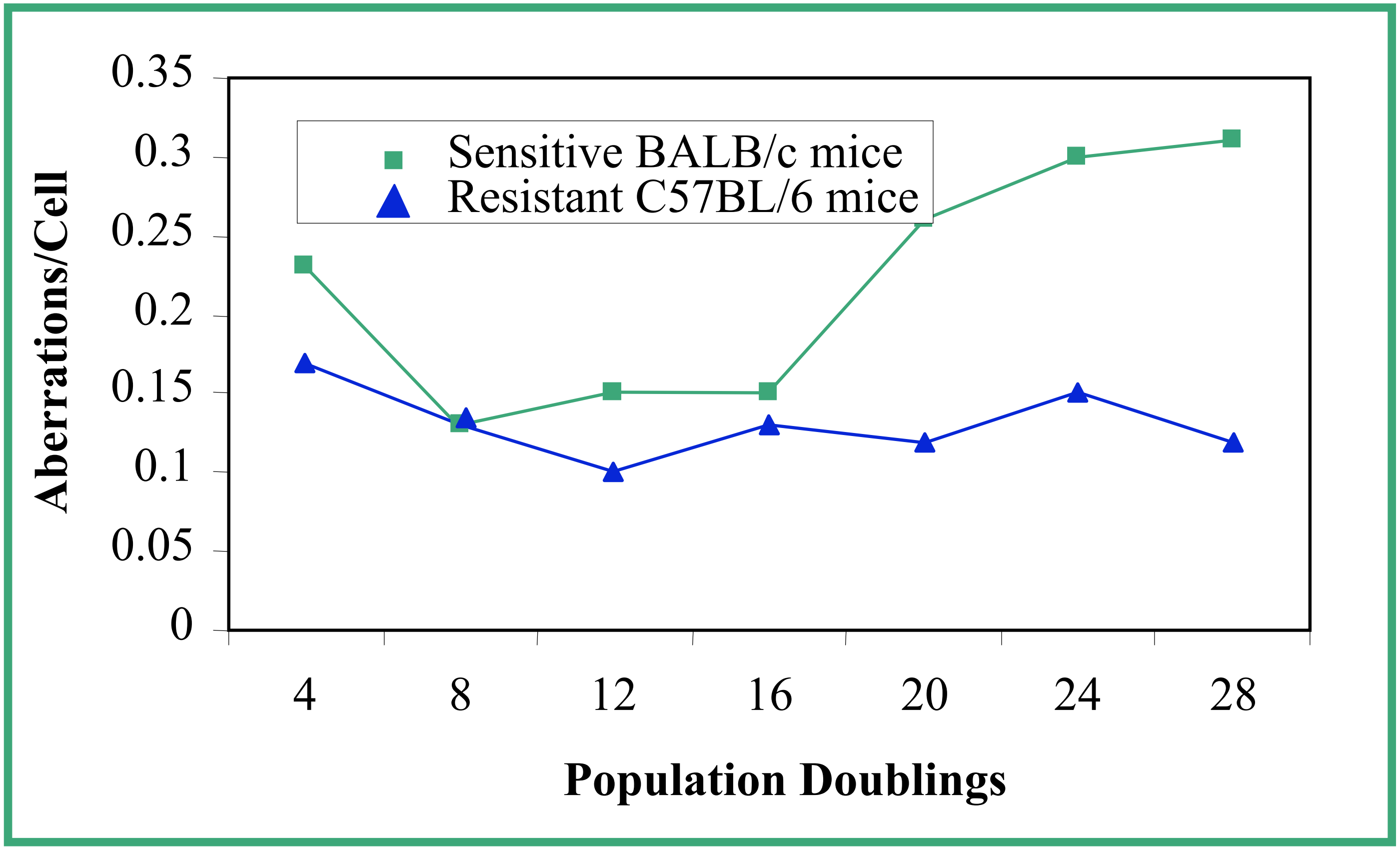
Genomic Instability

New Paradigm

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



Genomic Instability can be demonstrated in some strains of mice



B. Ponnaiya & R.L. Ullrich, 1998

Mechanisms involved in new phenomena

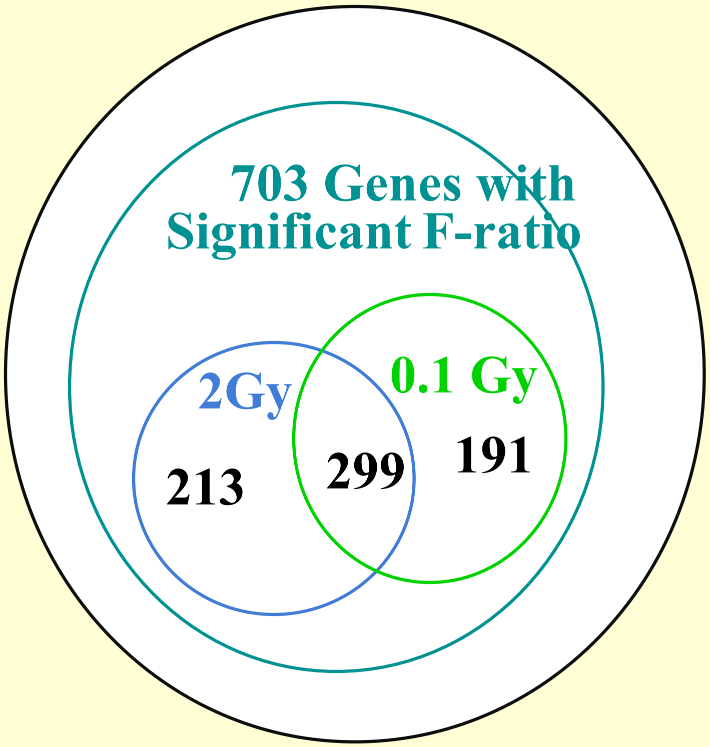
- Altered gene expression
- Impact of oxidative status of the cell
- Radiation-induced changes in differentiation pathways
- Cell/cell, cell/matrix interactions
- Nutrition and radioprotectants

Radiation-related Gene Induction

It has been shown that certain genes are inappropriately induced, or "turned on" or "turned off" by radiation.

The genes involved depend on the radiation dose delivered.

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



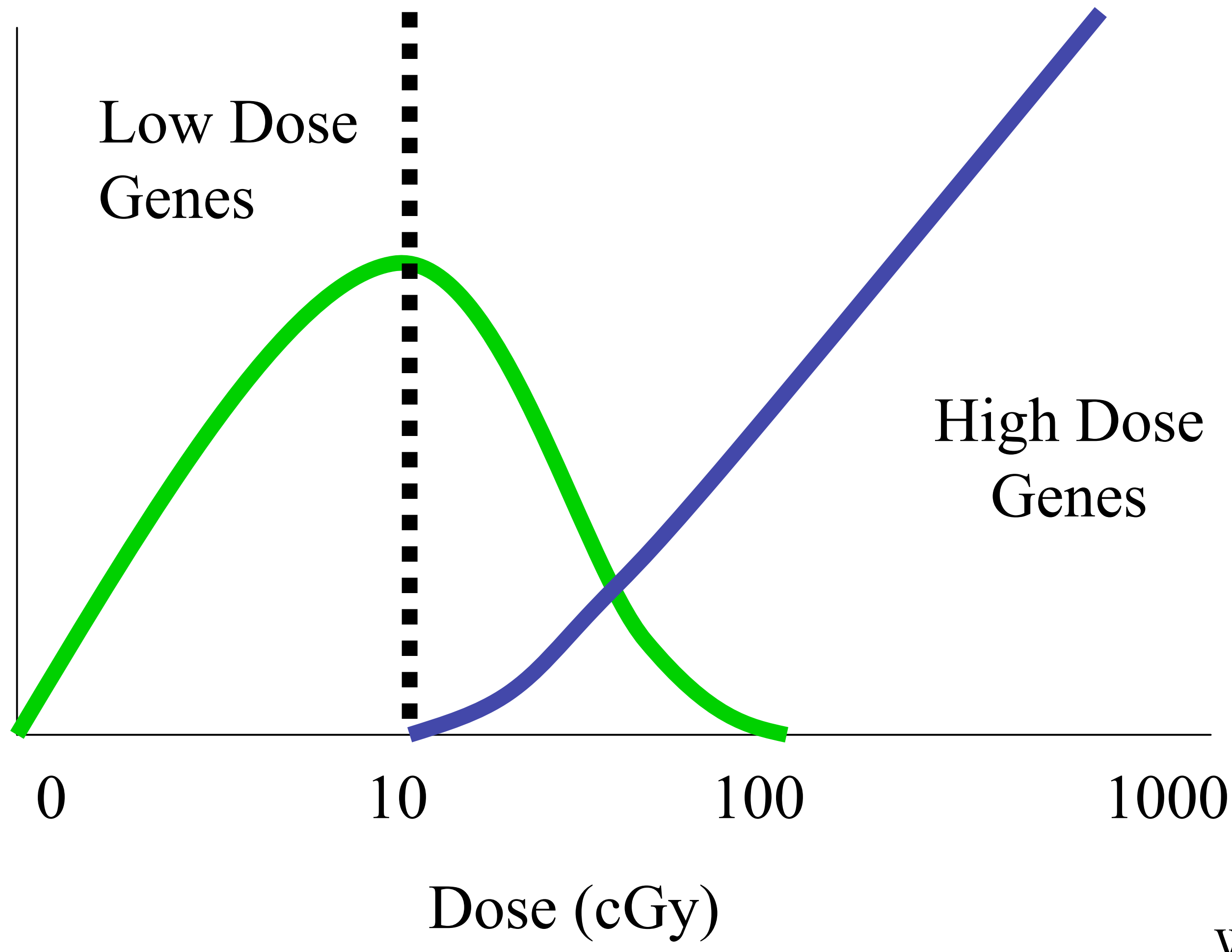
Total gene set contains nearly 10,000 genes

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

Radiation-induced changes in gene expression



Wyrobek

Protective Response

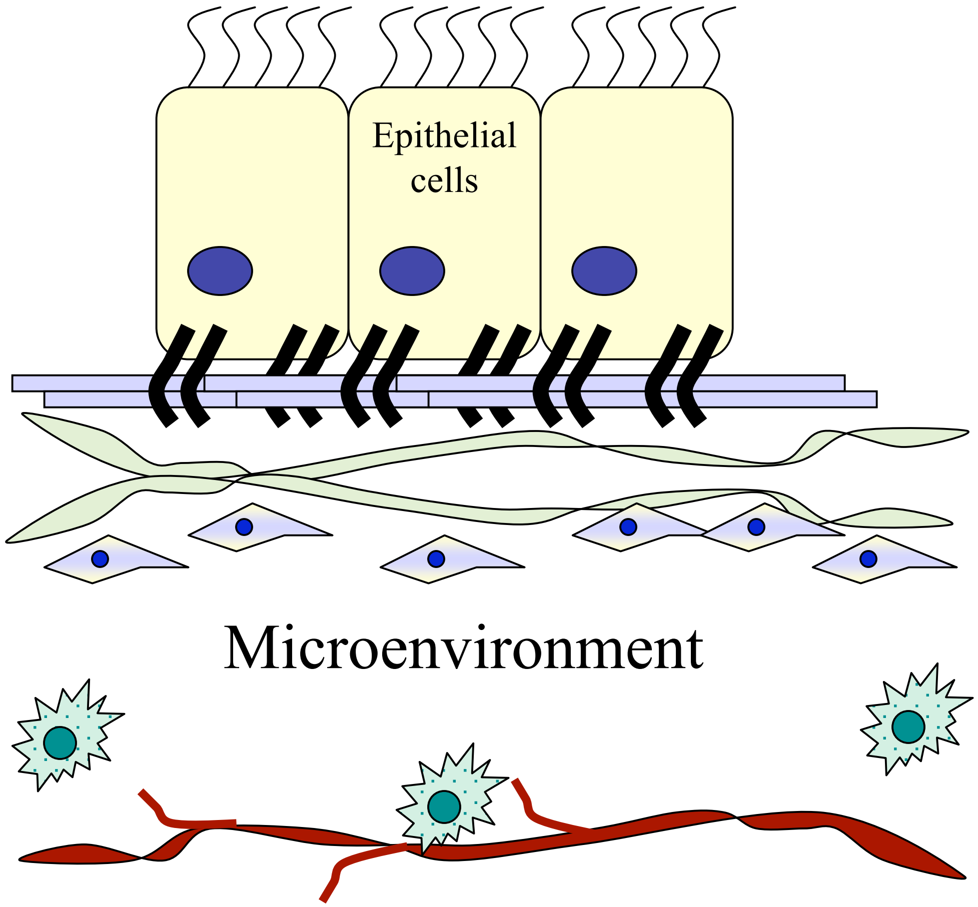
It was found that low-dose IR exposures modulated genes involved in stress response, synaptic signaling, cell-cycle control and DNA synthesis/repair, suggesting that low-dose IR may activate protective and reparative mechanisms as well as depressing signaling activity.

Yin 2003

DNA damage and signaling

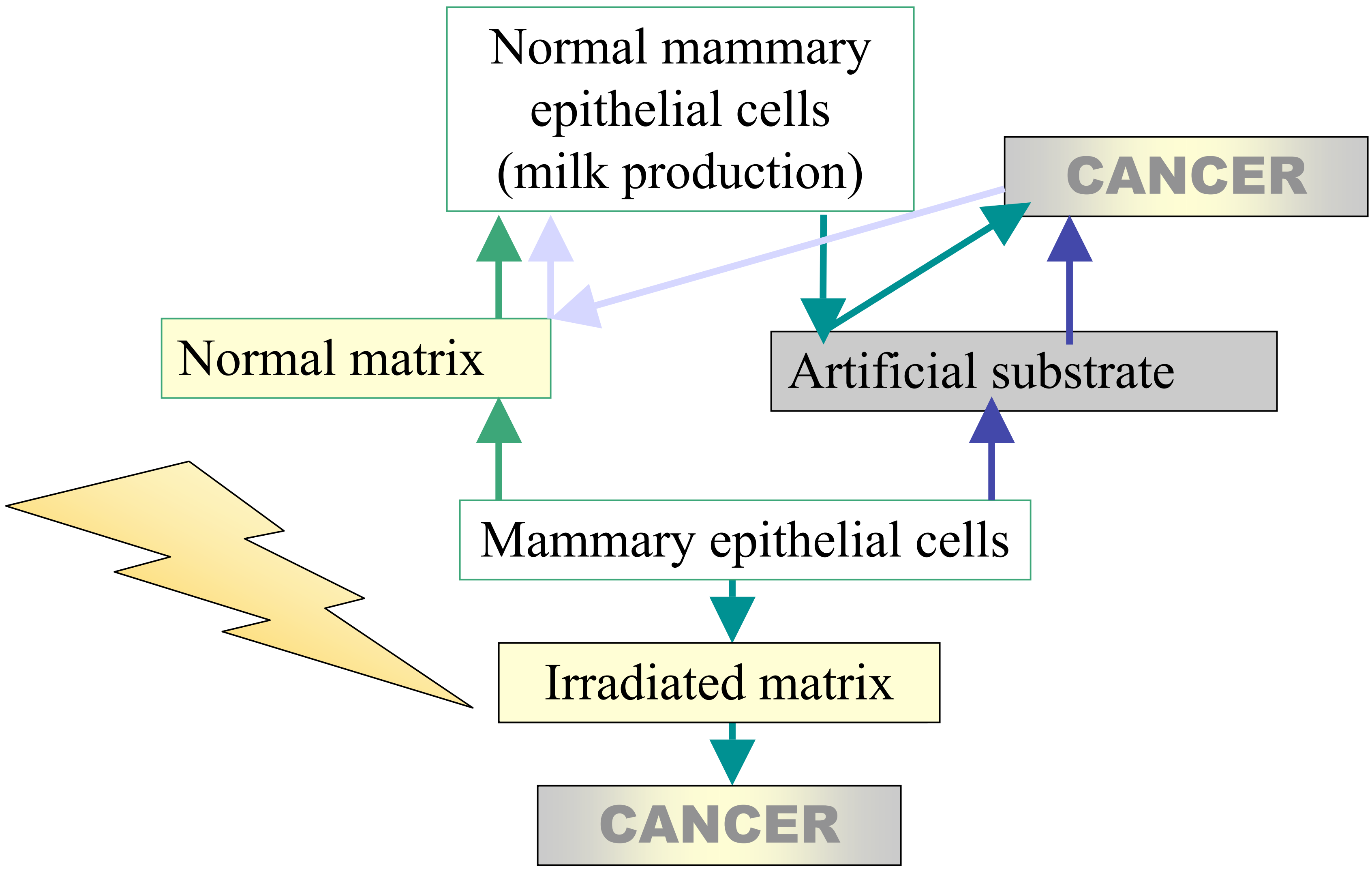
- Alterations in gene expression
- Changing redox status of the cells
- Modifying signaling pathways
- Modification of cell cycle
- Alterations in differentiation

Dynamic Interactions with Microenvironment



Park et al. 2000

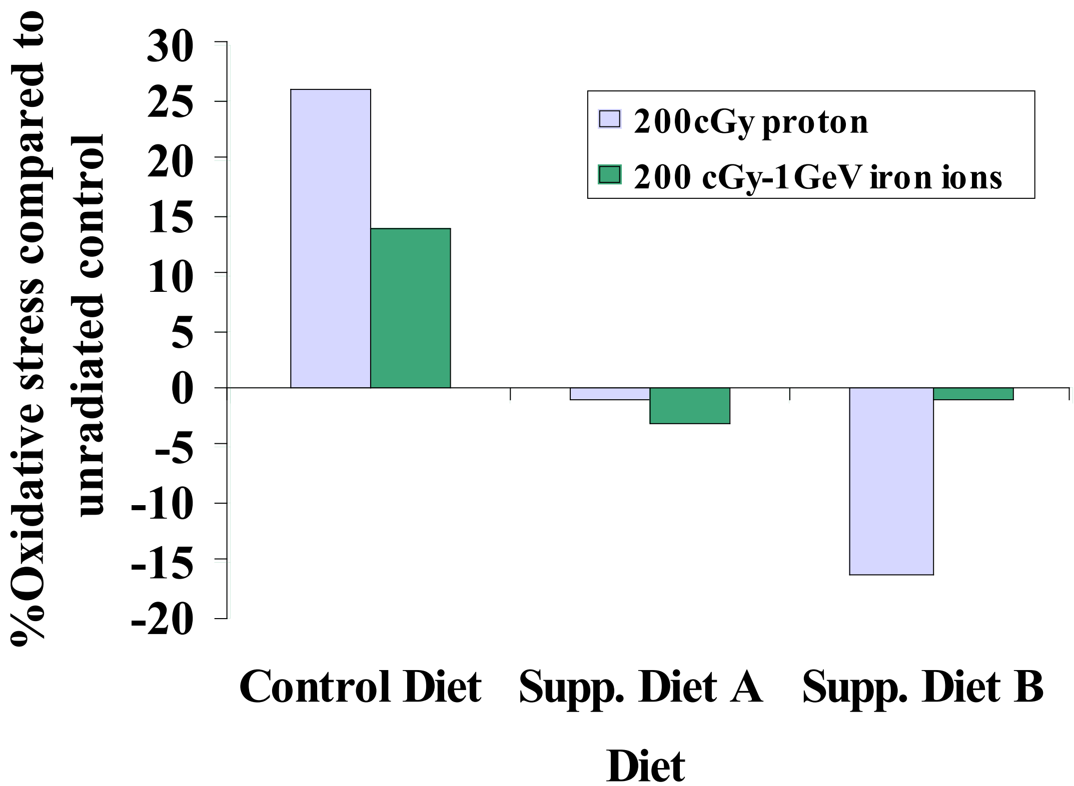
It takes a tissue to make a tumor...



Barcellos-Hoff et al. 2000

Dietary Intervention

Supplements reduce Oxidative Stress Levels after Radiation



Guan, et al 2004

Summary of New Paradigms

- **Hit theory shift to bystander paradigm**

  A cell does not have to be hit in order to be biologically altered

- **Mutation theory shifts to gene expression paradigm**

  Radiation induces changes in gene expression that may alter subsequent responses in a large fraction of the cell population

- **Single mutation cancer theory shifts to tissue paradigm**

  Tissues respond as whole and not as individual cell

- **LNTH challenged by adaptive response & genomic instability**
  - Adaptive response may result in protective, nonlinear dose-responses
  - Genomic instability or bystander effects could result in either super-linear or sub-linear dose-responses

Radiation is a rather poor mutagen and Carcinogen

- It is a very good cell killer
  - Induction of apoptosis
  - Chromosome cell death
  - Necrosis
  - Wide use in radiation therapy

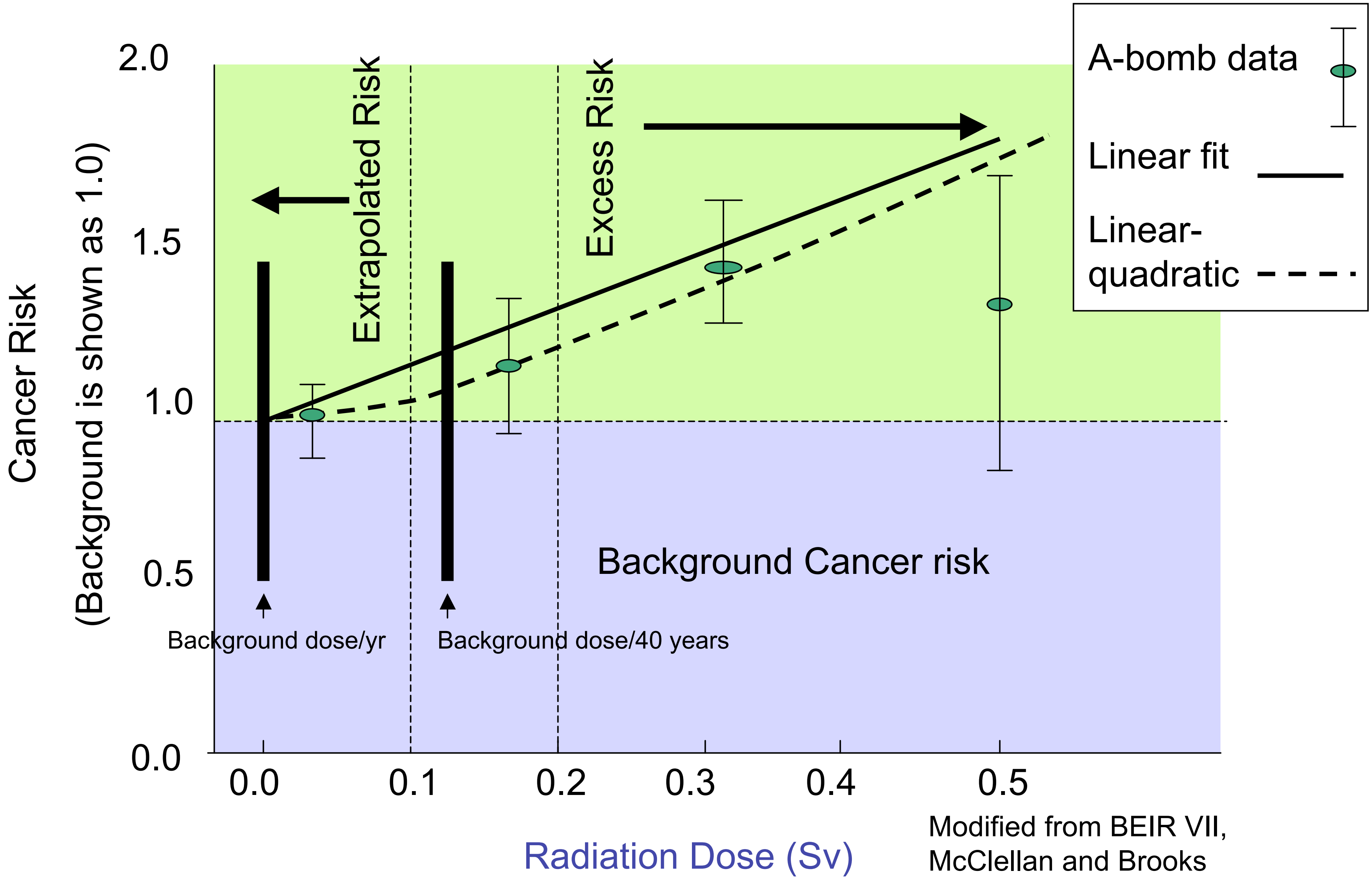
Summary:
"My View on Low Dose Cancer Risk"

- Radiation is not a major environmental carcinogen. It takes a large amount of radiation to produce an increase in cancer frequency.
- Both non-linear and linear models must be considered in determining dose-response relationships for radiation-related human cancer.
- Single hit, single DNA damage/mutation, single cancer biophysical model must be modified to accommodate modern molecular biology.
- Additional research is needed to define mechanisms of action for observed low dose biological responses before they can be used in cancer risk estimates.
- Scientific basis for radiation standards is needed to help define the shape of the dose-response relationships in the low dose regions.

BEIR VII

- Good review of the literature, summaries and conclusions, "**The risk from radiation is small**."
- Failure to acknowledge the differences between real data and extrapolated risks using the LNT-H.
- Dismissal of new mechanistic biological data that demonstrate non-linear biology.
- Failure to include the caveats in conclusions and public summaries.
- Since the risk is small it takes a lot of radiation to produce excess cancers.

Solid Cancer Risk and Radiation Exposure



Modified from BEIR VII, McClellan and Brooks