Biology versus Epidemiology

The need for an integrated model of radiation risk

Richard J. Vetter, Ph.D. FAAPM FHPS

Mayo Clinic

Rochester, MN

Acknowledgements

William Morgan, Ph.D.

Director

Radiation Biology & Biophysics

Pacific Northwest National Laboratory

Richland, Washington

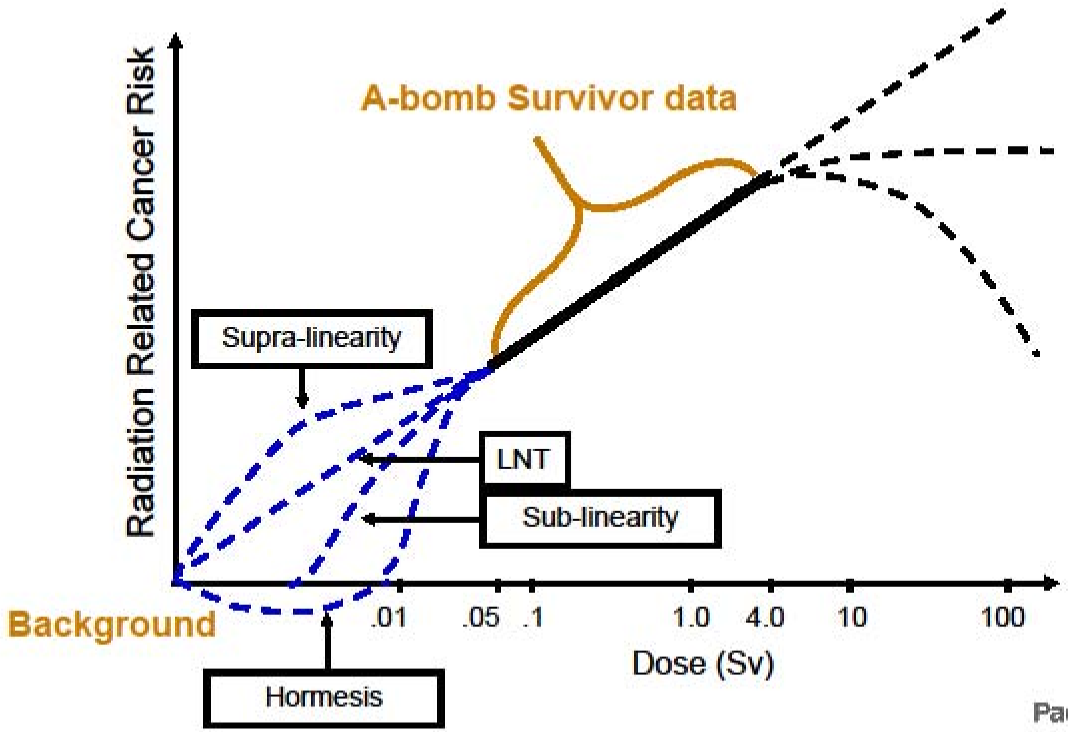
Perceptions of Risk vs. Benefit

Perceptions of Risk

STEPHANIE KLEIN-DAVIS | The Roanoke Times

Mellisa Williamson, 35, a Bullitt Avenue resident, worries about the effect on her unborn child from the sound of jackhammers.

The dilemma for radiation protection: what is the scientific basis for radiation standards to protect the public from exposures to low levels of ionizing radiation (<0.1 Sv) where there are considerable uncertainties in the epidemiological data.



Pacific Northwest
NATIONAL LABORATORY

Proudly Operated by Battelle Since 1965

Cancer Mortality ERR in LSS 1950-1997[a]

Dose (Sv)	ERR/Sv[b]	*P* Value[c]
0-0.05	0.9	0.15
0-0.1	0.64	0.30
0-0.125	0.74	0.025
0-0.15	0.56	0.045
0-0.2	0.76	0.003
0-0.5	0.44	<0.001
0-1	0.47	<0.001
0-2	0.54	<0.001
0-4	0.47	<0.001

[a]Preston et al. *Rad Res* 160: 381-407; 2003.

[b]BEIR VII ERR/Sv = 0.5 [c]One-side test that slope = 0

Health Physics Society Position

- Recommends against quantitative estimation of health risks below an individual dose of 5 rem in one year or a lifetime dose of 10 rem above that received from natural sources.
- For doses below 5–10 rem risks of health effects are either too small to be observed or are nonexistent.

Average Doses

Radiation Doses from Various Imaging Procedures

Procedure	Adult E (mSv)
Dental	0.005-0.01
Chest	0.02
CT	2-16
Fluoroscopy	5-70

Mettler, et al. 2008

Annual Dose Limits (mSv)

Effective Dose	50
Lens	150*
Skin	500
Single Organ	500
EPA PAG	20

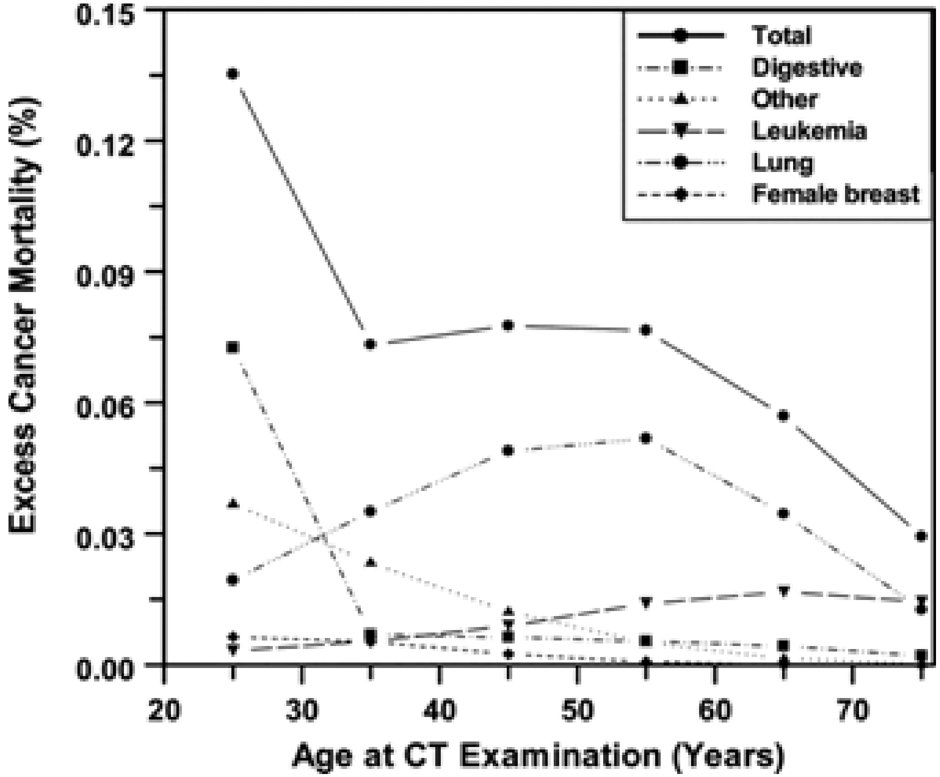
ICRP 103 recommends 20

LNT

- Even the smallest quantity of radiation exposure carries some finite cancer risk.
- Thus, eliminate radiation exposure, reduce it ALARA, or optimize it.

Risk from Medical CT

Figure 3. Graph shows excess cancer mortality risks estimated to be associated with radiation from a single full-body CT examination at a given age.

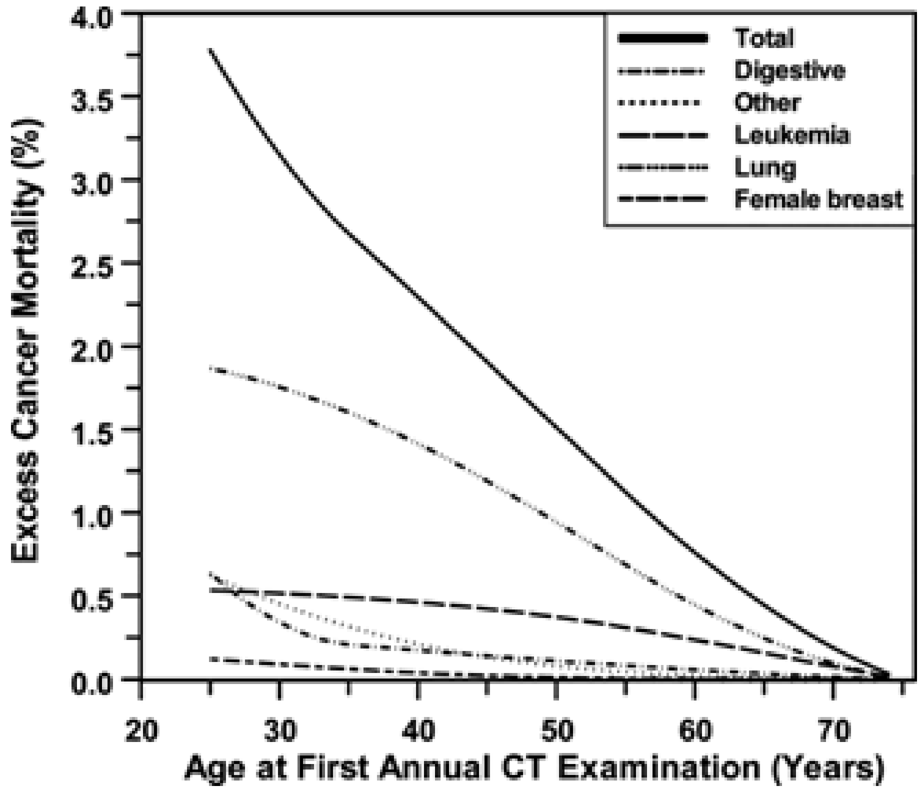


Brenner D J , Elliston C D Radiology 2004;232:735-738

Radiology

Risk from Medical CT

Figure 4. Graph shows excess cancer mortality risks estimated to be associated with radiation from annual full-body CT examinations.



Brenner D J , Elliston C D Radiology 2004;232:735-738

Radiology

Radiation Risks in Medicine

- Radiation risk from nth scan = 5×10^{-2} Sv^{-1}
  - For patient with history of 1 scan, additional risk = 5×10^{-2} Sv^{-1}
  - For patient with history of 10 scans, additional risk = 5×10^{-2} Sv^{-1}
  - For patient with history of 100 scans, additional risk = 5×10^{-2} Sv^{-1}

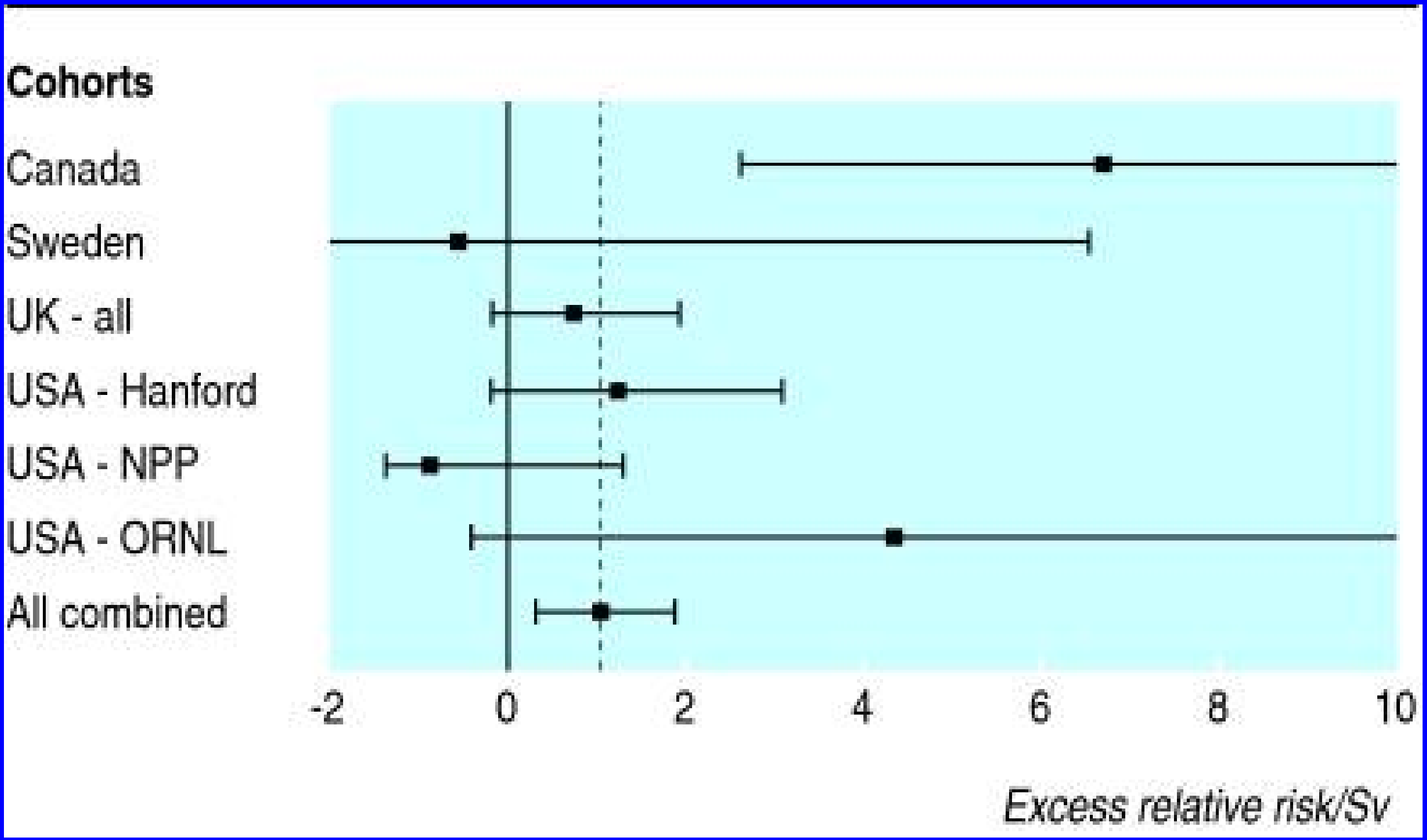
Radiation Risks in Medicine

- LNT: medical imaging may cause up to 2% of future cancers in the United States[1]
- Cumulative dose estimates for patients are of little clinical relevance and never constitute a logical reason to avoid an imaging evaluation that is otherwise medically indicated[2].

- [1]Brenner & Hall; *N Engl J Med* 2007; 357:2277–2284
- [2]Durand; AJR 2011; 197:160–162

Excess Relative Risk per Sv in Workers

(all cancer excluding leukemia in cohorts with more than 100 deaths; 407,391 workers in 15 countries; NPP=nuclear power plants)



Ninety per cent of workers received cumulative doses < 50 mSv and less than 0.1% received cumulative doses > 500 mSv.

Cardis *et al. BMJ*. 2005 July 9; 331(7508): 77.

Comments on Cardis

- Shigematsu. (2005 BMJ 331 August 9): ERR due to radiation loses statistical significance when the Canadian data are excluded.
- Lagarde. (2005 BMJ 331 August 9): ERR estimates reported may actually be underestimating the real risks.
- Debrouwer. (2005 BMJ 331 Sept 9): non-systematic bias, but maybe not, can make the results of the studies dubious.
- McGeoghegan. (2005 BMJ 331 Oct 3): elimination of Canada and smokers eliminates significance.

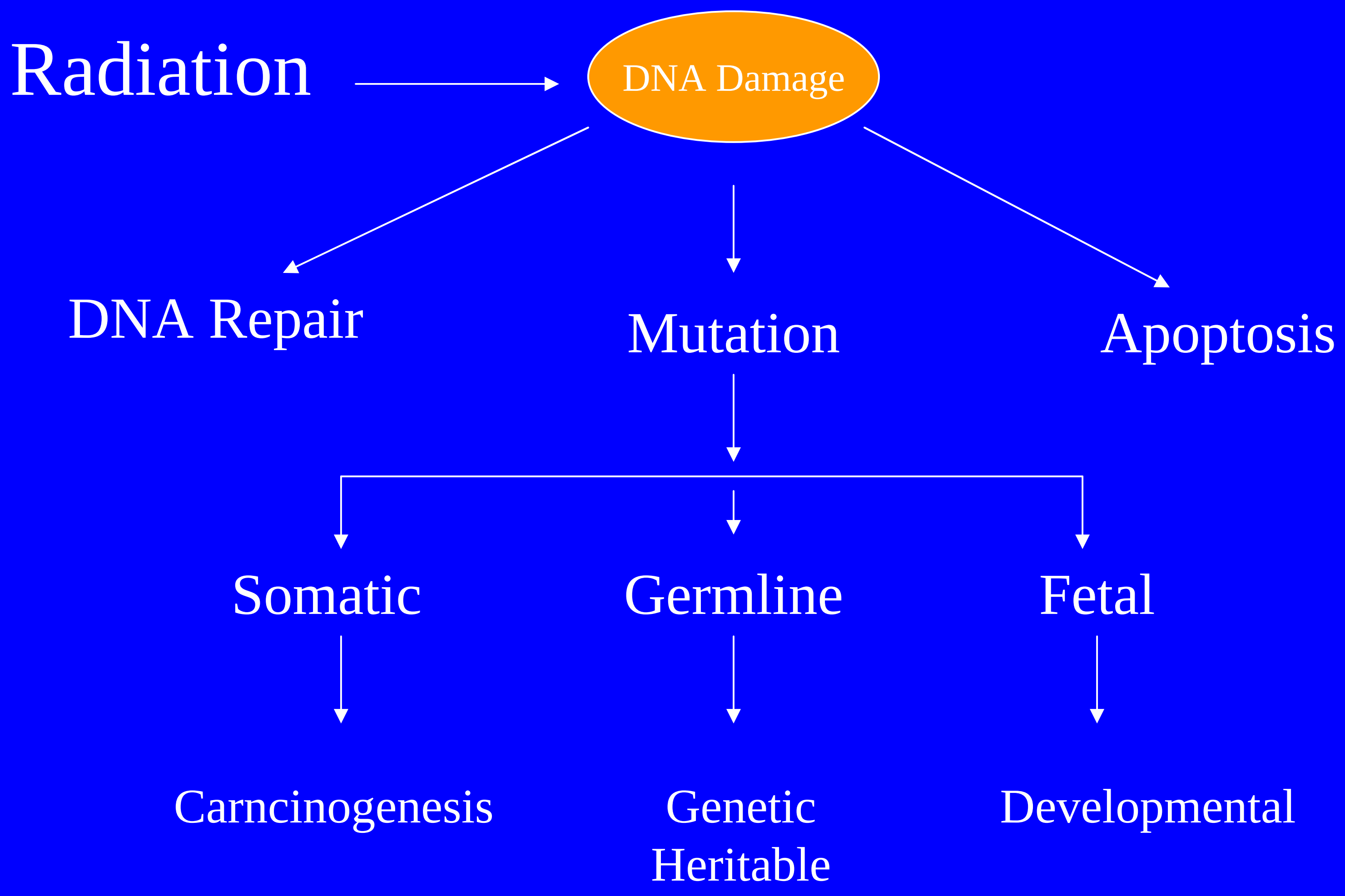
On the Other Hand - Biology

- Complex biological systems have physiological barriers and <u>repair mechanisms</u> against damage and disease.
- <u>Primary damage linear</u> with dose, <u>secondary damage often non-linear</u>.
- Cellular processes block damage.
- Propagation to clinical disease is complex.

In the Context
Of Radiation Protection

- How to extrapolate biological effects at low doses to risk?
- Are extrapolations from “high dose” acute exposures appropriate when human exposure is primarily chronic low dose exposure?

The Current Paradigm of Radiation Risk



Hot Topics in Radiobiology

- Low dose radiation hypersensitivity
- Adaptive responses
- Epigenetic modifications
- Non-targeted genomic instability
- Non-targeted bystander effects
- Non-cancer effects

Adaptive Response

- When large radiation exposure is preceded by a small “tickle” dose, the effect of the large dose is sometimes diminished.

- <u>Small doses of radiation appear to stimulate protective responses</u>, triggering DNA repair mechanisms and the elimination of severely damaged cells (apoptosis).

Adaptive Response

- Your first summer day at the beach, you don't spend 8 hours in the sun.
- You begin with an hour or two and add additional time as your skin adapts to the sunny condition and develops protective mechanisms

Radiation Induced Neoplastic Transformation *In Vitro*

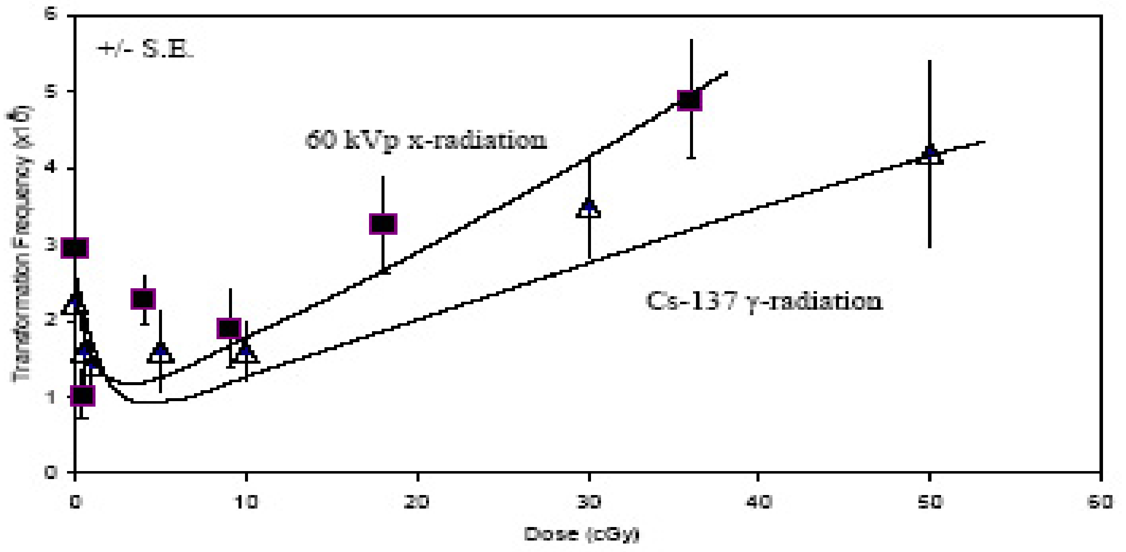


Figure 2

Redpath et al. 2001

Bystander Effects
(Field Effect in Cancer)*

- Signals sent by bystander cells may help repair the damaged cell, or they may trigger apoptosis in damaged cell.

OR

- Signals in damaged cell may disrupt normal function of bystander cells.

*Slaughter et al., Cancer 1953;6:963–968.

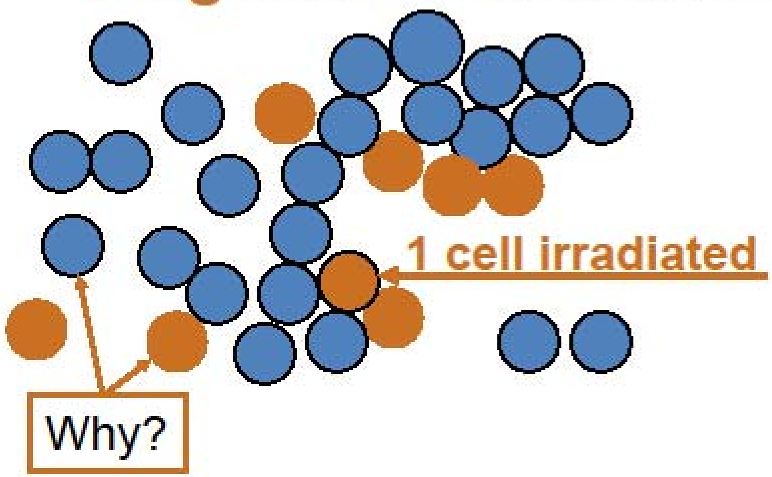
Observed Bystander Effects

- Changes in gene expression.
- Mutations.
- Apoptosis.
- Chromosome aberrations.
- Cell transformation.
- Cancer.
- Changes in sister chromatid exchanges.

Radiation induced bystander effects:

Effects observed in cells that were not irradiated but were “bystanders” at the time of irradiation

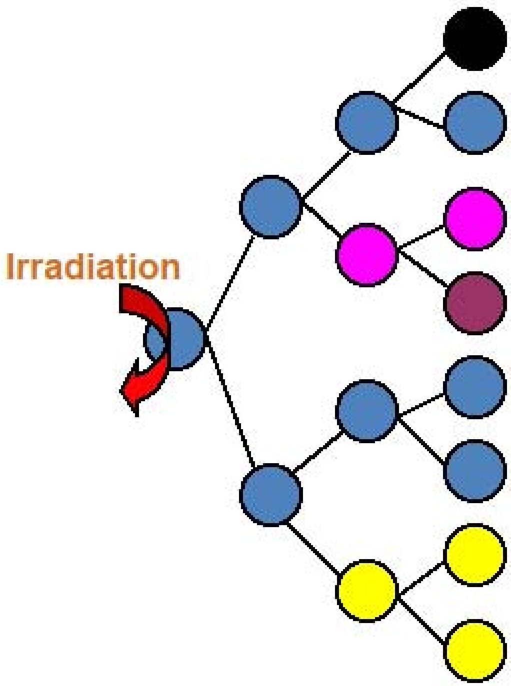
Single cell microbeam irradiation



gene expression
mutation
transformation
micronuclei
cell killing

Radiation-Induced Genomic Instability

Increased rate of genomic alterations in the progeny of irradiated cells



Manifests as:

chromosomal rearrangements
micronuclei
aneuploidy
delayed mutation
(spectrum different)
gene amplification
cell killing

Non clonal - not necessarily a fixed genetic change that is passed on.

Genomic Instability
(Delayed Genetic Effects)

- Detrimental effects that occur several cell generations after radiation exposure.
- Often, cells repair DNA damage and reproduce normally.
- In some cases genetic damage is observed several generations after damage occurred.

Genomic Instability

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

DNA Damage & Repair

- DNA damage caused by radiation exhibits multiply damaged sites.
- Single strand breaks are more common in normal endogenous DNA damage.
- Double strand breaks are more common in radiation induced damage.

DNA Damage & Repair

- Single strand break repair is usually error free.
- Double strand breaks can be either error free or error prone, containing a high error rate.
- <u>Data suggest non-linear process</u>.

Extrapolation from Experimental Systems

- What does *in vitro* cell culture tell us about what happens in the human?
- What do *in vivo* models tell us about what happens in the human?
- How to extrapolate from *in vivo* models to humans?

Radiation Response Model

- Public & Worker Protection based on LNT
- Realities: Tissue sensitivity varies with:
  - Age
  - Sex
  - Socio-economic status
  - Diet & lifestyle
  - Genetic makeup & race
  - Dose & dose rate
  - Radiation quality

Questions

- How to design a system that limits risk?
  - Most sensitive organ?
  - Most sensitive individual?
- How do we assign individual human risk?
- What science do we need to accomplish this?
- Where do we set the “threshold”
  - for regulatory purposes?
  - for clinical purposes?

Conclusions

- Epidemiology isn’t sensitive enough to provide definitive information at low doses.
- Radiobiology research will continue to elucidate mechanisms, but not population risk.
- Use of LNT works for prospective protection of public health but doesn’t provide accurate results for risk.

Conclusions

- LNT: biology suggests that not all systems respond to radiation linearly.
- Regulatory use of LNT is “safe bet.”
- Use of LNT to calculate risk from medical radiation is “risky.”