Essential radiobiology for radiation epidemiologists

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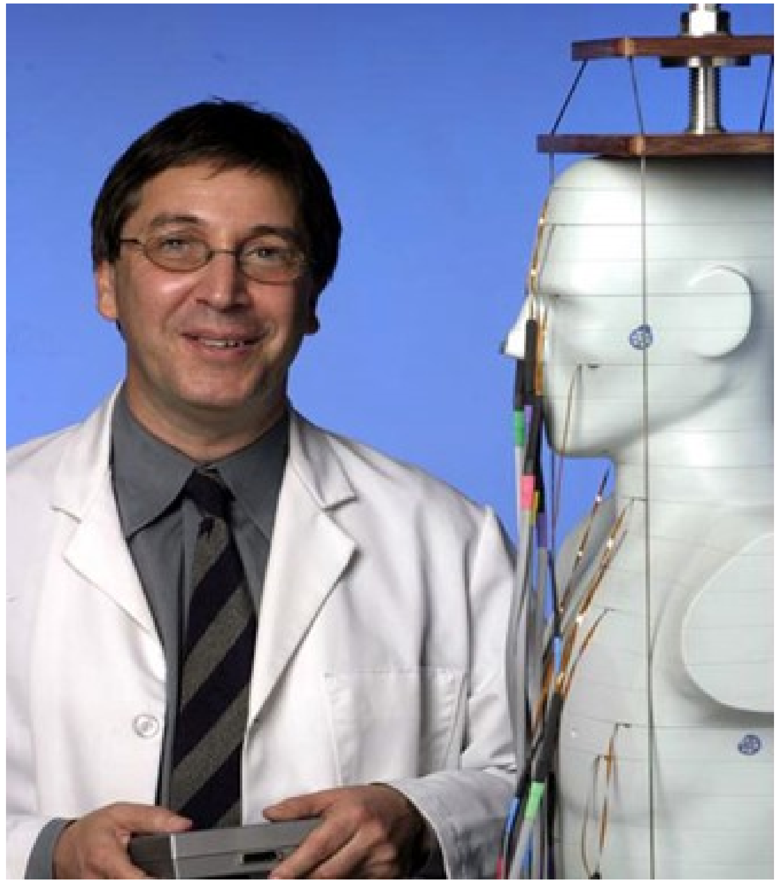


DCEG Radiation Epidemiology and Dosimetry Course 2019

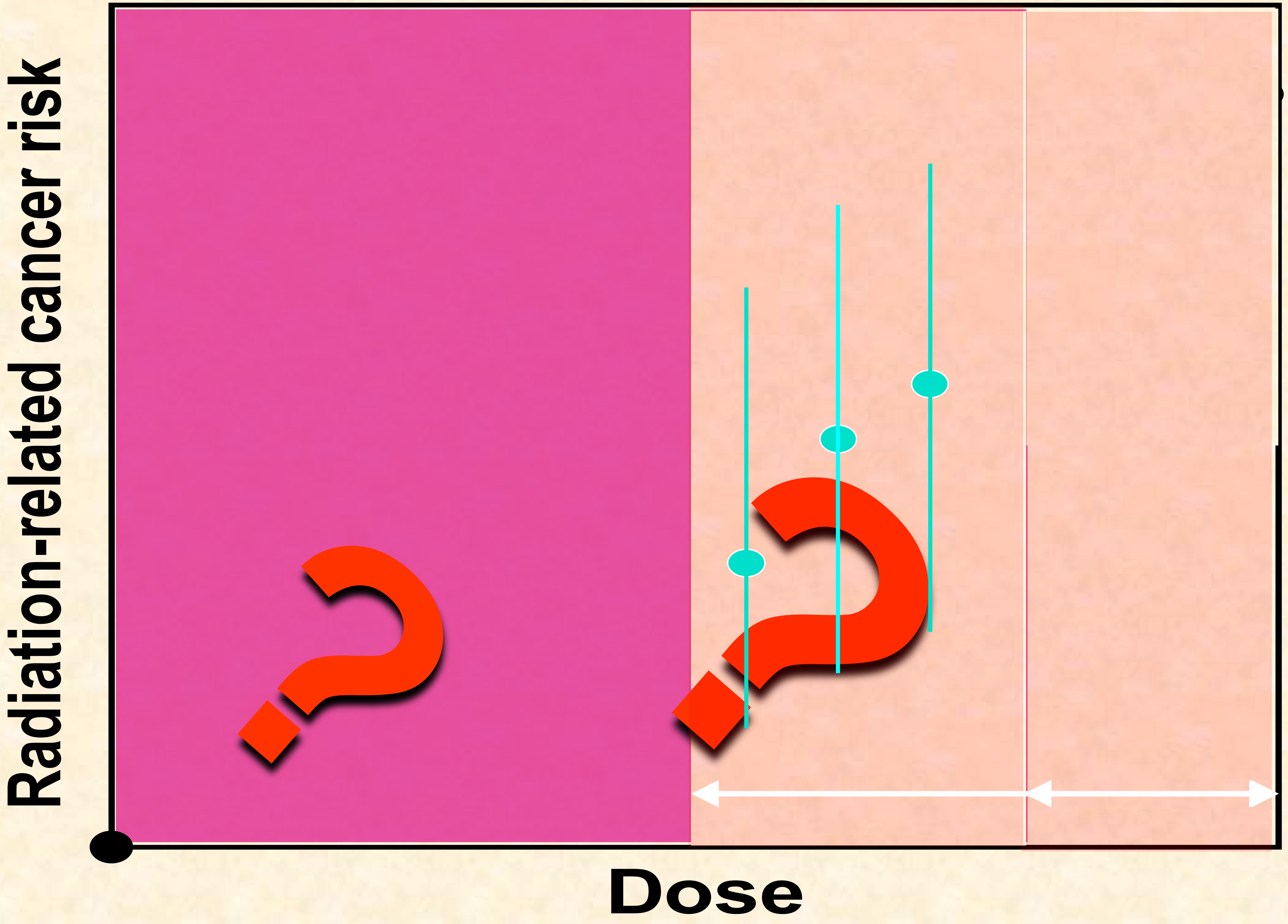
NIH NATIONAL CANCER INSTITUTE

Do epidemiologists need radiobiology?

- The exposure situations that we are interested in these days are generally not those that are amenable to quantitative radiation epidemiology

- Extrapolations:
  - *Dose*
  - *Dose rate*
  - *Radiation quality*
  - *Age / genetics*

What is the problem?



About as low dose as epidemiology can go:

Solid cancers in A-bomb survivors exposed to doses from 5-100 mSv

Small but statistically significant increase in risk

	Cancer incidence (1958-98)
Study population (5-100 mSv)	27,789
Total solid cancers observed	4,406
Solid cancers expected (controls)	4,325
Radiation-related excess solid cancers	81

Preston *et al* 2007

Low-dose trend tests for solid cancers in A-bomb survivors

Cancer Mortality

- 5 – 100 mGy P=0.04
- 5 – 150 mGy P=0.006

Cancer Incidence

- 5 – 100 mGy P=0.08
- 5 – 150 mGy P=0.01

www.melodi-online.eu/Preston.pdf

The 2012 UK CT Study

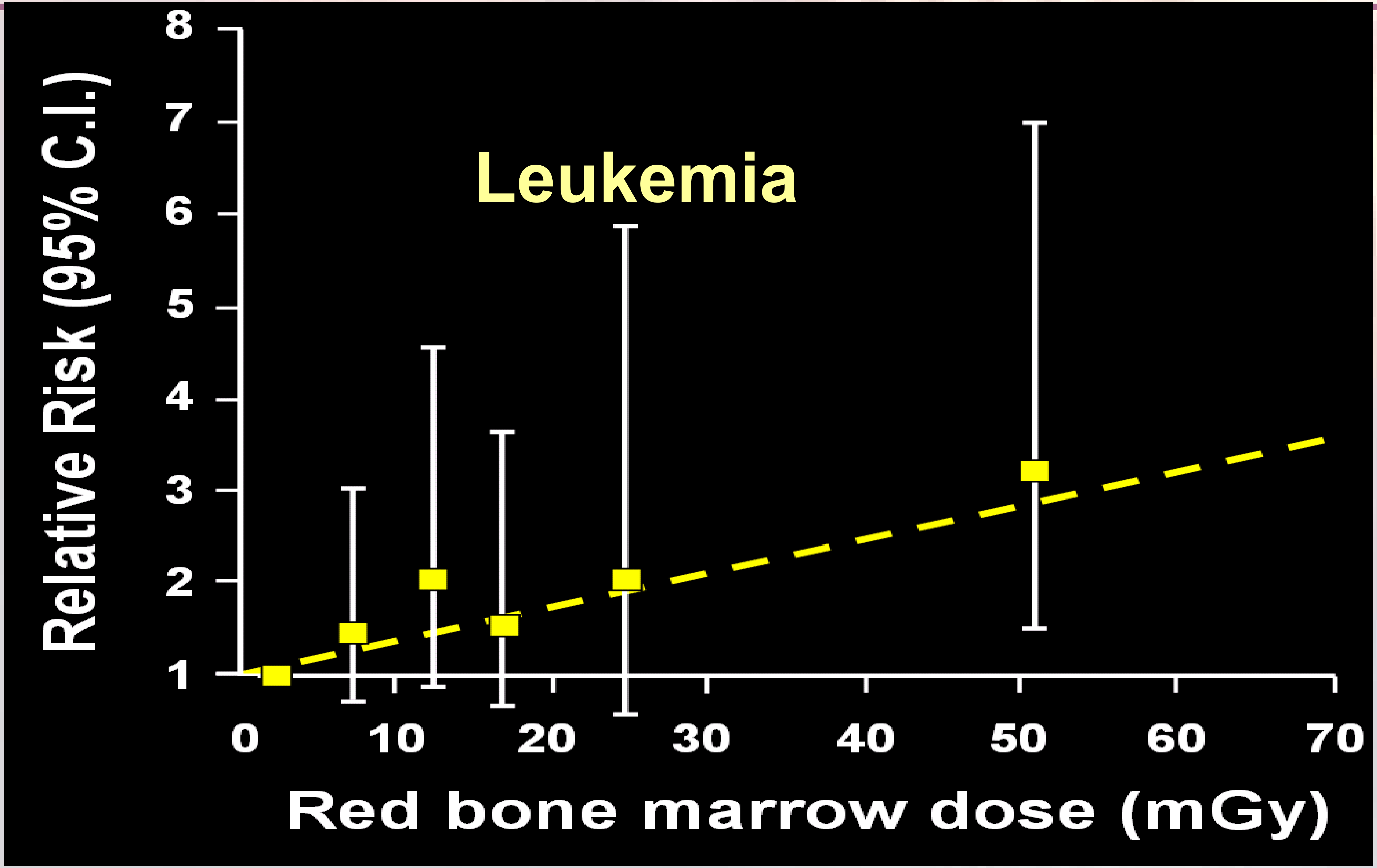
Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study

Mark S Pearce, Jane A Salotti, Mark P Little, Kieran McHugh, Choonsik Lee, Kwang Pyo Kim, Nicola L Howe, Cecile M Ronckers, Preetha Rajaraman, Sir Alan W Craft, Louise Parker, Amy Berrington de González

www.thelancet.com **Published online June 7, 2012** DOI:10.1016/S0140-6736(12)60815-0

~10 year follow-up of 175,000 patients who received CT scans in the UK, age <22, between 1985 and 2002

- **Statistically significant linear associations seen between bone-marrow dose and leukemia risk (p=0.01) in the 5-50 mGy range**

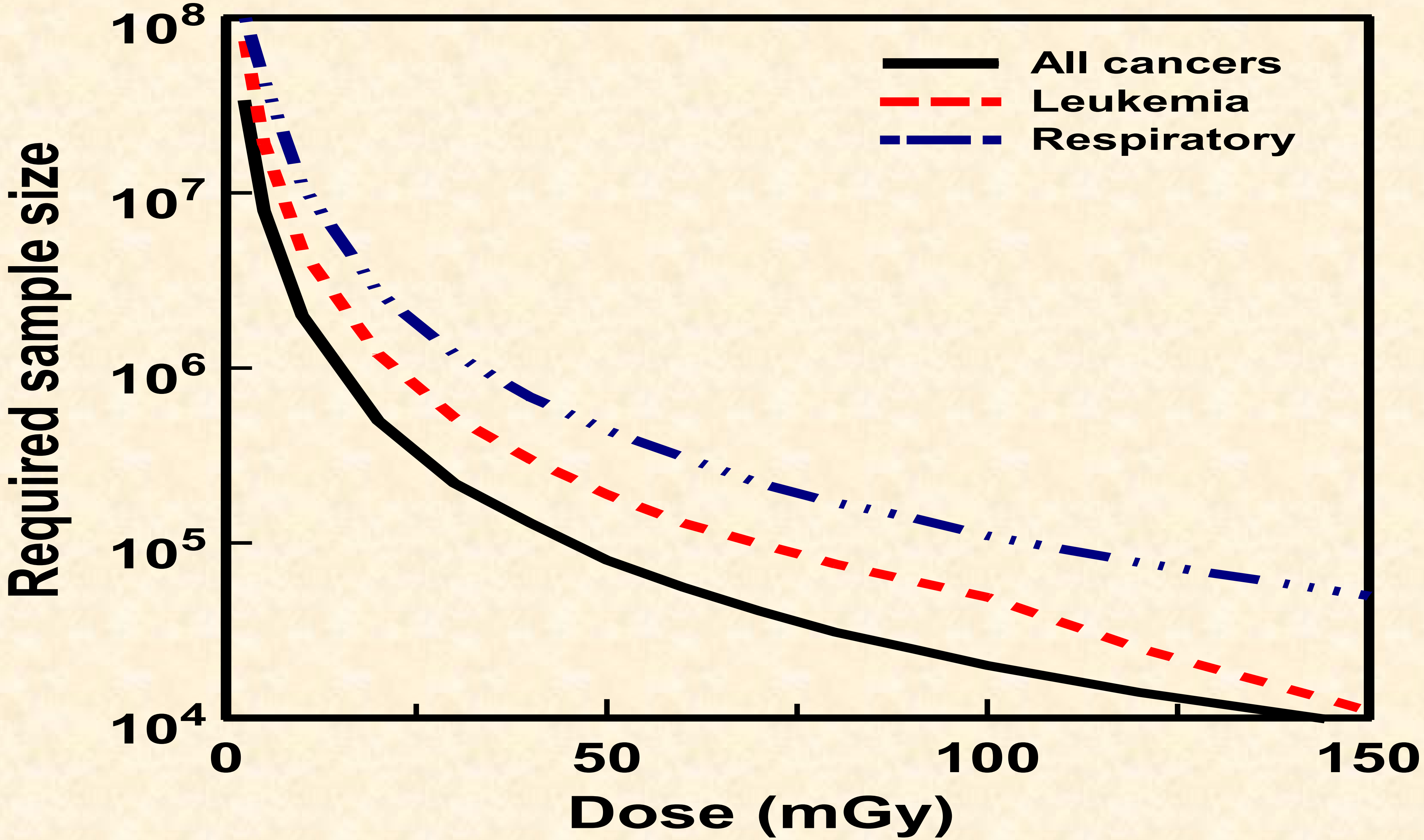


Why can't we get useful information from epidemiological studies at lower doses?

- We don't have any "fingerprints" to uniquely identify a radiation-induced cancer
  - So epi studies currently involve looking for a radiation-associated increase in cancer rates relative to a background (unirradiated) population

- ~40% of any study population will get cancer anyway
  - So looking for smaller and smaller excess risks due to lower and lower radiation doses requires bigger and bigger studies

Size of cohort required to detect a significant increase in cancer mortality



From NRC 1995

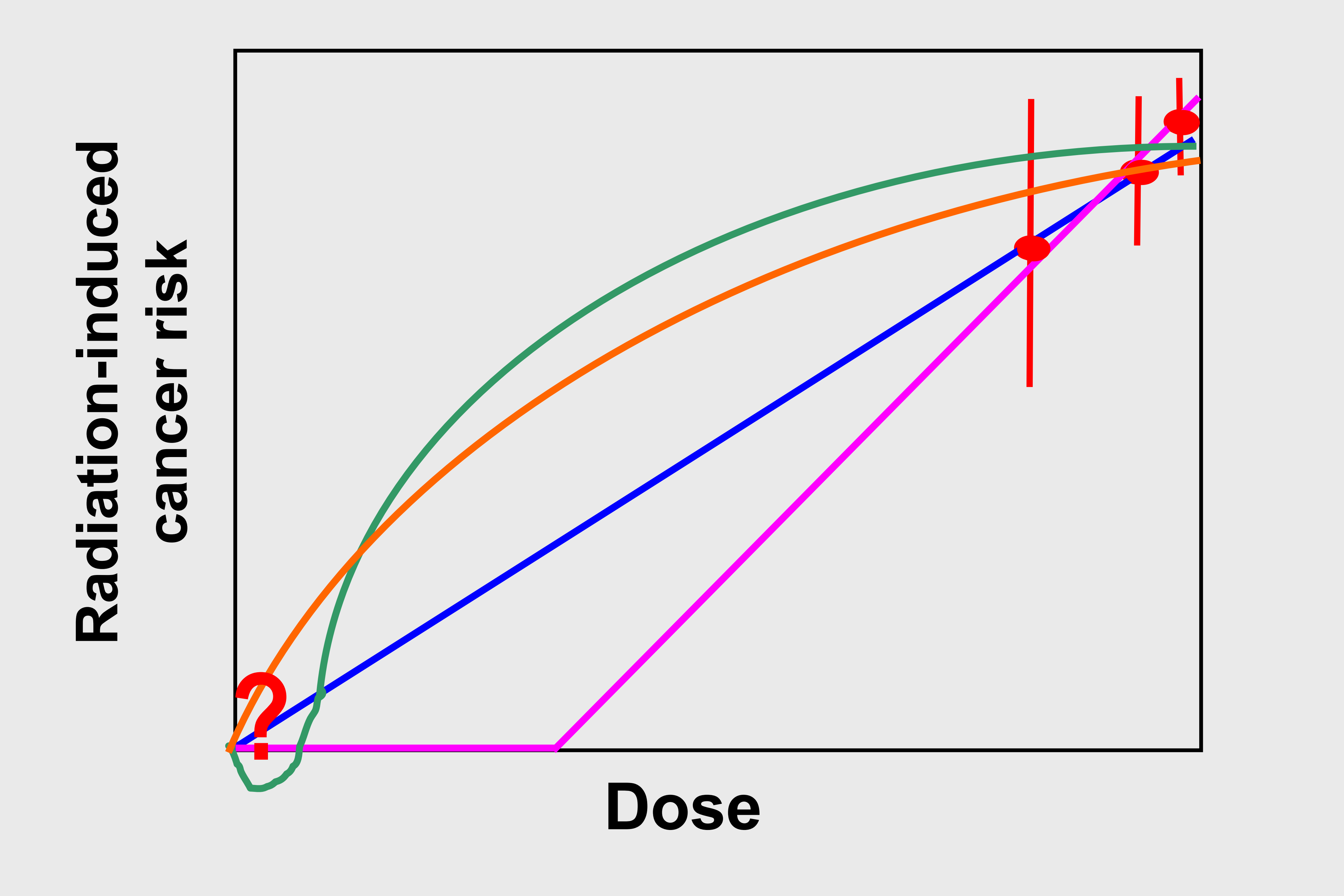
Three Studies of Mortality in Radiologists

STUDY	Relative Risk	
Matanowski (US)	1.2	Statistically significant increase
Berrington (UK)	0.68	Statistically significant decrease
Carpenter (UK)	1.03	No significant change

For the foreseeable future, we will continue to have to either scale or extrapolate the radiation-related cancer risks we need, based on higher dose epidemiological data

- To lower doses
- To different radiation qualities
- To different dose rates
- To populations with different background cancer risks
  - Different ages
  - Different genetic sensitivities

Estimating the risks associated with still lower doses of ionizing radiation



Can laboratory radiobiology studies help?

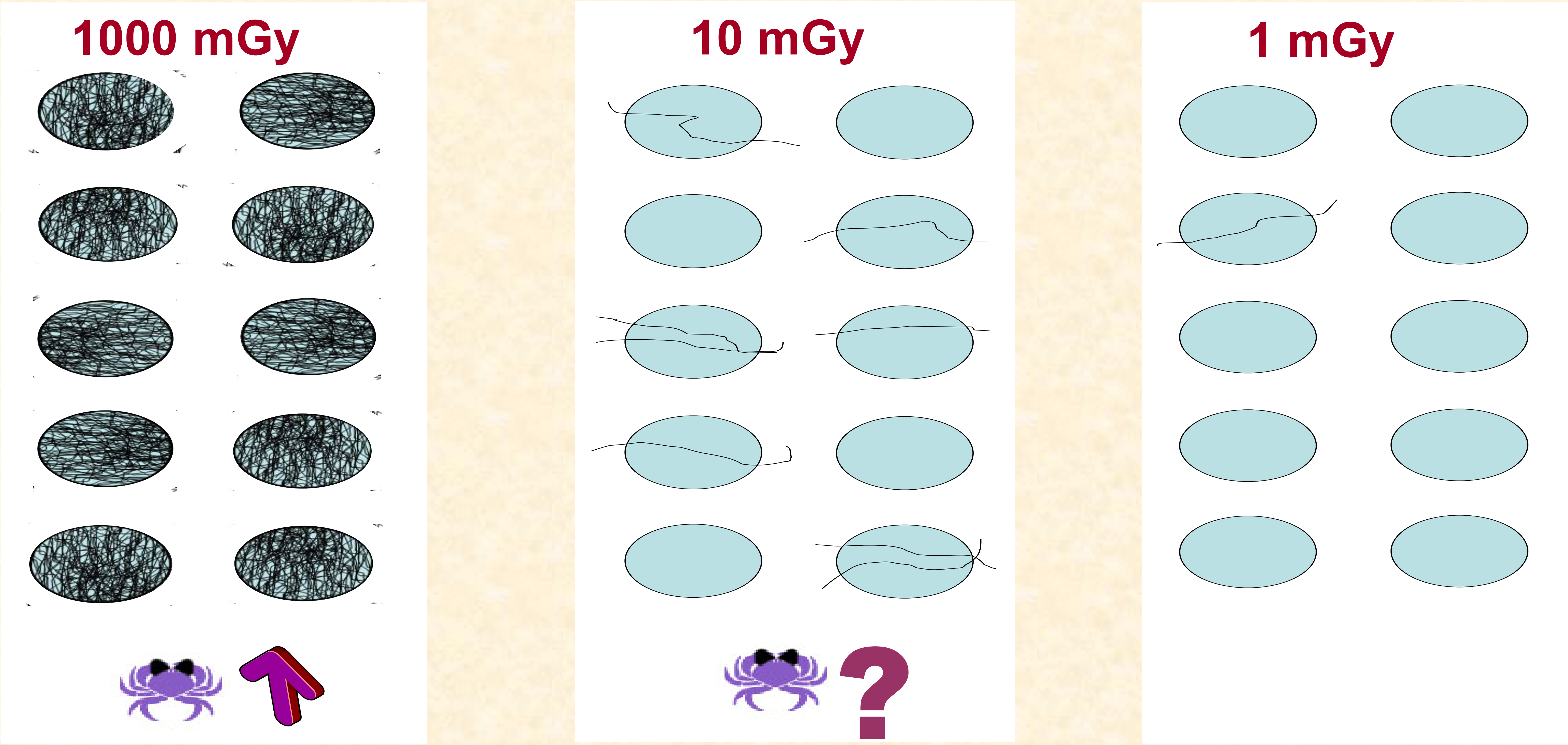
Not directly… we have no proven laboratory systems for quantifying radiation-induced cancer risks in man

But indirectly…. they can help us understand how to extrapolate measured radiation-induced cancer risks at high doses to lower doses

Can laboratory radiobiology studies help?

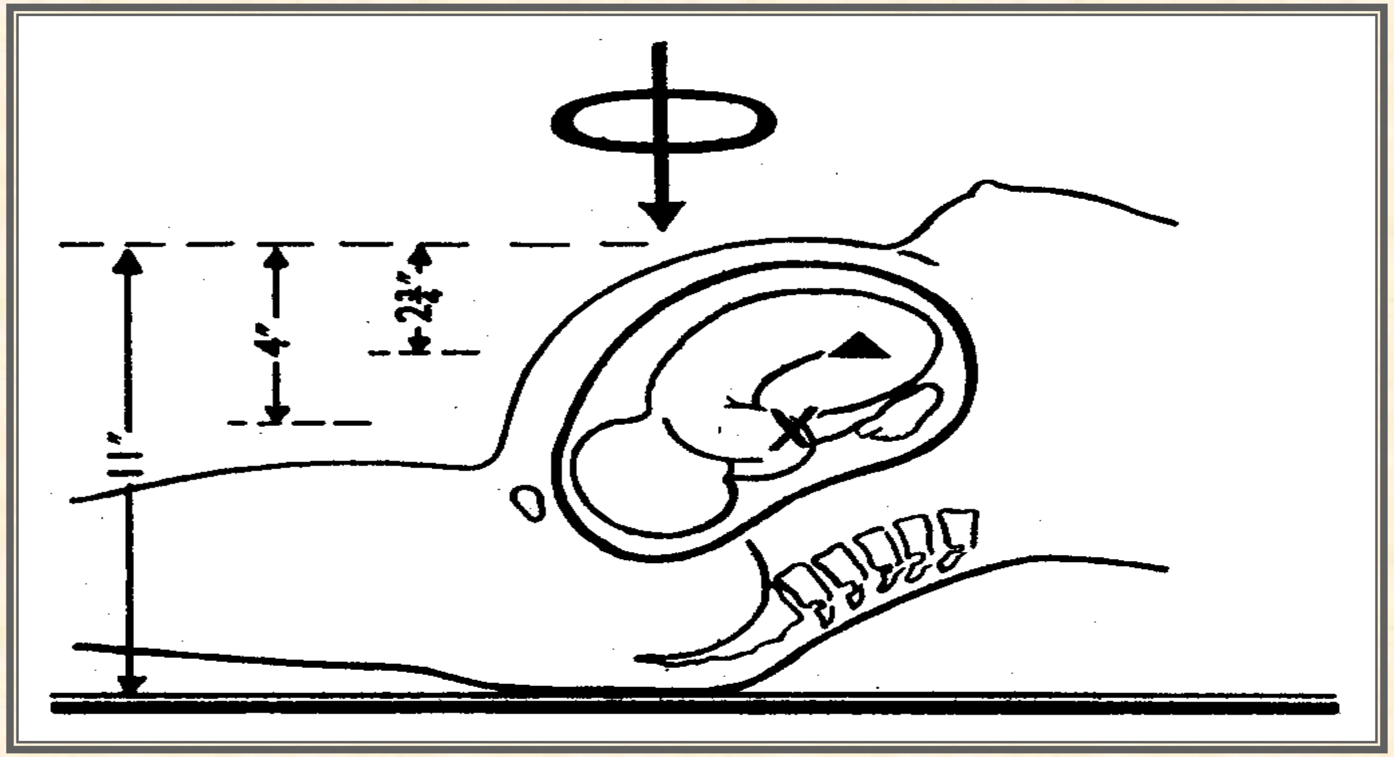
Radiation-induced cancer risks at different doses: The Biophysical argument

Radiation-induced cancer risks at different doses



Childhood cancer after in-utero x-ray exposure

Pelvimetry or obstetric abdominal exam

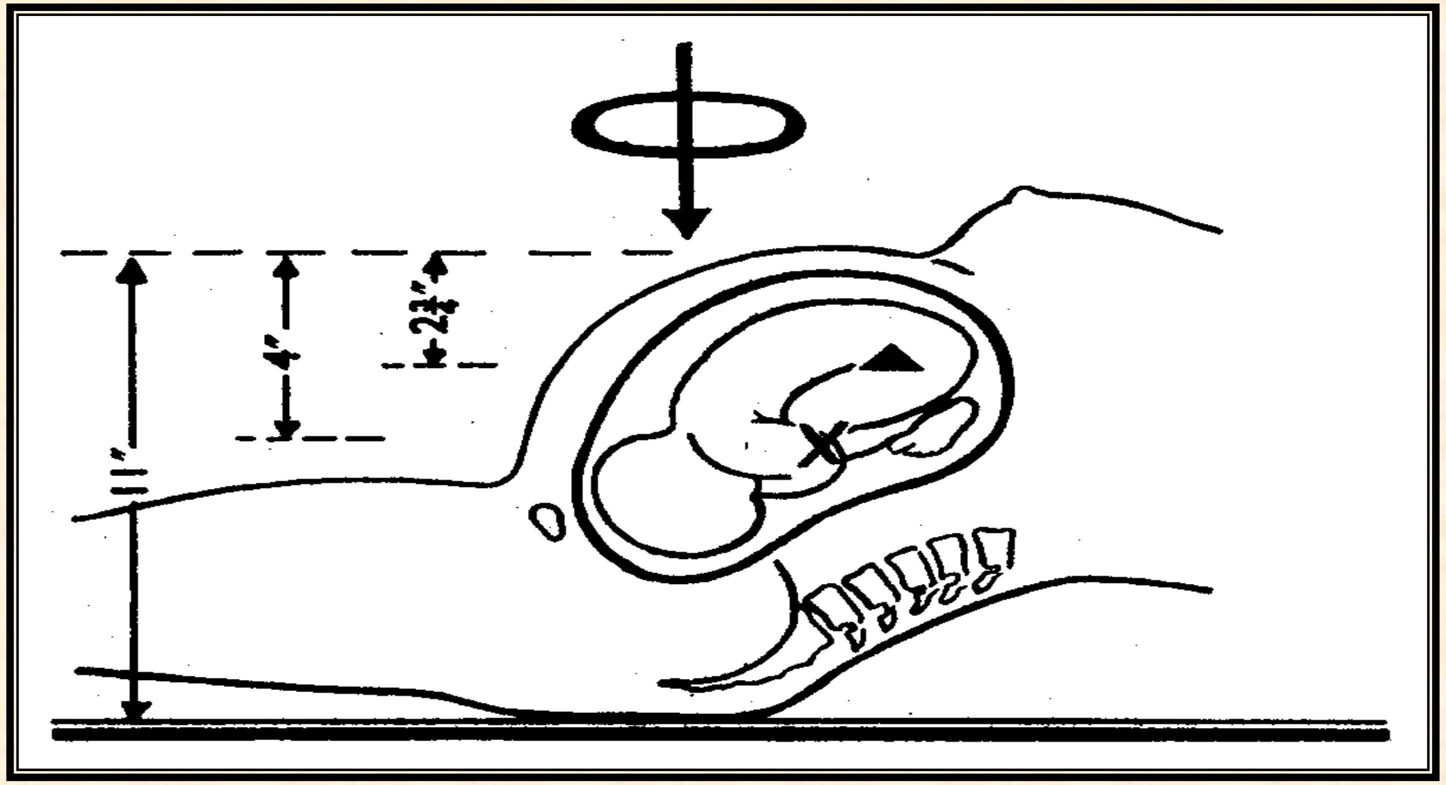


Mean dose ~6 mGy, 80 kVp x rays

Corresponds to a mean of ~1 photon / cell nucleus

The Oxford Survey of Childhood Cancers

- **15,000 case control pairs**
- **Mean dose ~ 6 mGy**
- **Significant increase in childhood cancer after *in-utero* x-ray exposure**

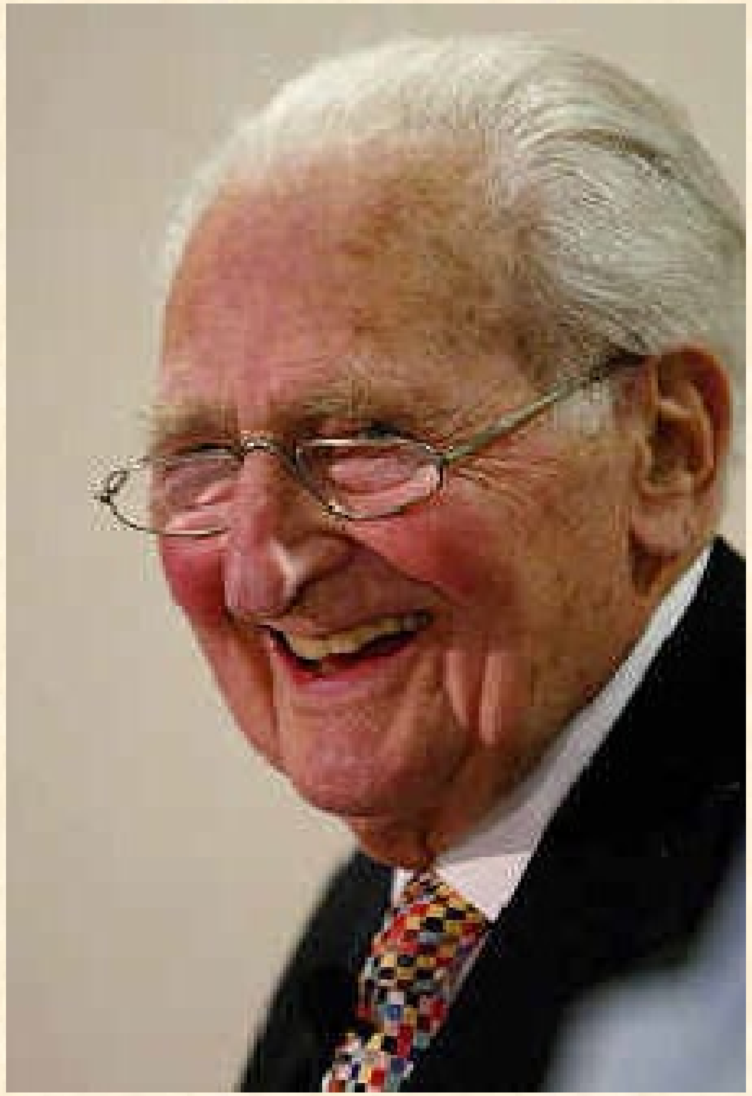


Doll and Wakeford 1997

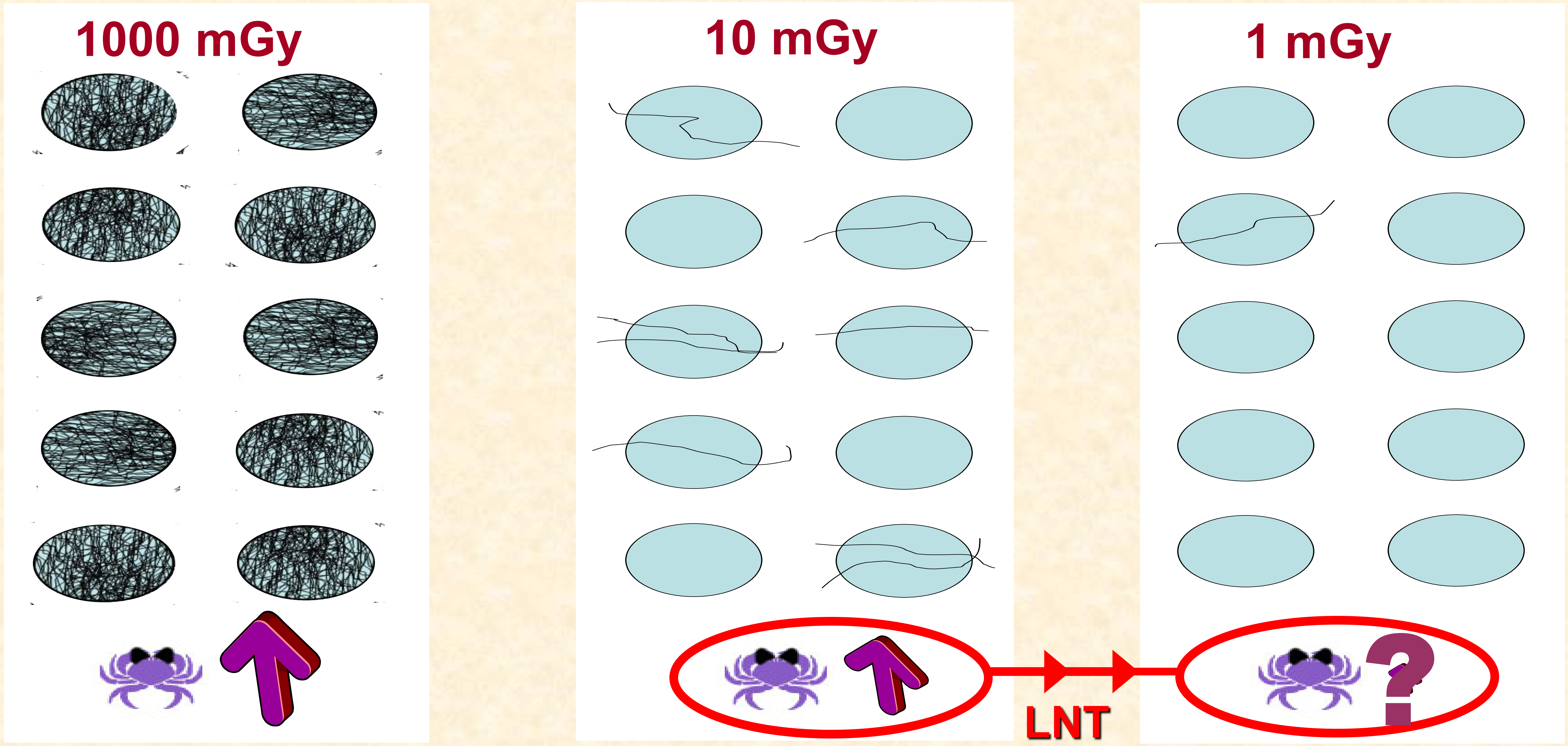
Can in-utero x-ray exposure to ~6 mGy cause cancer?

- "It is concluded that radiation doses of the order of 10 mGy received by the fetus *in utero* produce a causal increase in the risk of childhood cancer".

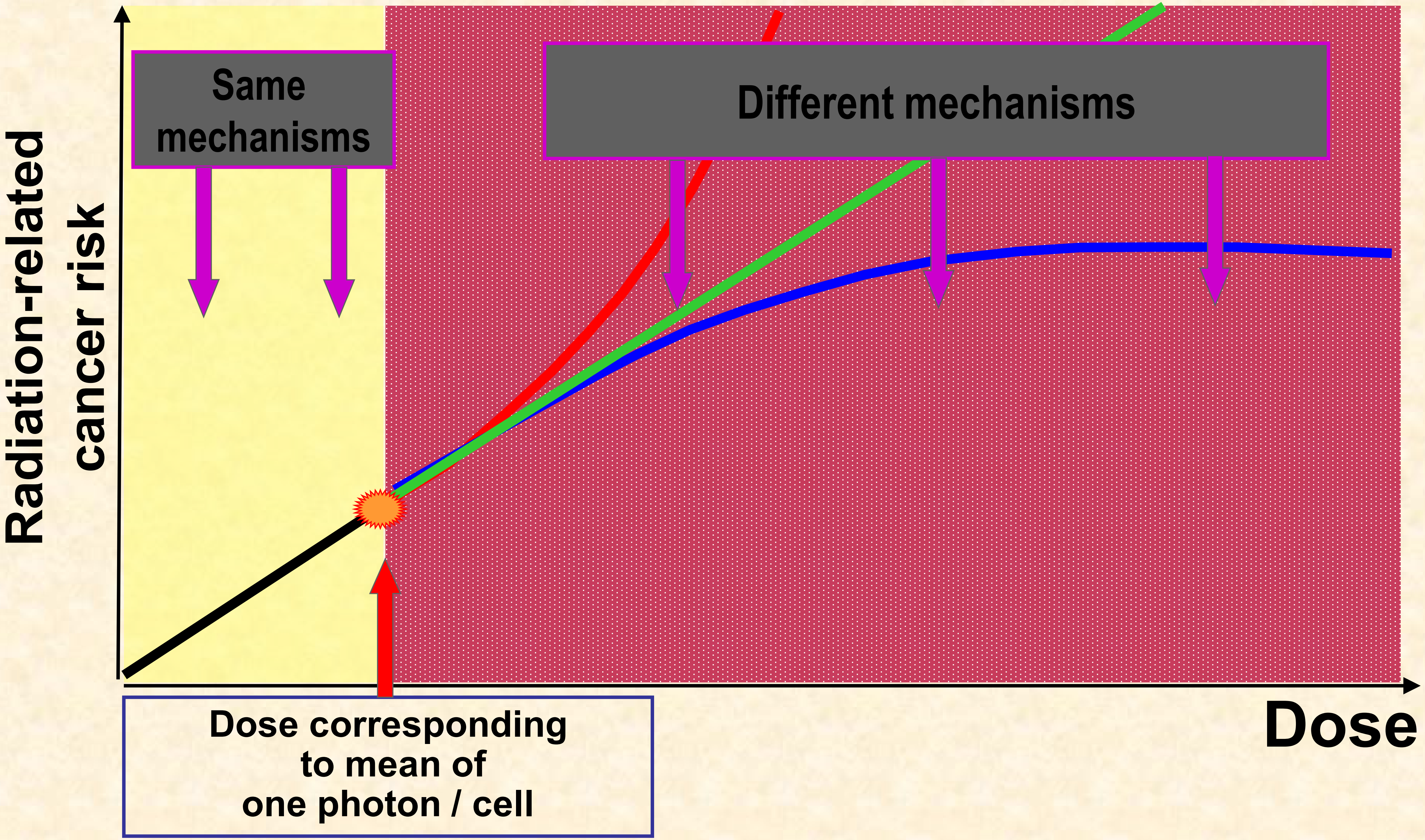
Doll and Wakeford 1997



The Oxford Survey of Childhood Cancers



The biophysical argument



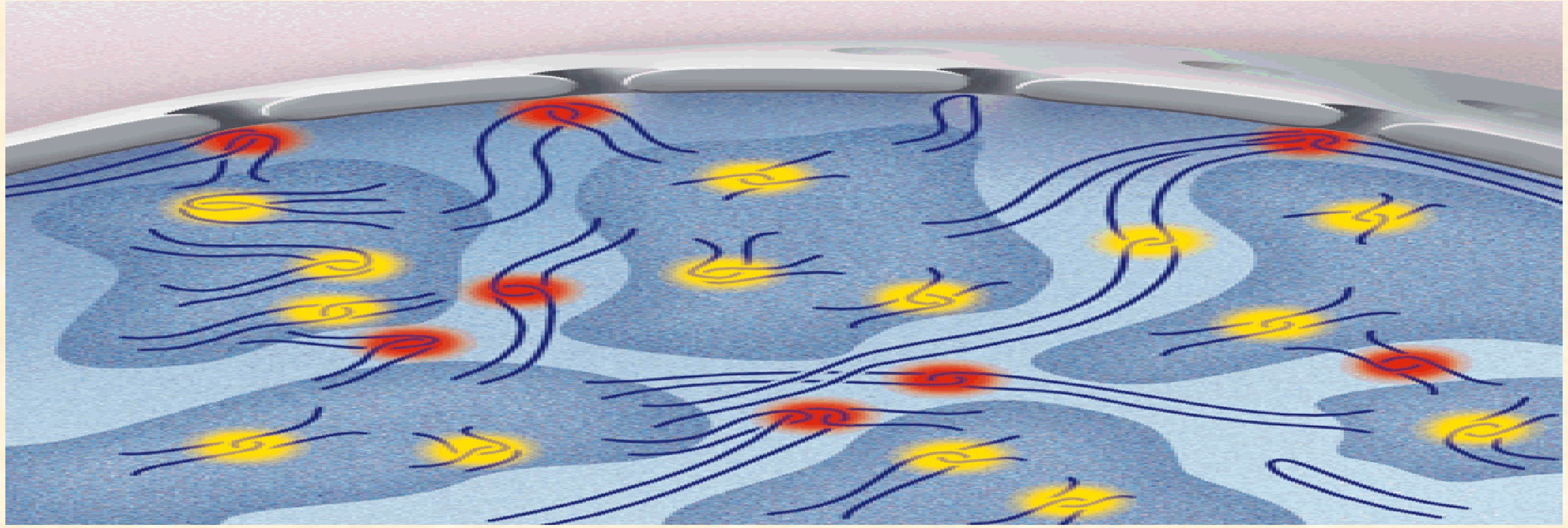
The biophysical argument makes a number of assumptions that can be questioned

- **Repair mechanisms: Can our very efficient DNA repair mechanisms always repair small amount of DNA damage?**
  - » **We have incredibly efficient DNA repair mechanisms, but occasionally they result in misrepair.**
- **Immunosurveillance: Can immune systems "mop up" any small cluster of premalignant cells?**
  - » **Not so likely or we'd never get cancer**
- **Assumes the development of tumors from a single damaged cell, independent of surrounding damaged cells**
  - » **But cells do talk to each other – the local microenvironent is important**

DNA Repair

- We have been exposed to ionizing radiation for billions of years, and have developed exceedingly efficient DNA repair mechanisms

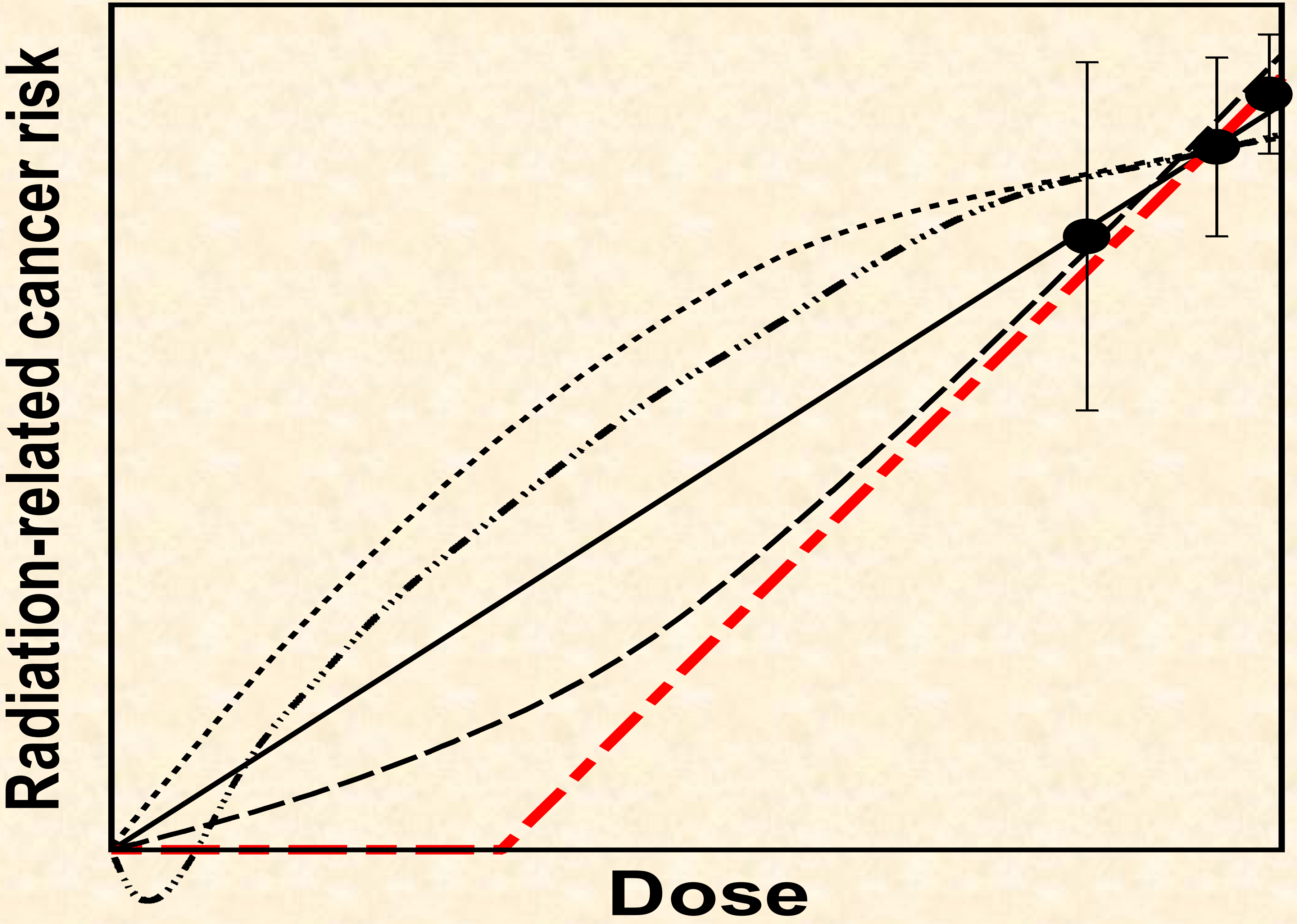
- But it is known that, along with DNA repair,
there is always a small probability of DNA misrepair



Immuno-surveillance and the biophysical argument

- If immuno-surveillance or other processes could always "mop up" small numbers of pre-malignant cells, the biophysical argument would not hold

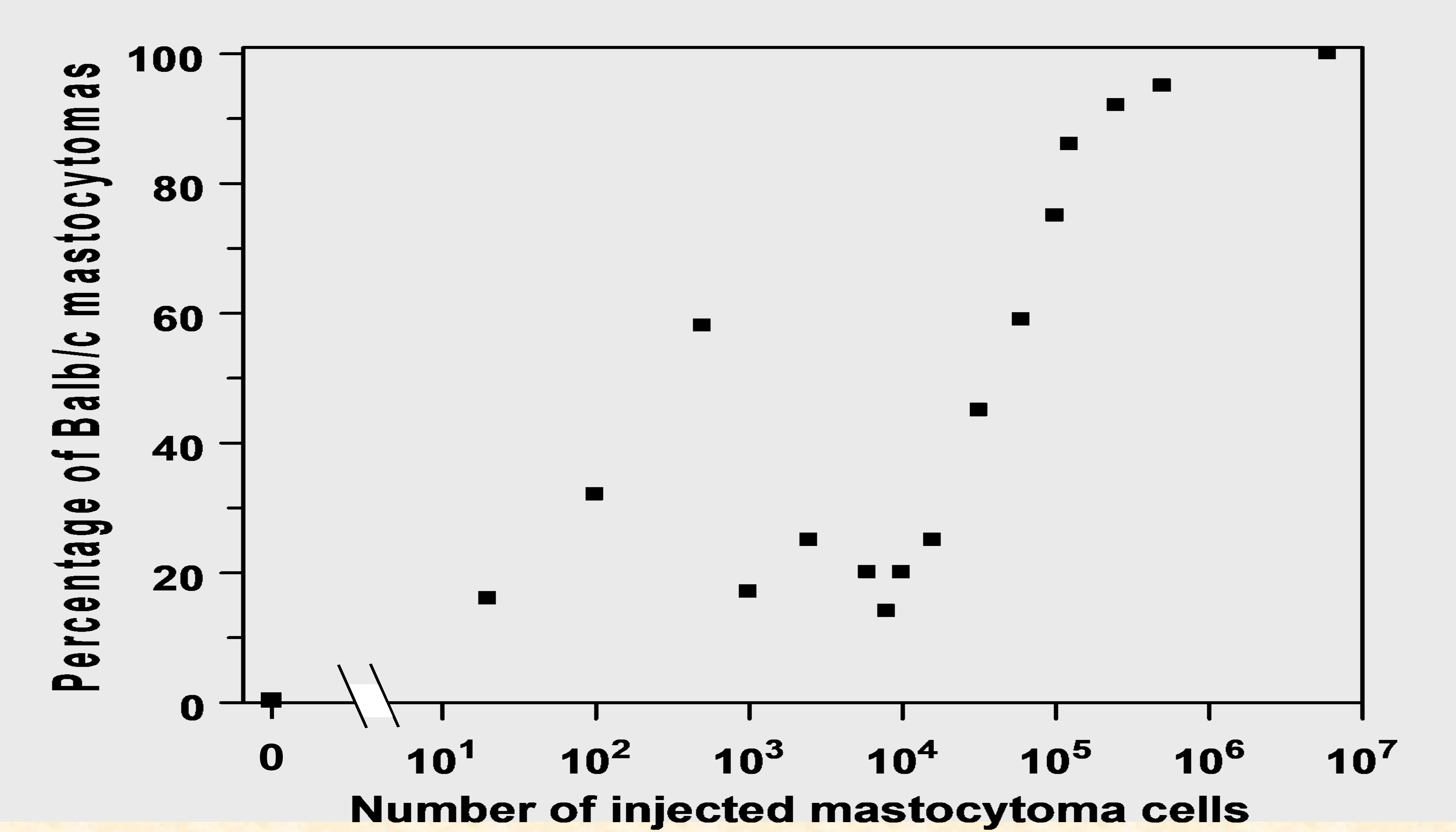
Immuno-surveillance and the biophysical argument



Immuno-surveillance and low-dose risks

- If immuno-surveillance or other processes could indeed always “mop up” small numbers of pre-malignant cells, we would never get cancer!

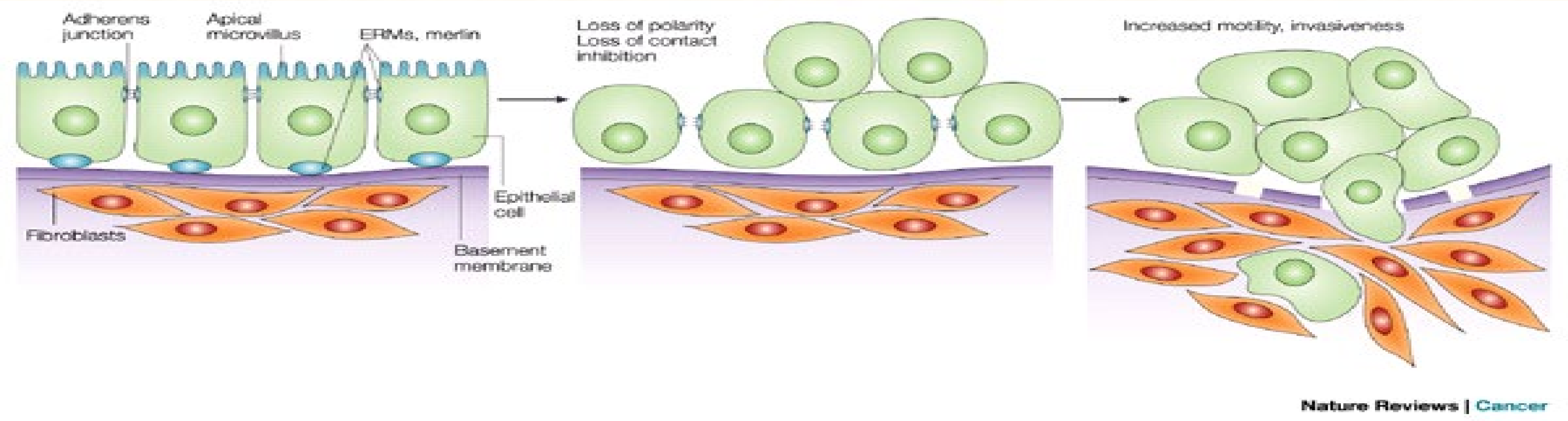
"Sneaking Through" immune surveillance



Kölsch *et al*. 1973

Weaknesses of the biophysical argument

- The argument refers to the development of monoclonal tumors by independently developing cells
- We know that cells talk to each other, and we know that the local microenvironment is important



The significance of inter-cellular communication for radiation-induced cancer

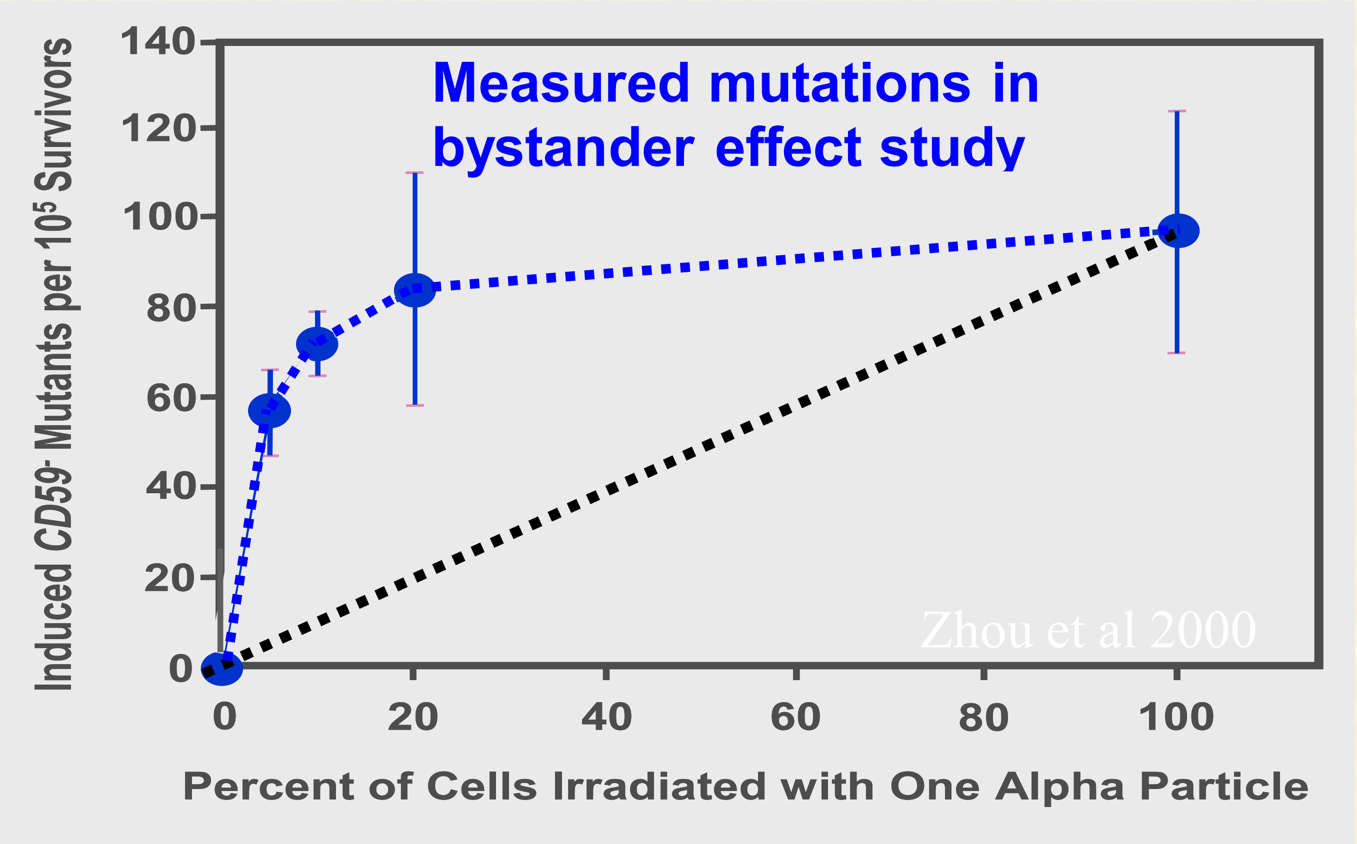
- The biophysical argument refers to the development of monoclonal tumors by autonomous (independently developing) cells

- Are radiation-carcinogenic processes counteracted / amplified by mechanisms at the inter-cellular, tissue or organism level?

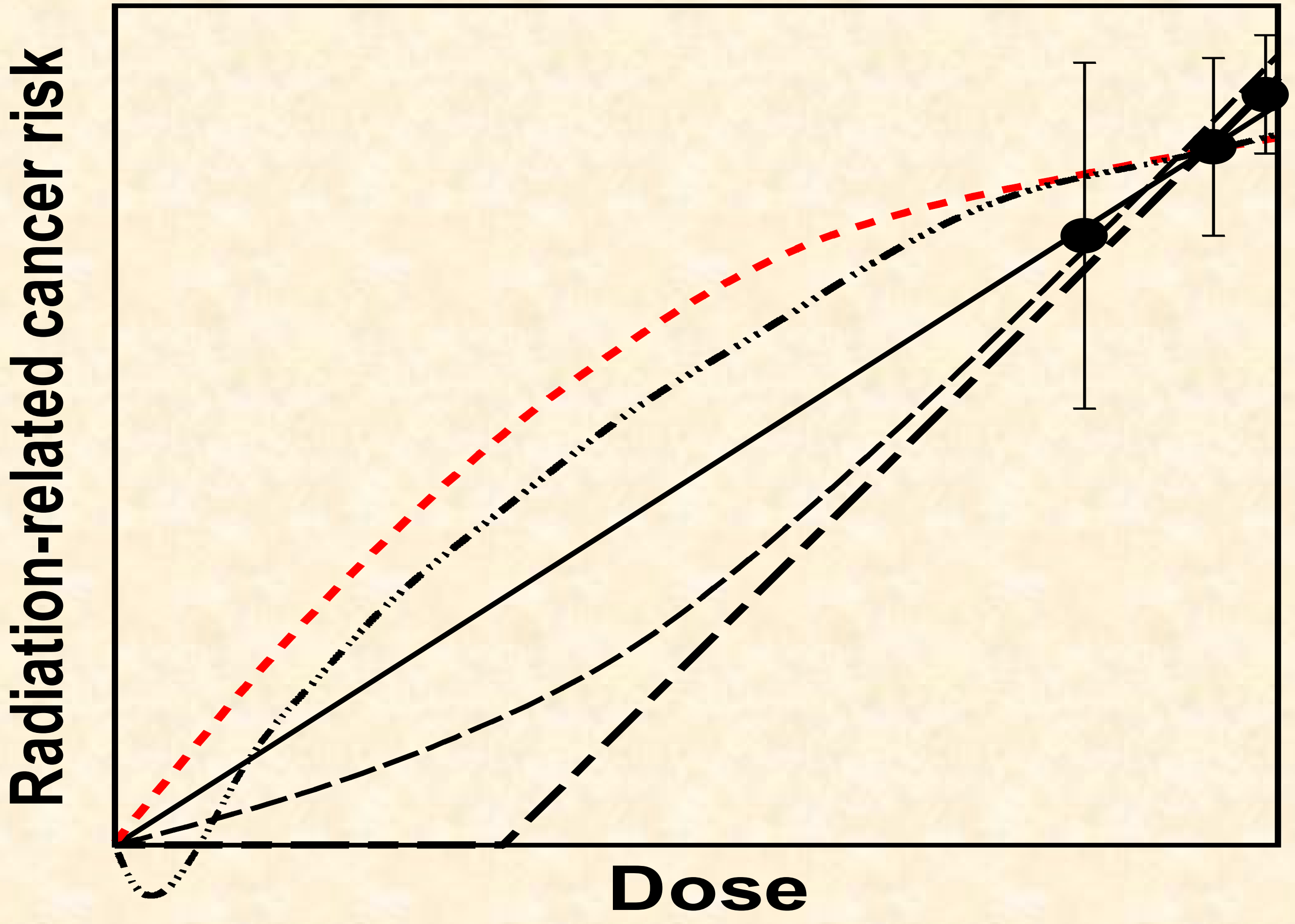
Cells in tissues do certainly talk to each other, but what are the implications for low-dose risks?

- The most quantified radiation-related inter-cellular response is the bystander effect

- Where bystander responses have been quantitated,
  they have shown saturation



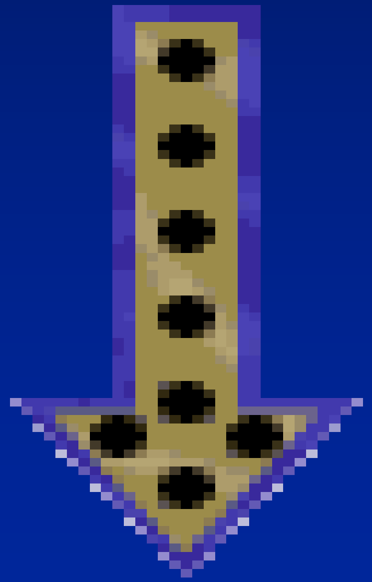
What we know of the effect inter-cellular communication suggests that it might modify the dose-response upwards at low doses



...but we don't know a lot, quantitatively

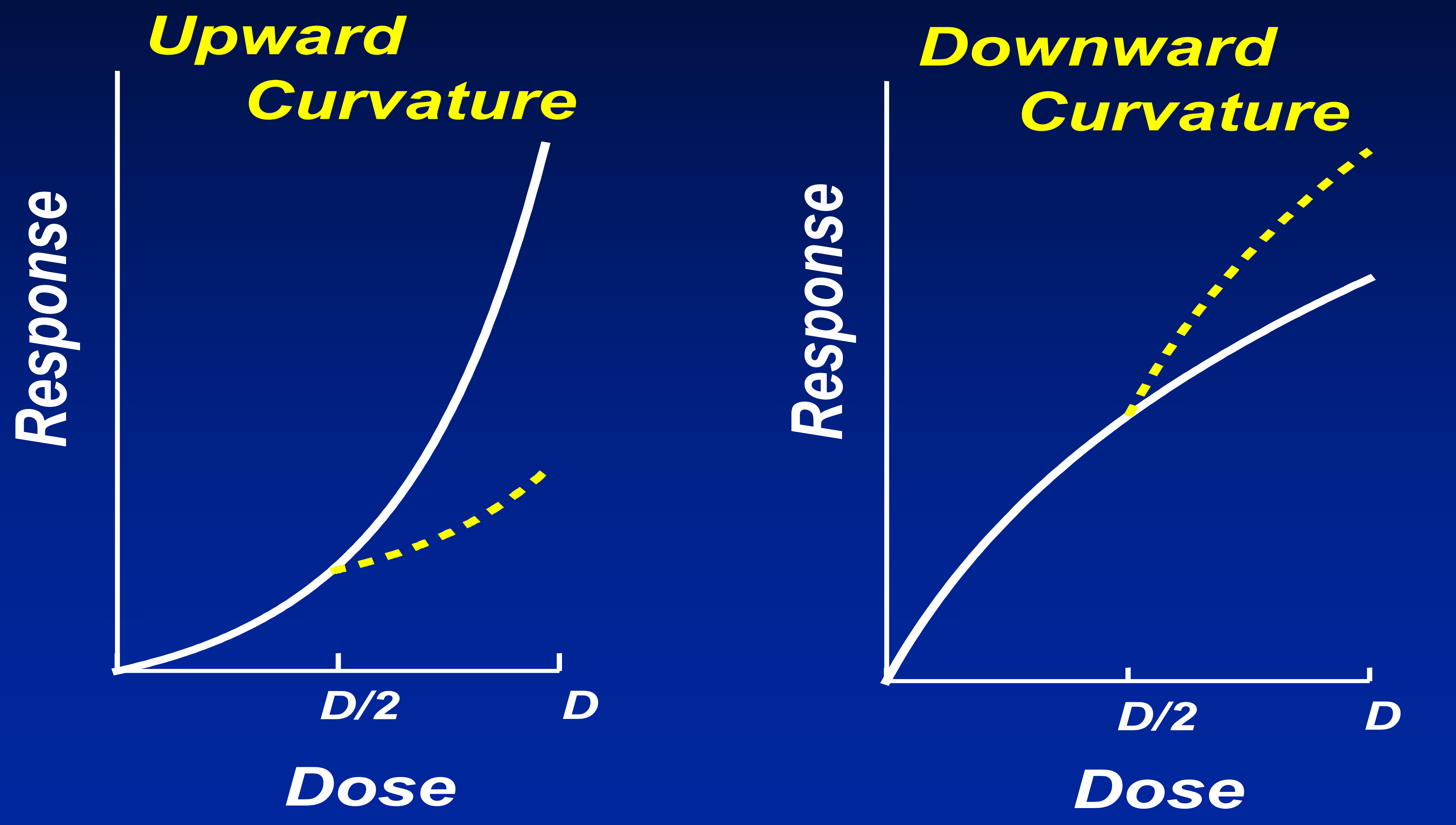
Dose Rate Effects

Shape of the
acute dose-response curve
at low doses

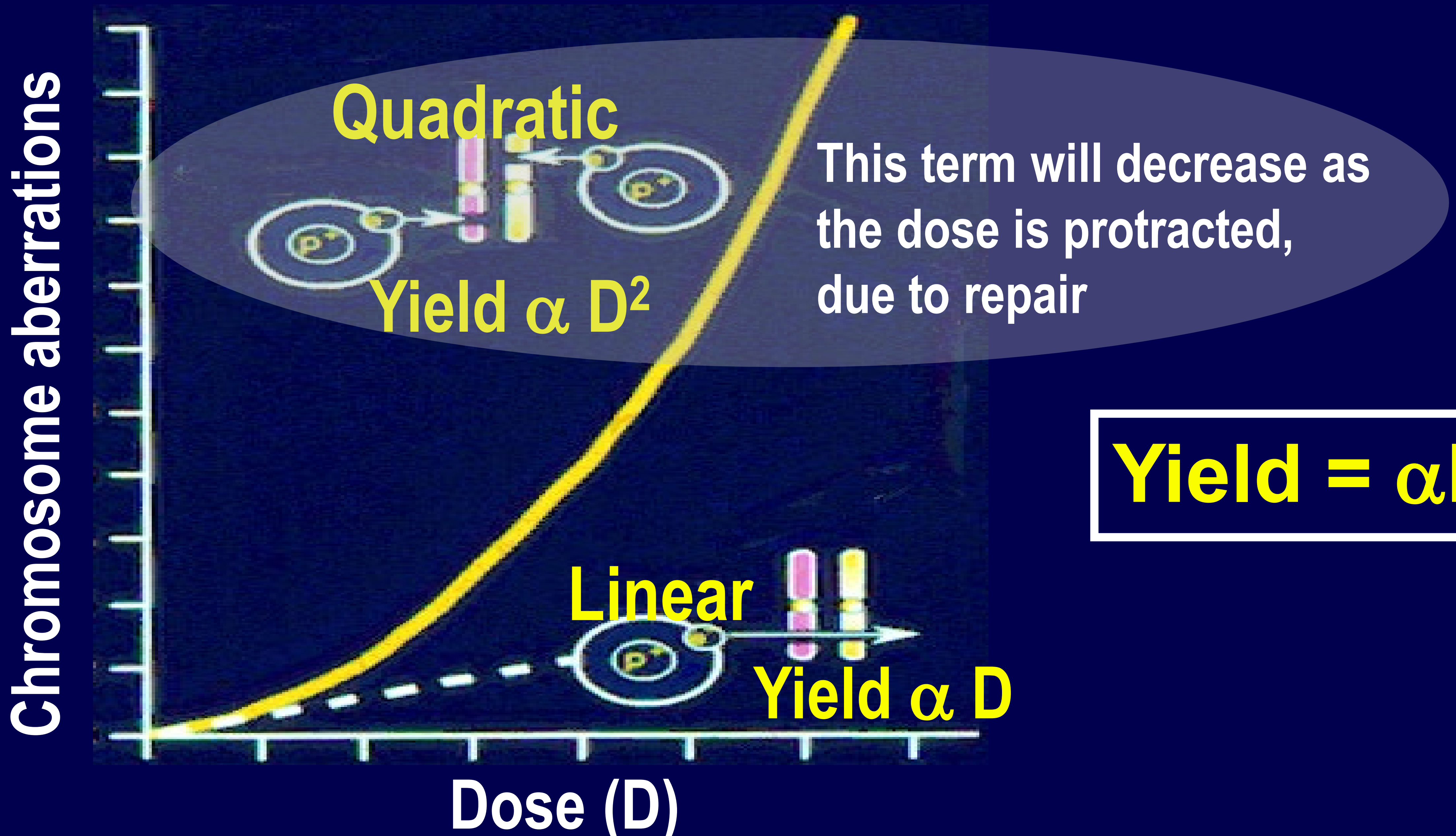


Dose rate effects

Splitting the Dose into Fractions

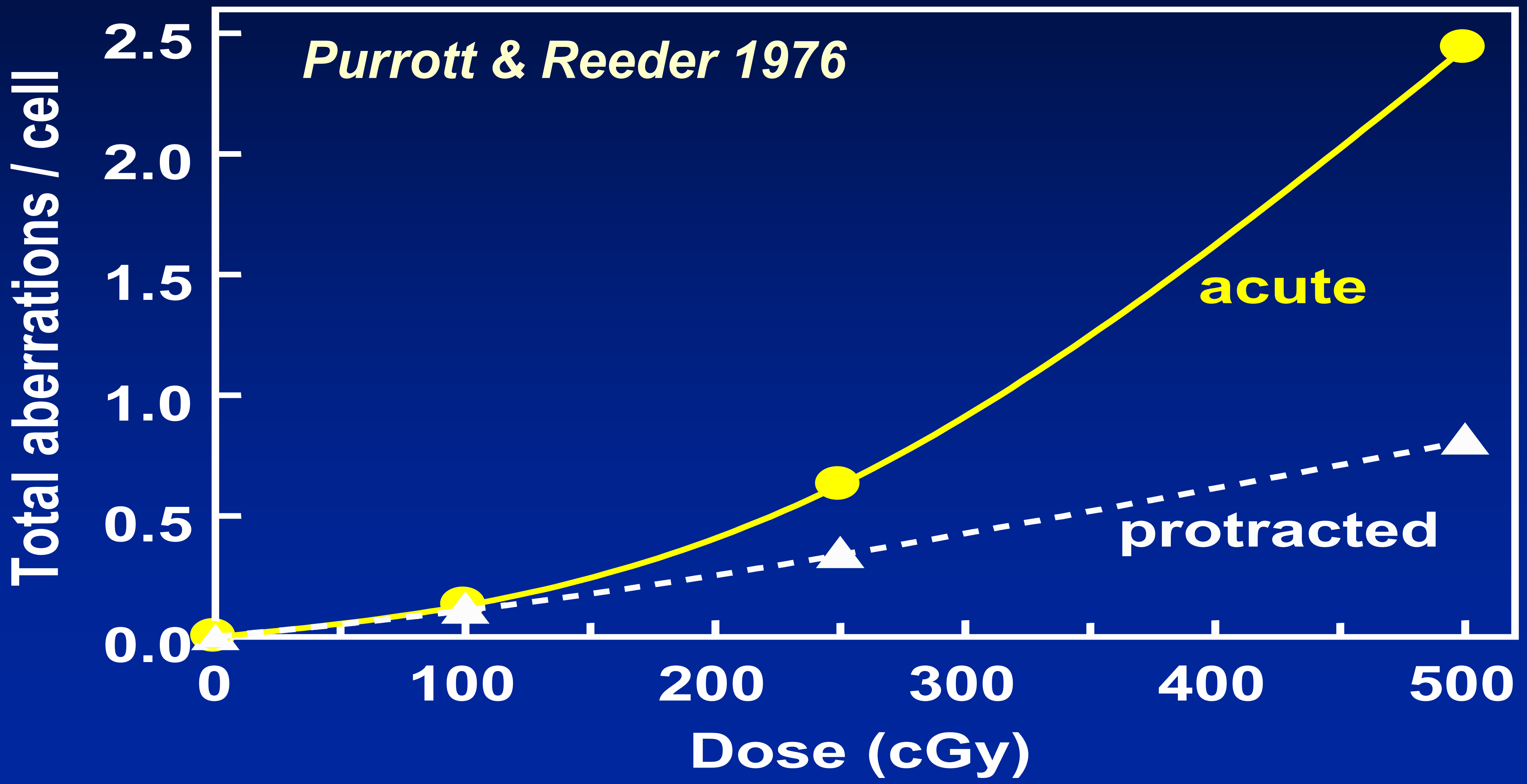


1 hit → linear
2 independent hits → quadratic

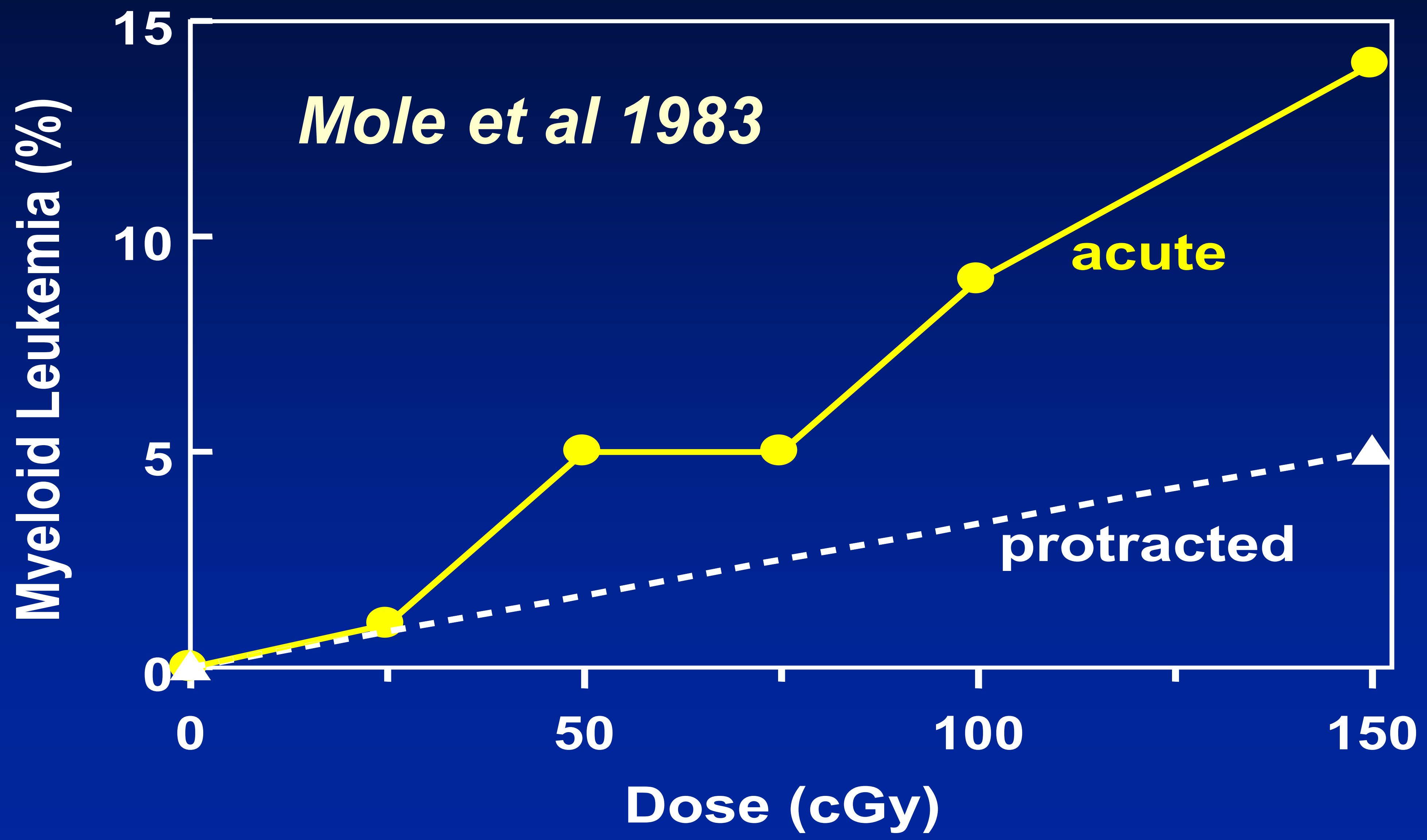


$$Yield = \alpha D + \beta D^2$$

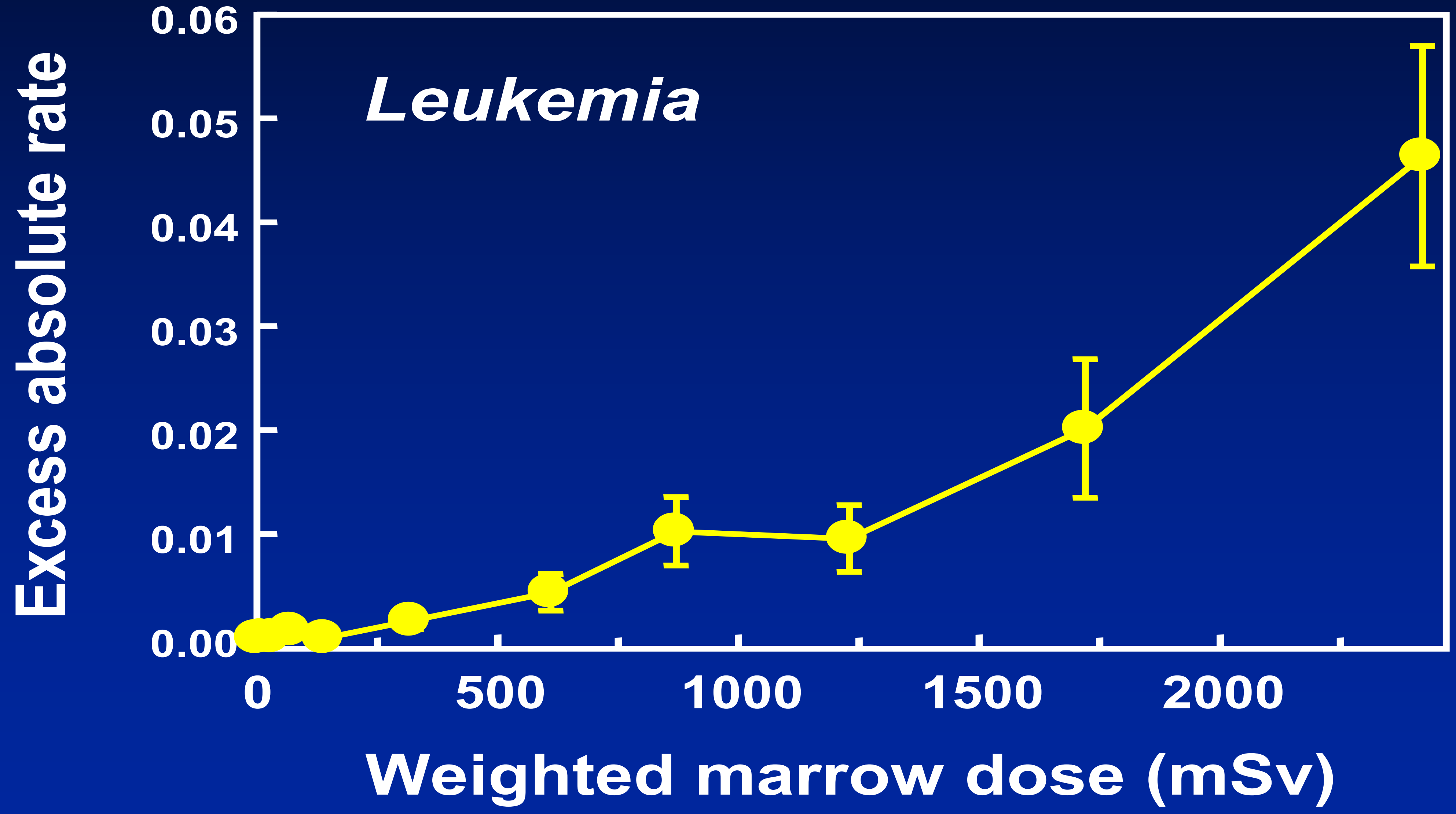
Aberration induction in human lymphocytes 10 cGy/h vs 400 cGy/h



X-ray induction of myeloid leukemia in CBA/H mice



Excess leukemia in A-bomb survivors (Pierce *et al* 1996)

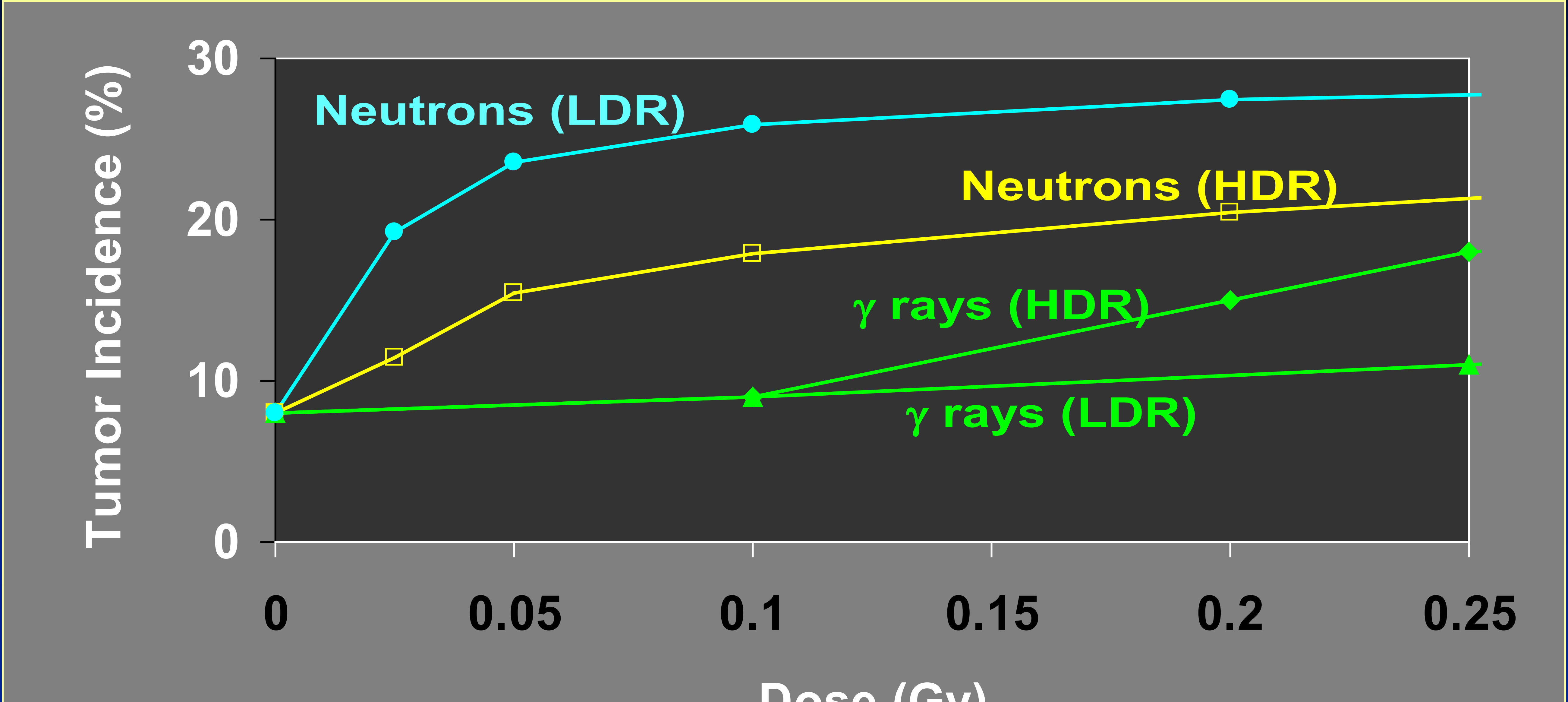


The inverse dose-rate effect...

for densely-ionizing exposures such as radon

For a given dose of **densely-ionizing** radiation, lowering the dose rate **increases** the cancer risk

Mammary tumors induced in BALB/c mice by low doses of γ rays and neutrons, HDR and LDR



Courtesy R.L. Ullrich

Relative Biological Effectiveness

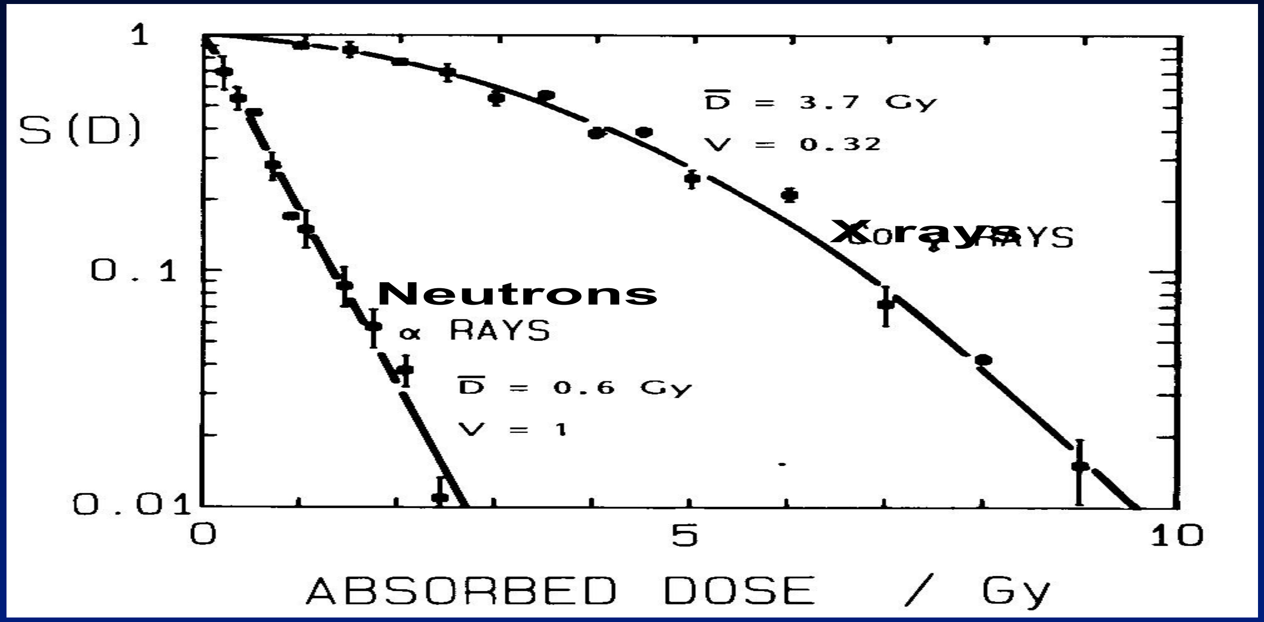
$$\text{RBE} = \frac{\text{Dose for given probability of effect by reference radiation}}{\text{Dose for given probability of effect by radiation of interest}}$$

Relevance of RBE

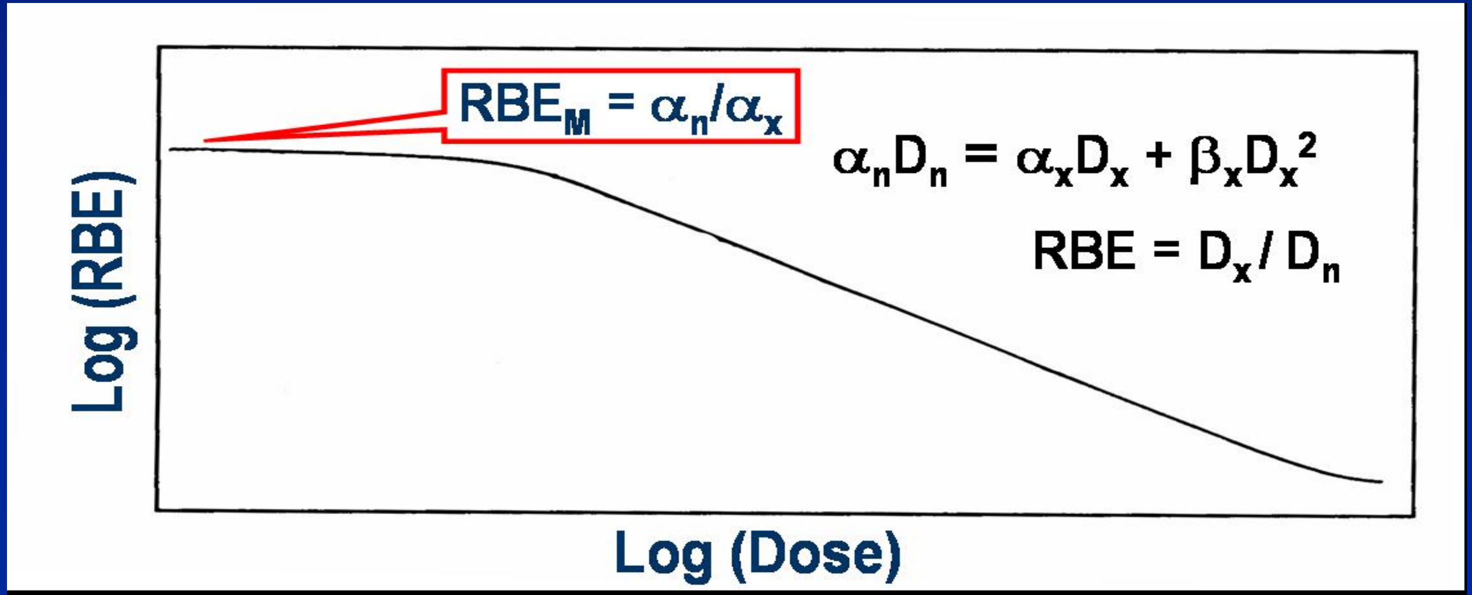
- Radon
- Mammography
- Neutrons
- I-131
- Space radiation
- Heavy ion radiotherapy

RBE is typically dose dependent

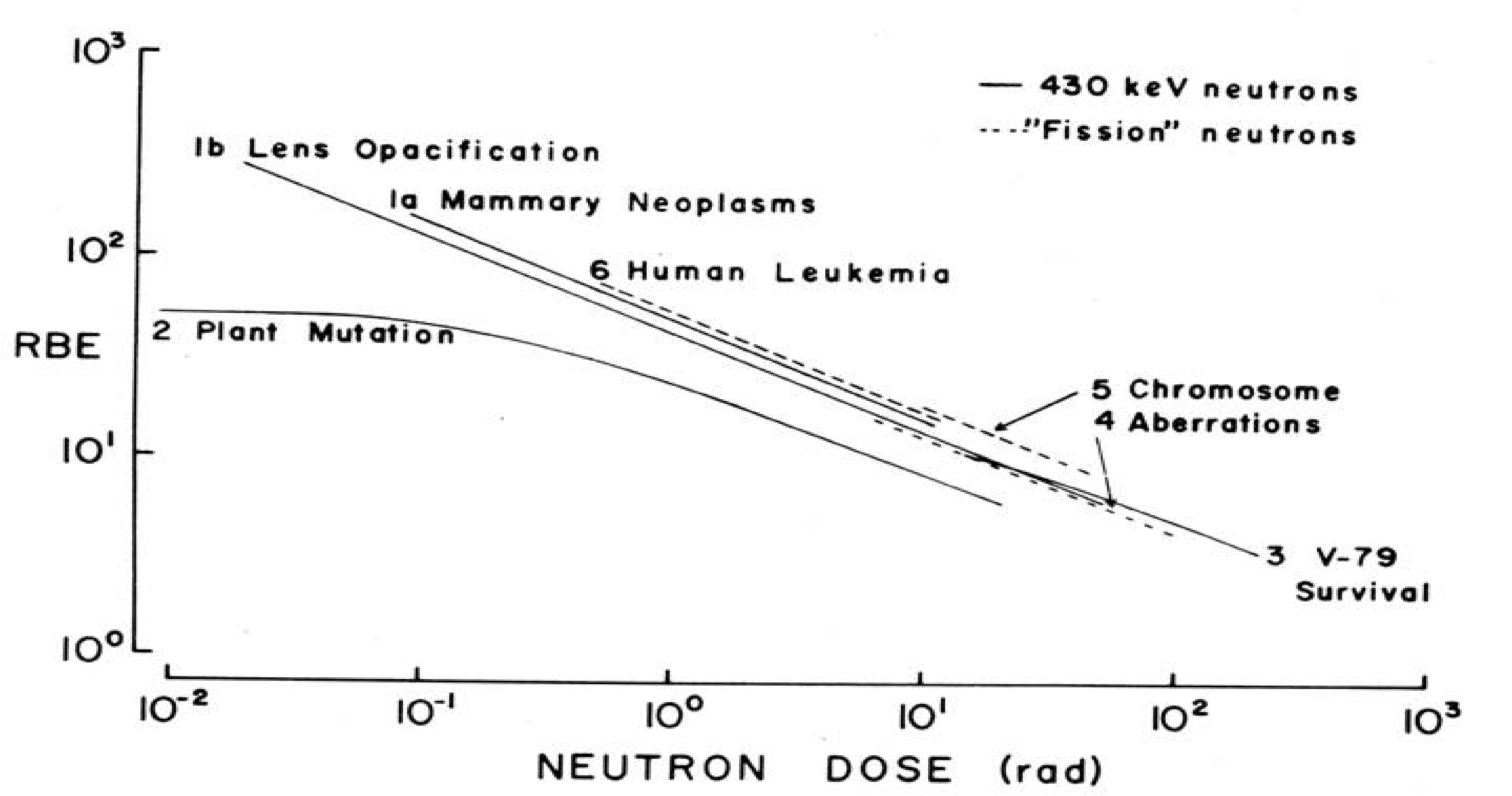
Photons have curved dose-response relations, while those for high-LET radiations are straighter



RBE is dose dependent, with a constant maximal value (RBE_M) at low doses

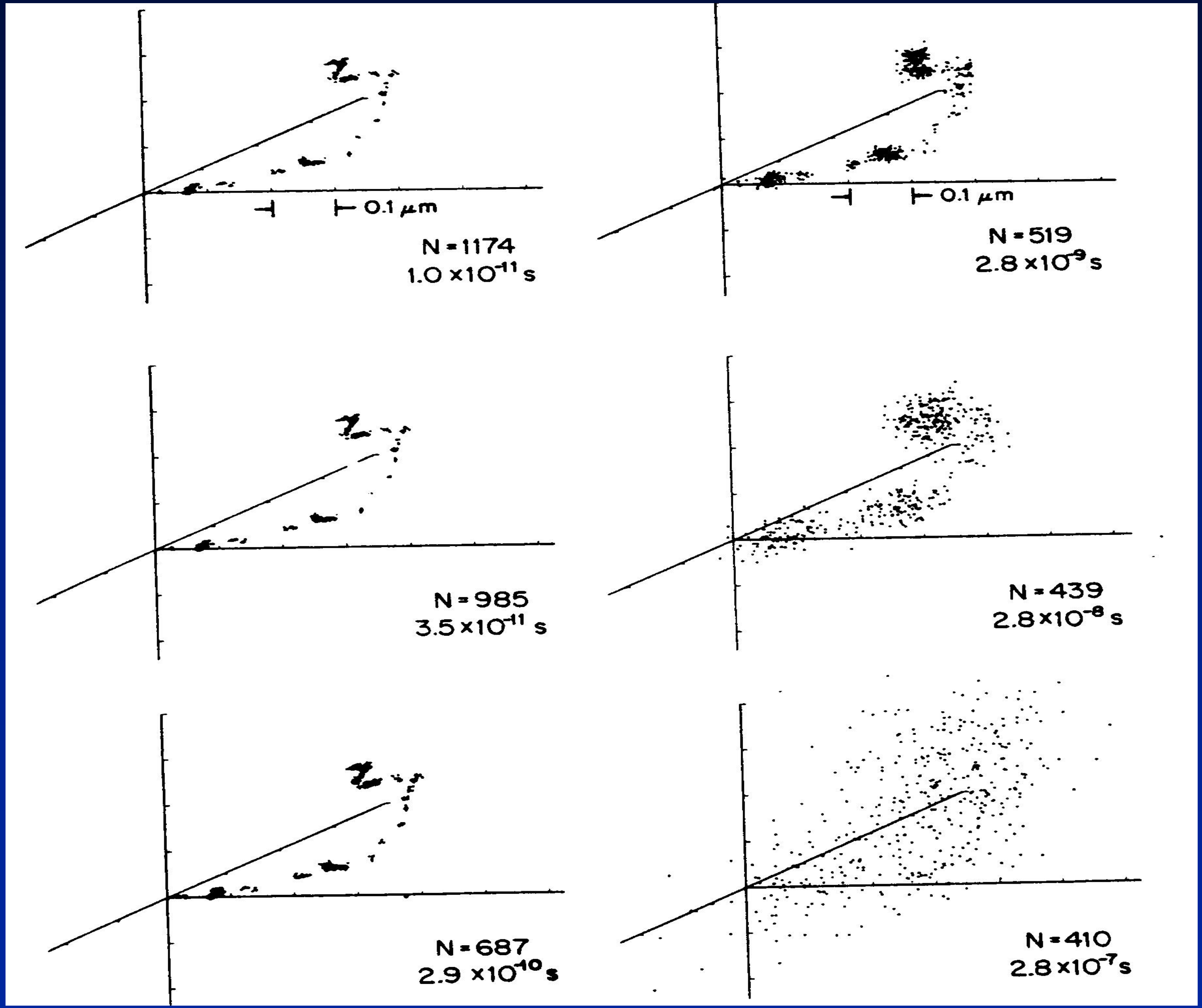


Neutron RBE vs dose for a variety of endpoints



Rossi 1980

RBE **must** be due to the initial track structure

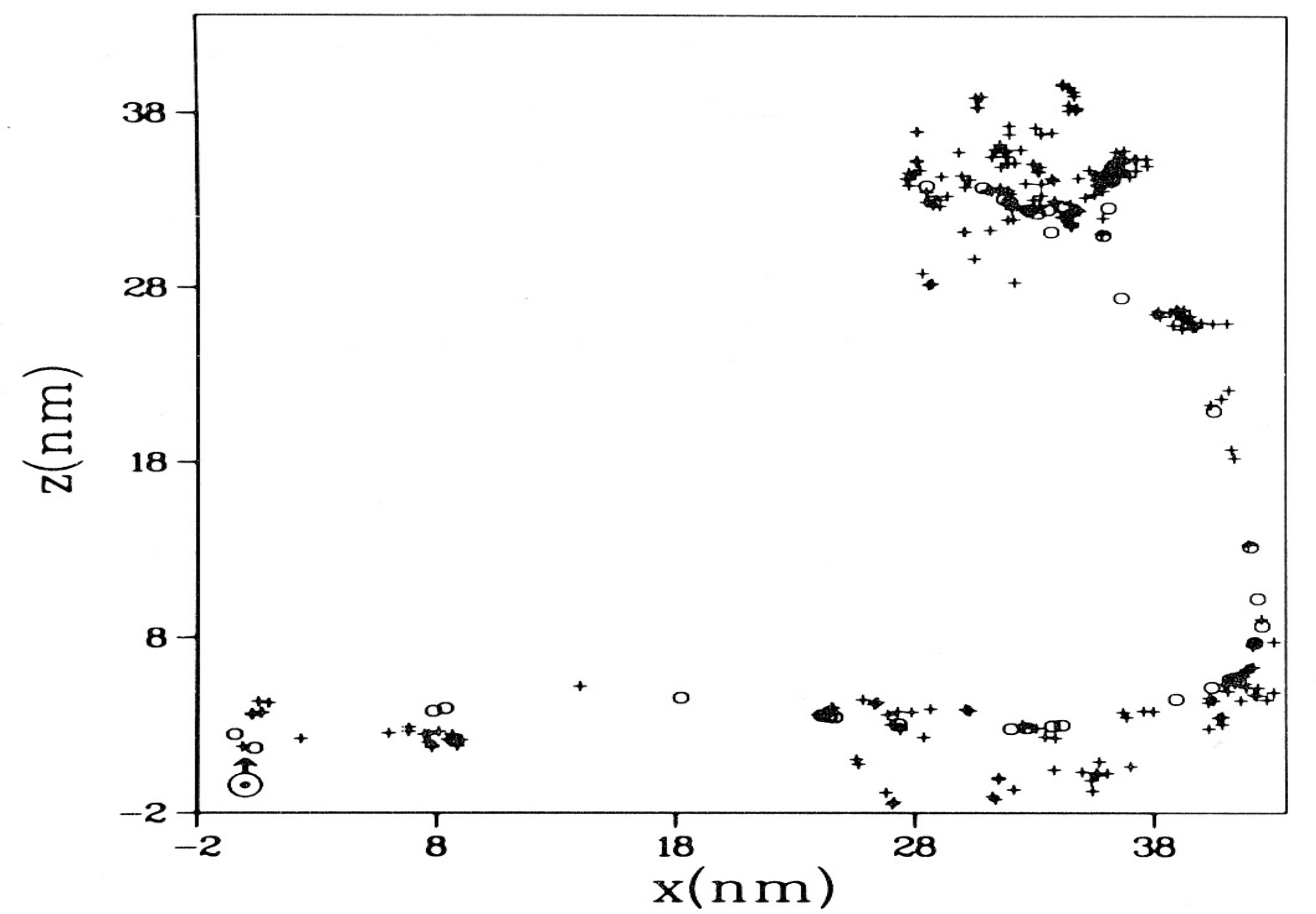


Wright et al, 1982

Microdosimetry - The Study of Track Structure

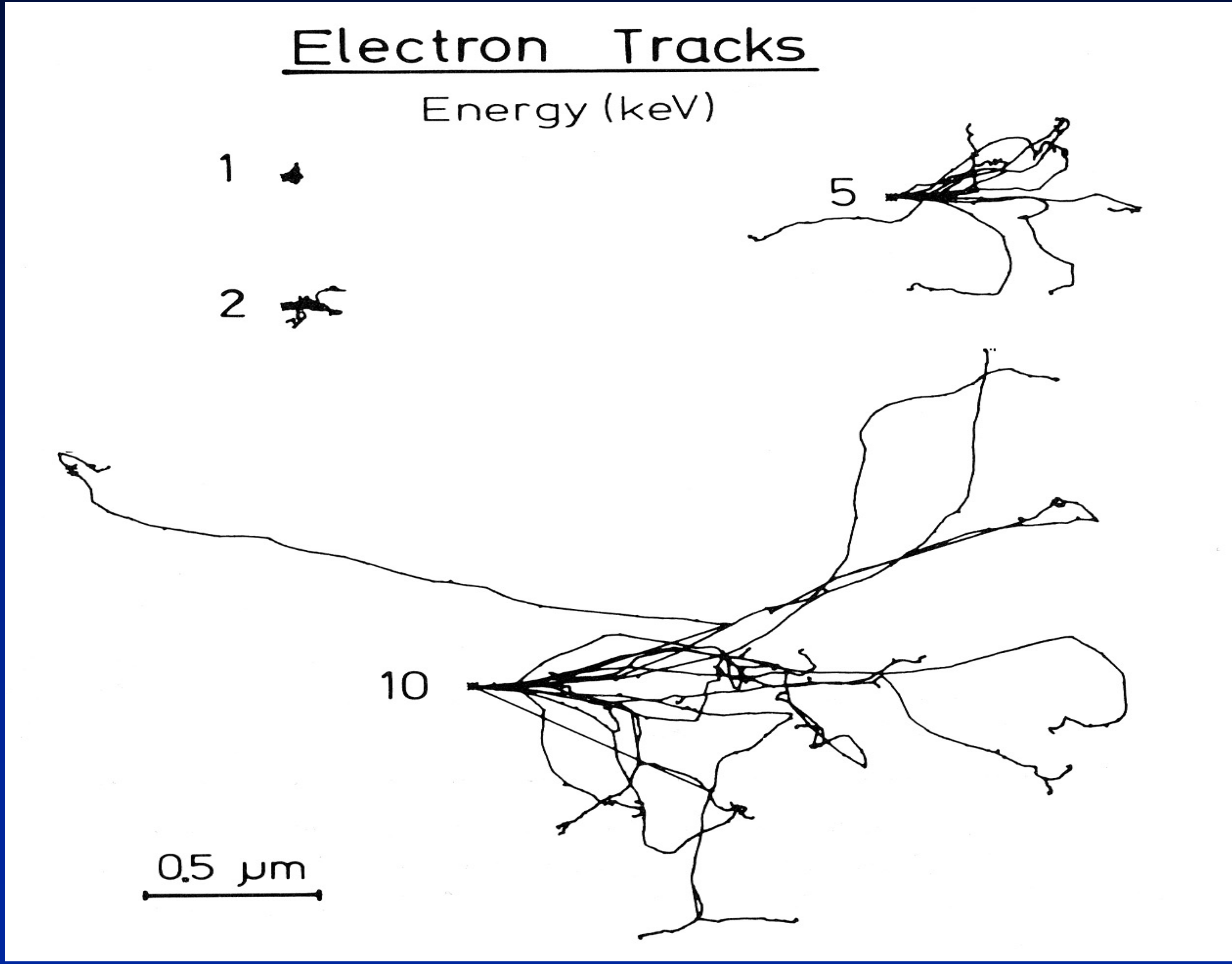
- Ionizing radiations deposit energy in a fundamentally different way from that of other mutagens or carcinogens
- The energy imparted, and the subsequent radiation products are not distributed in simple uniform patterns.
- The radiation track is structured, with energy depositions occurring in clusters along the trajectories of charged particles.
- The characterization of energy depositions on micrometer (and smaller) scales is the field of *microdosimetry*

Simulated track of 1 keV electron



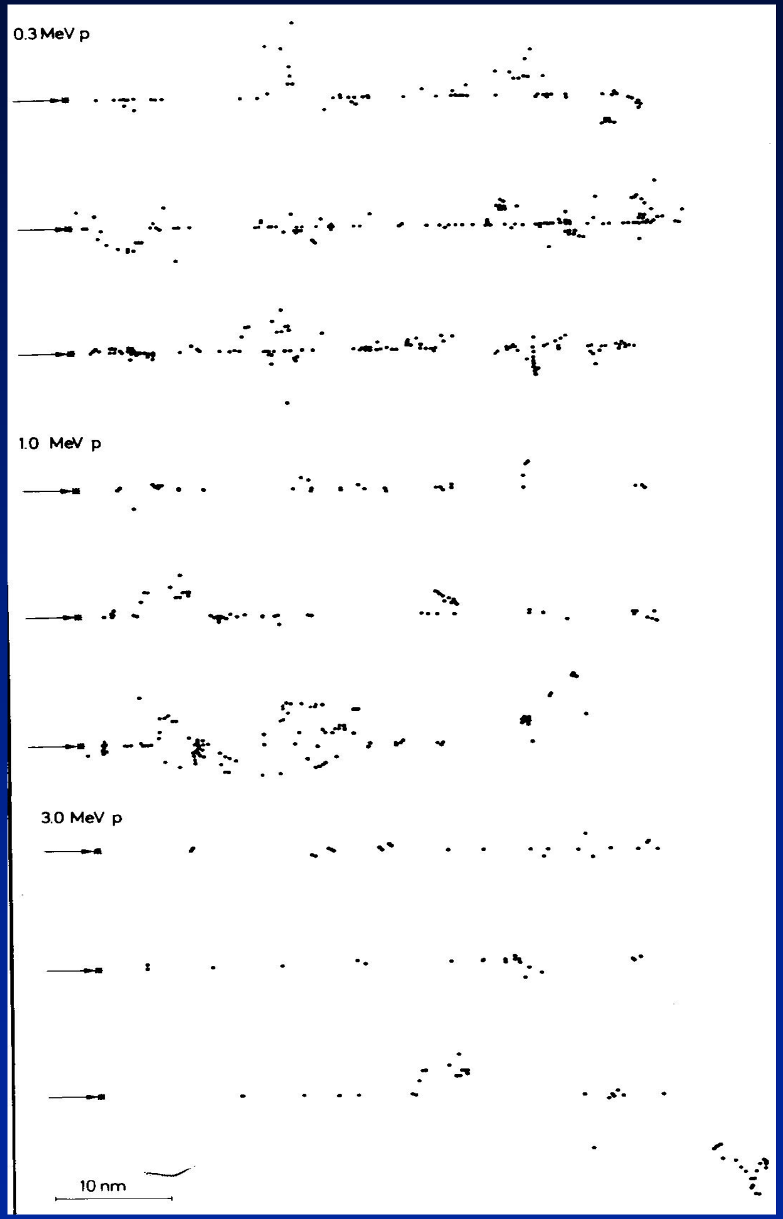
Zaider & Brenner 1983

Electron tracks of different energies

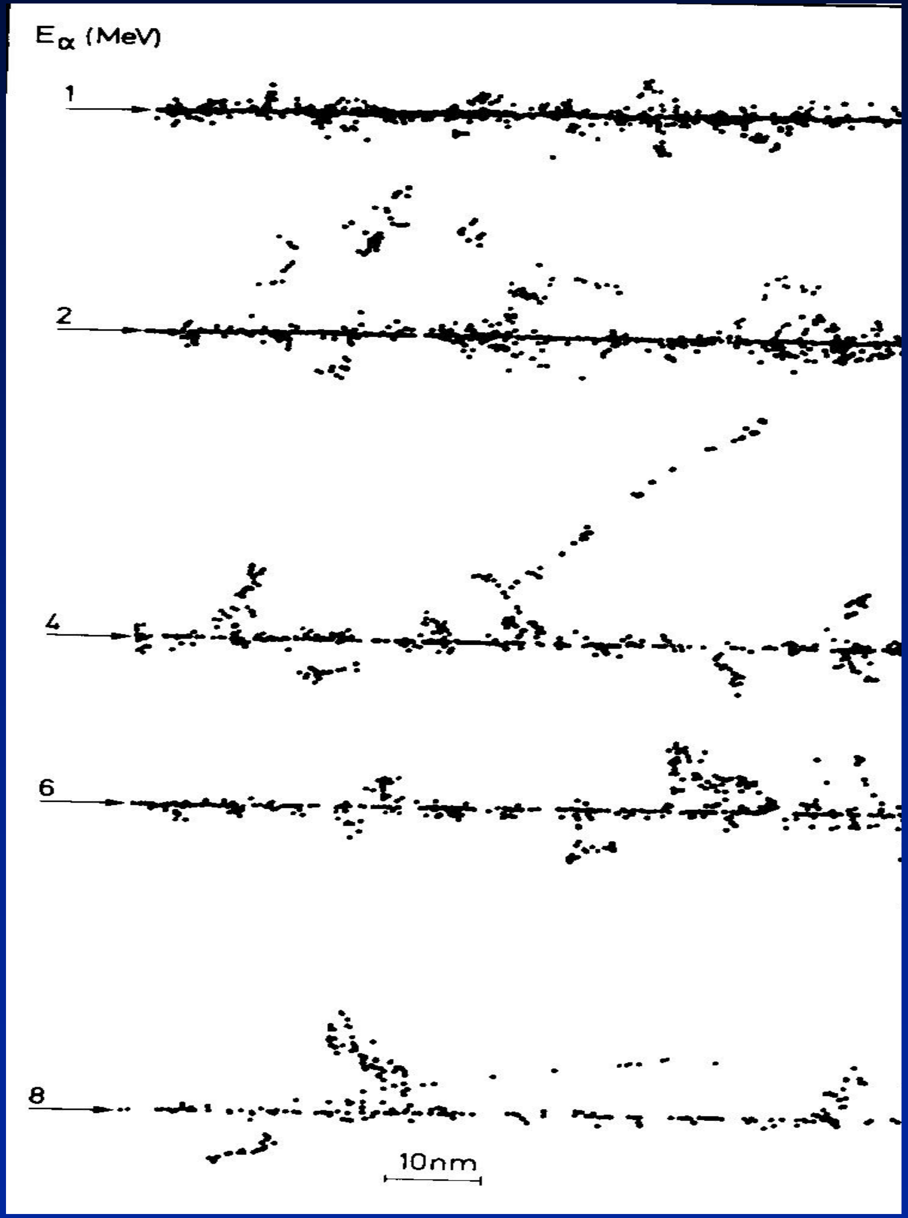


Paretzke 1987

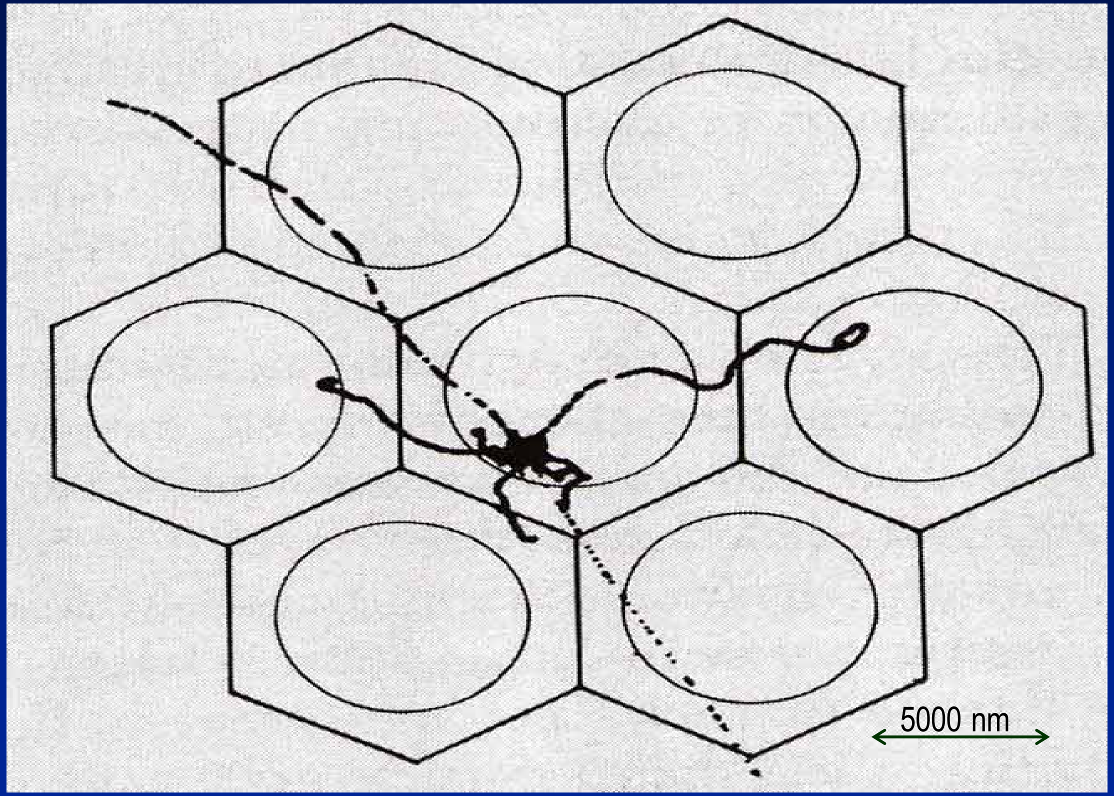
Simulated charged-particle tracks



protons



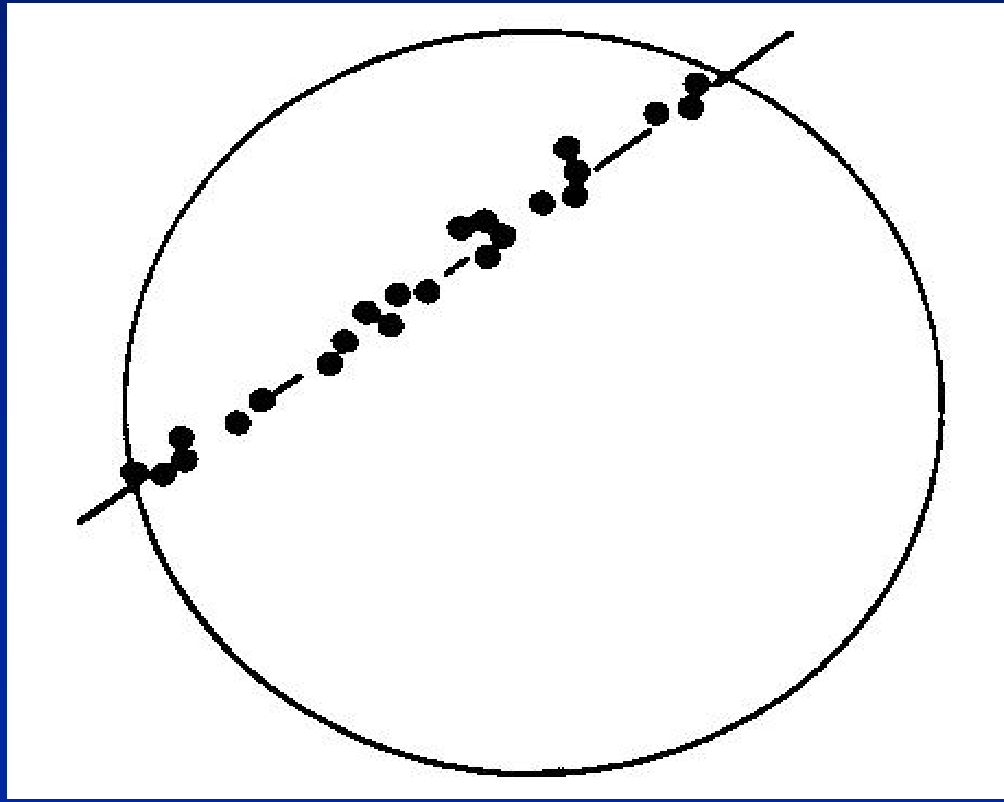
alpha particles



Cosmic-ray iron ion passing through lens of eye

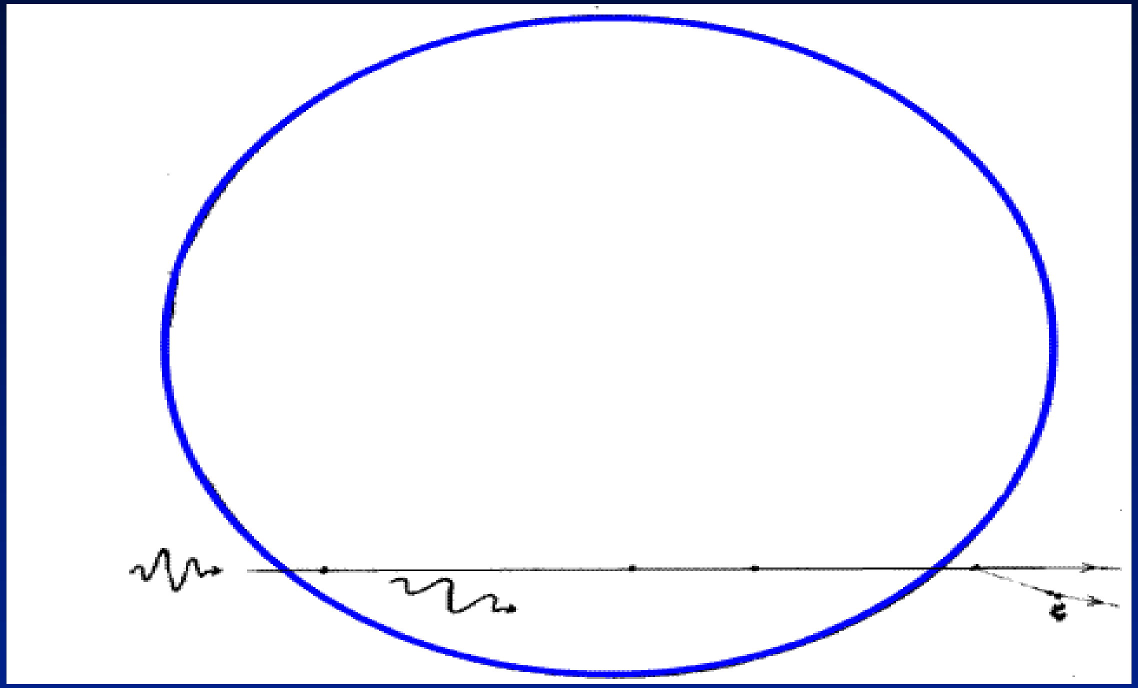
Microdosimetric Unit: Lineal Energy (y)

Energy deposited in a target
by a single radiation track, divided by
the mean chord length of the target

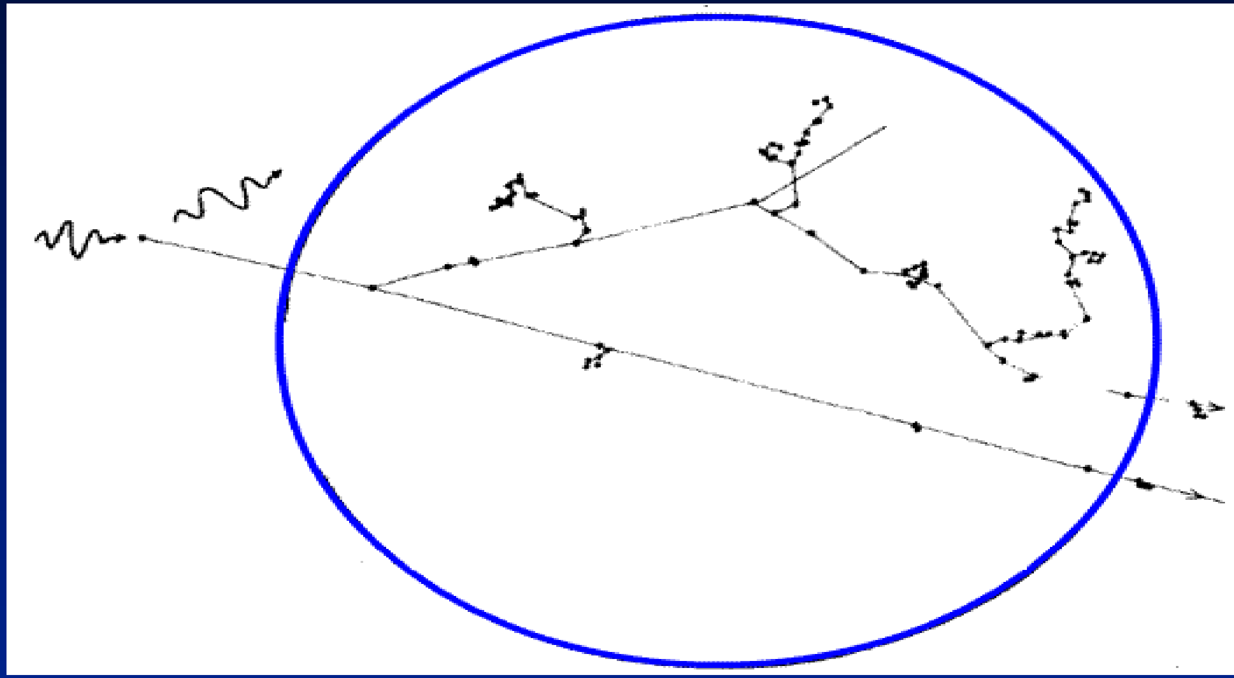


Microdosimetry:

<u>Stochastics</u> of ionizing radiation energy deposition



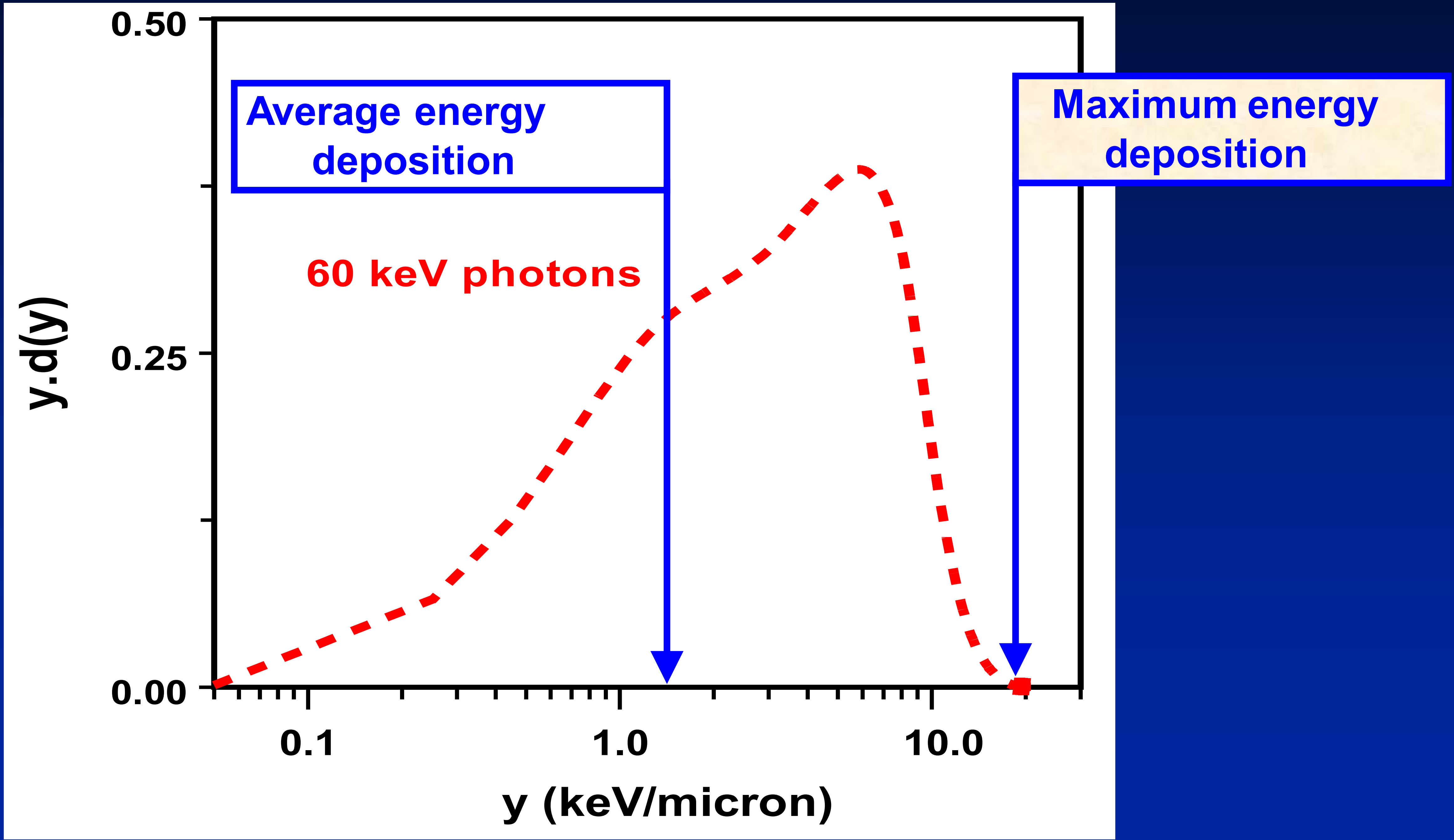
Simulation of single gamma ray passing through cell nucleus



Simulation of single gamma ray passing through cell nucleus

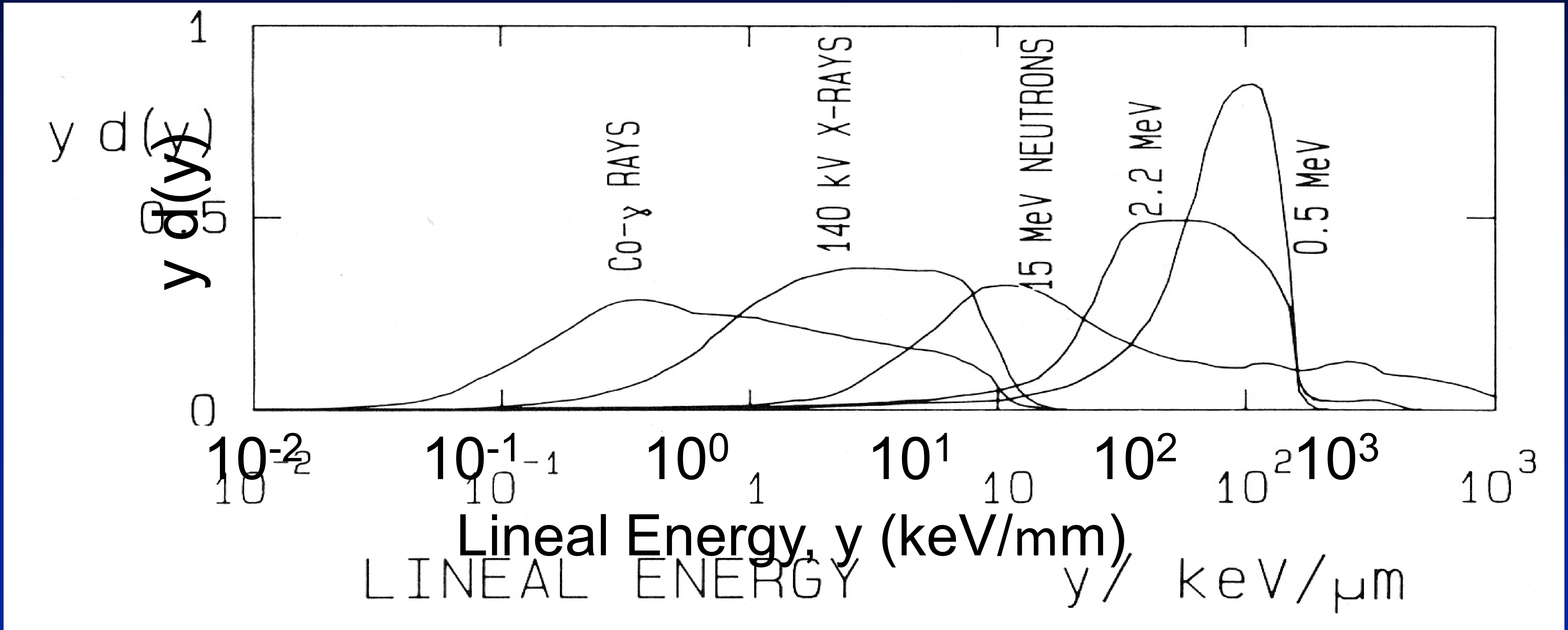
"Can a single photon really cause significant damage to the genome?"

The distribution of energy depositions in a cell nucleus by a single photon

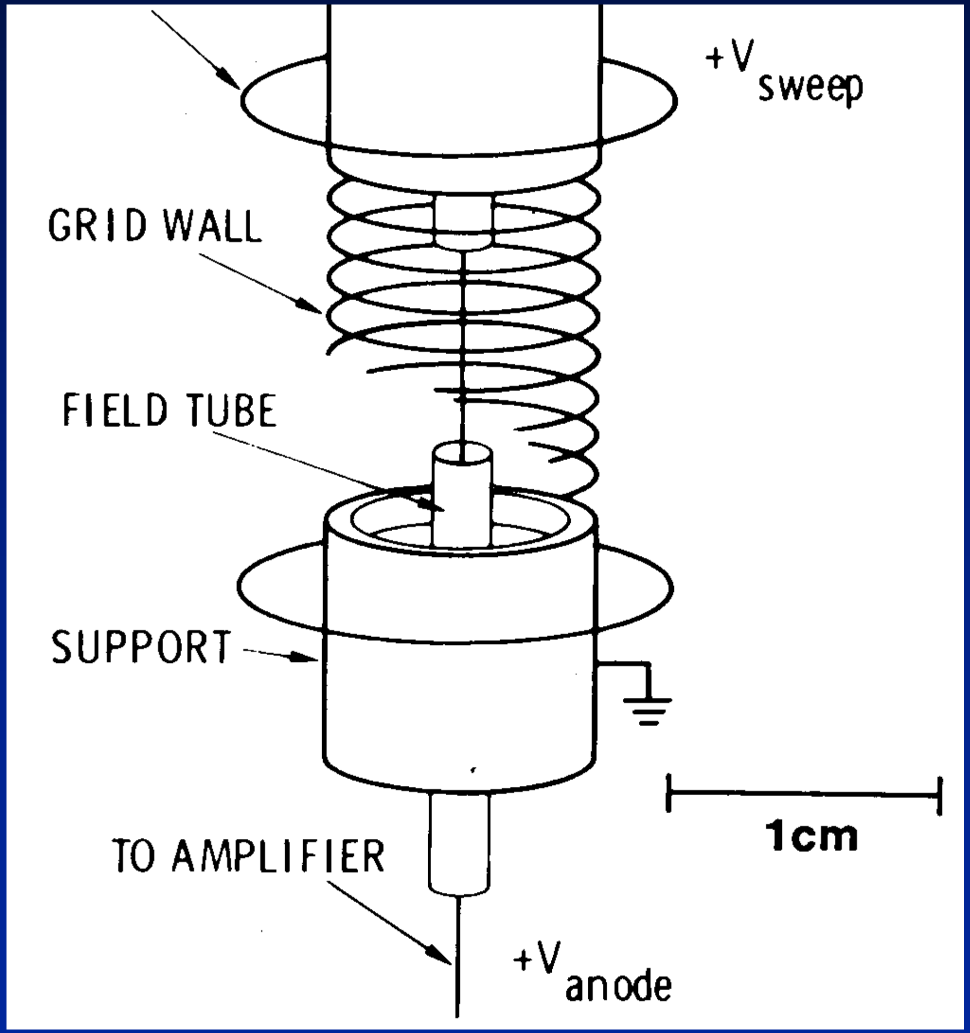


Microdosimetric Distributions:

Distributions of energy deposition in micron site sizes



Microdosimetric spectra can be calculated or measured

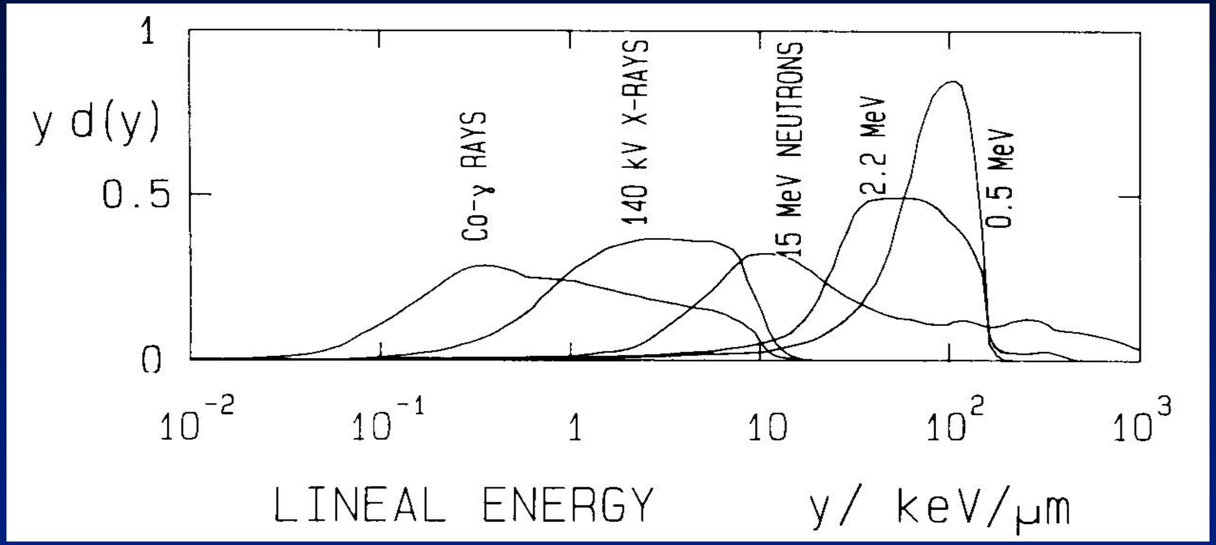


From track structure to RBE_M

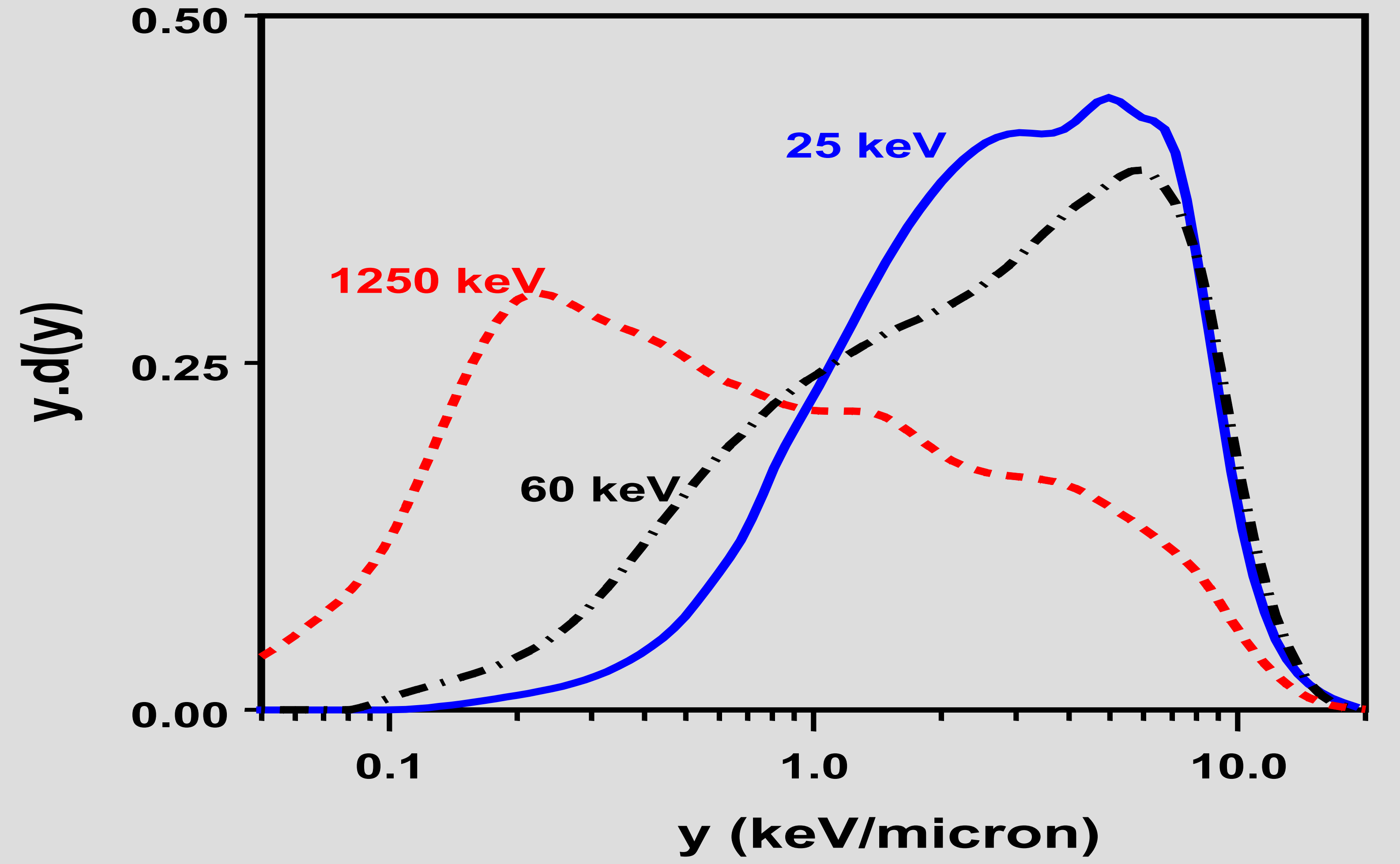
Biological response function

$$RBE_M = \int d(y)\ r(y)\ dy$$

Microdosimetric spectrum

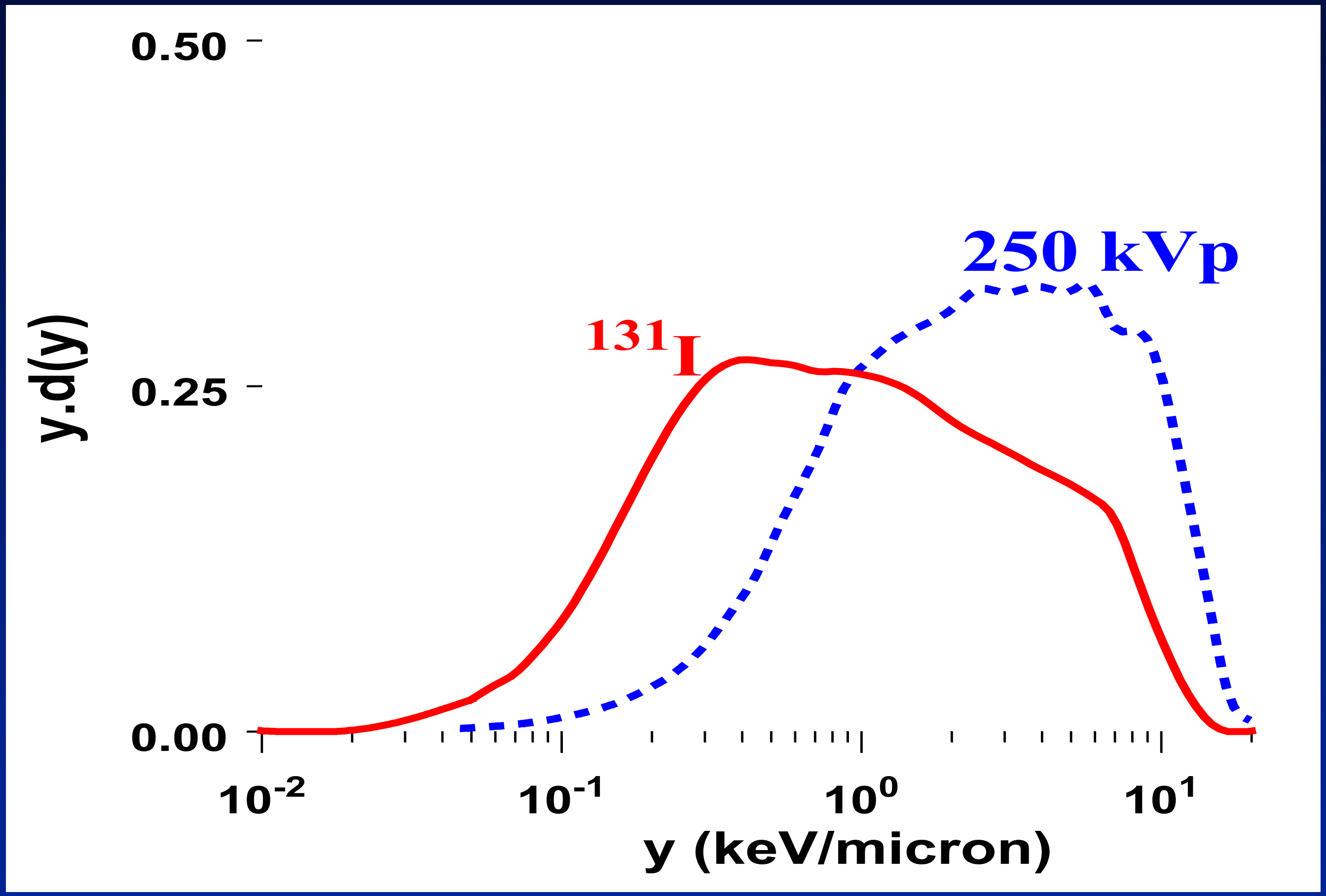


Different photon energies produce quite different microdosimetric spectra



So, for example, mammographic x rays have an RBE of 2-3, compared to high energy photons

Low dose RBE of ^{131}I *vs.* 250 kVp x rays



- Based on microdosimetric spectra, RBE_M ~0.6

My time is up!

My Take-Home Message

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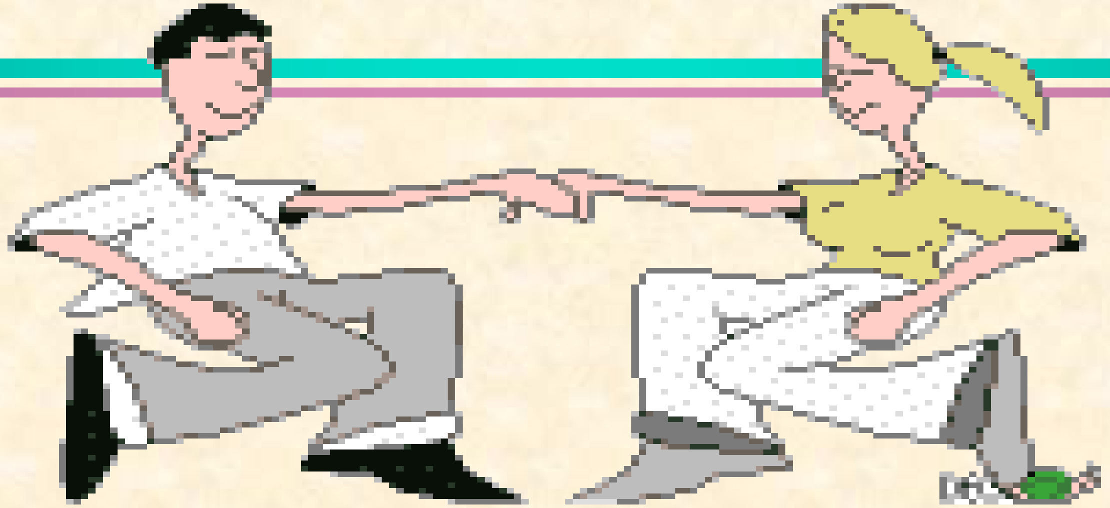
Interactions between
radiation epidemiologists and radiation biologists
are going to become increasingly important,
as our field focuses more and more
on the effects of low radiation doses

NCI 2019

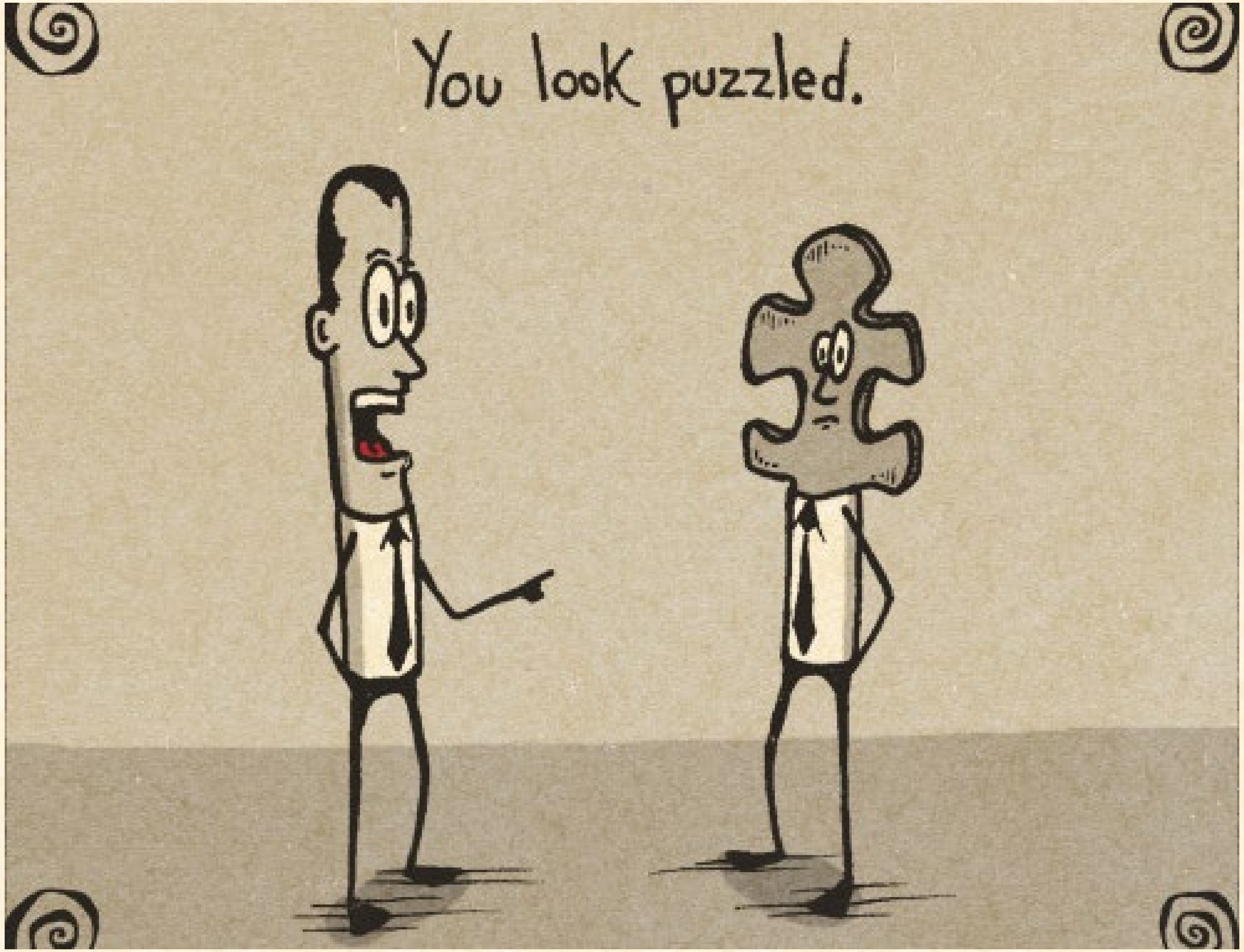
Radiation epidemiology



Radiation biology

In fond memory of Elaine Ron

A few questions.....



Pathology allows us to distinguish between a radiation-induced tumor and a sporadic tumor

A. True
B. False

Pathology allows us to distinguish between a radiation-induced tumor and a sporadic tumor

A. True

B. False

A-bomb survivor data shows increased radiation-induced cancer risks for doses….

A. Only above 3 Gy
B. At doses above 5 to 150 mGy
C. At doses above 5 to 150 μGy

A-bomb survivor data shows increased radiation-induced cancer risks for doses….

A. Only above 3 Gy

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C. At doses above 5 to 150 μGy

Giving the same radiation dose but lowering the dose rate.....

A. Typically increases radiation-induced cancer risks

B. Typically decreases radiation-induced cancer risks

C. Rarely has an effect on radiation-induced cancer risks

D. It all depends on the radiation type

Giving the same radiation dose but lowering the dose rate.....

A. Typically increases radiation-induced cancer risks
B. Typically decreases radiation-induced cancer risks
C. Rarely has an effect on radiation-induced cancer risks
D. It all depends on the radiation type

Relative Biological Effect (RBE) depends on the radiation dose

A. True
B. False

Relative Biological Effect (RBE) depends on the radiation dose

A. True
B. False

cancer.gov/dceg

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