Returning to our Roots: The New Radiation Biology

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CHECKING THE FOUNDATION: RECENT RADIOBIOLOGY AND THE LINEAR NO-THRESHOLD THEORY

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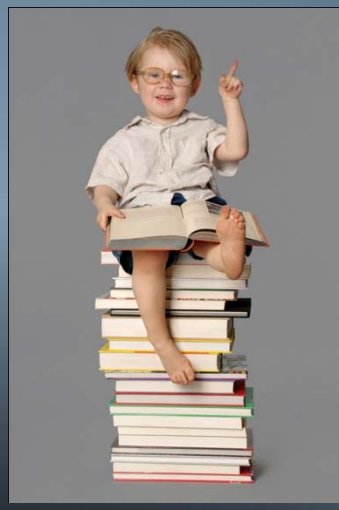
First Things First

- H_0: there is no relationship between radiation exposure and cancer risk
  - $R = c$
- H_1: cancer risk is linearly related to risk, without threshold (LNT)
  - $R = \alpha D + \beta$



Shifting the Burden of Proof

"…for many of the biological lesions which are precursors to cancer (such as mutations and chromosome aberrations) *the possibility of a linear-nonthreshold dose-response relationship at low radiation doses cannot be excluded*" (emphasis added)

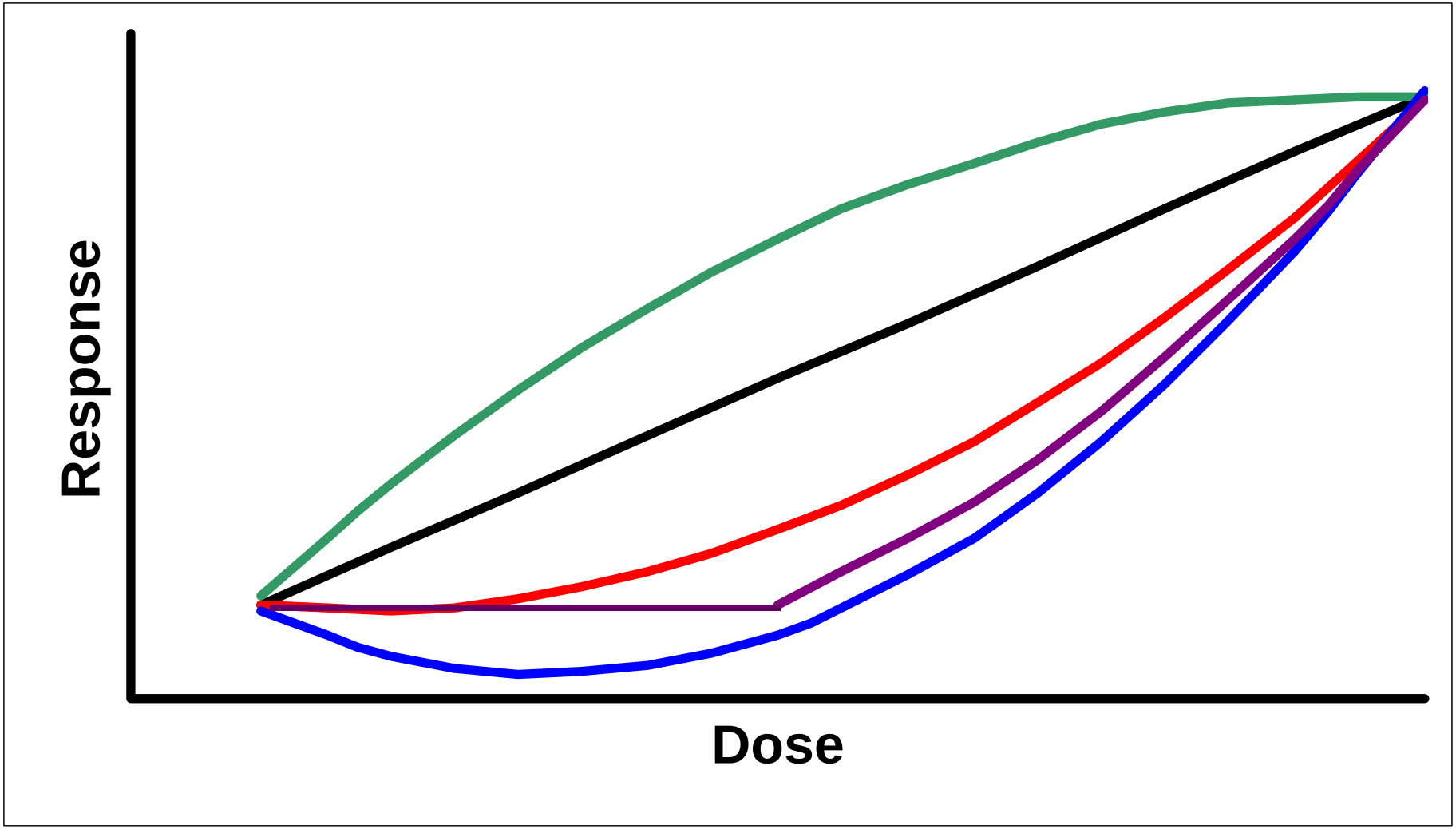
(NCRP 136, 2001)

Shifting the Burden of Proof

"Although other dose-response relationships for the mutagenic and carcinogenic effects of low-level radiation cannot be excluded, no alternative dose-response relationship appears to be more plausible than the linear-nonthreshold model "

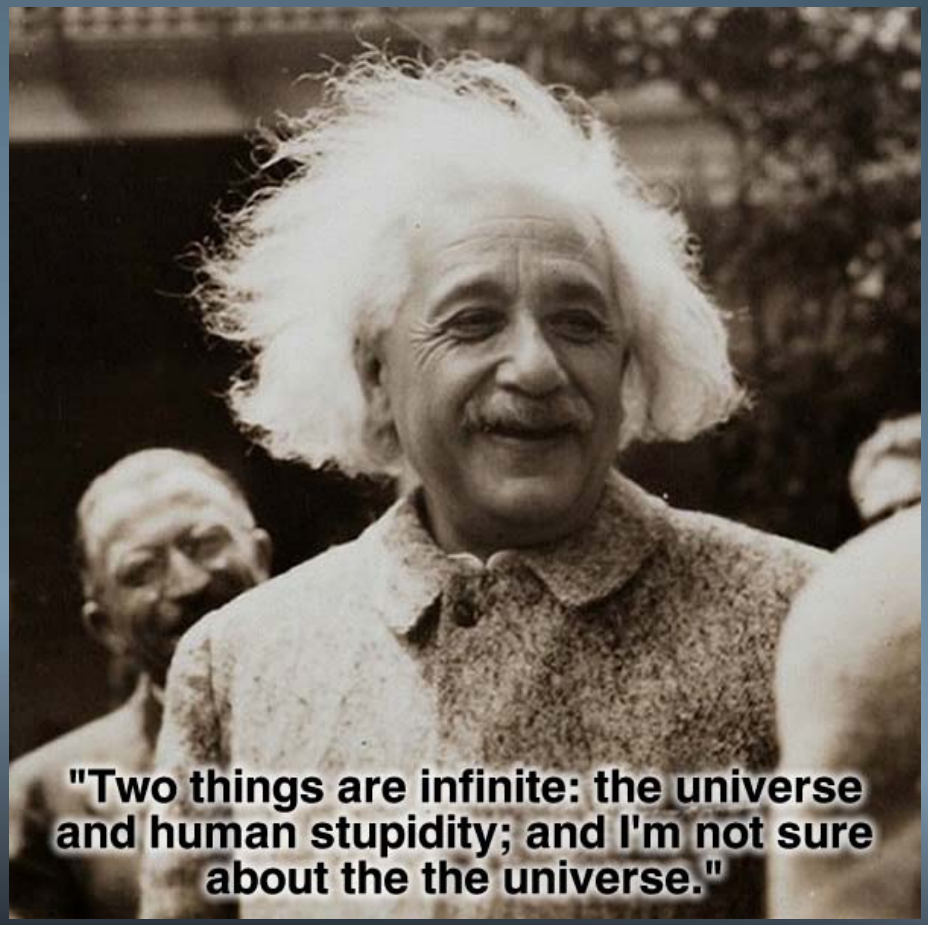
(NCRP 136, 2001)

Alternative Predictions



Occam's Razor

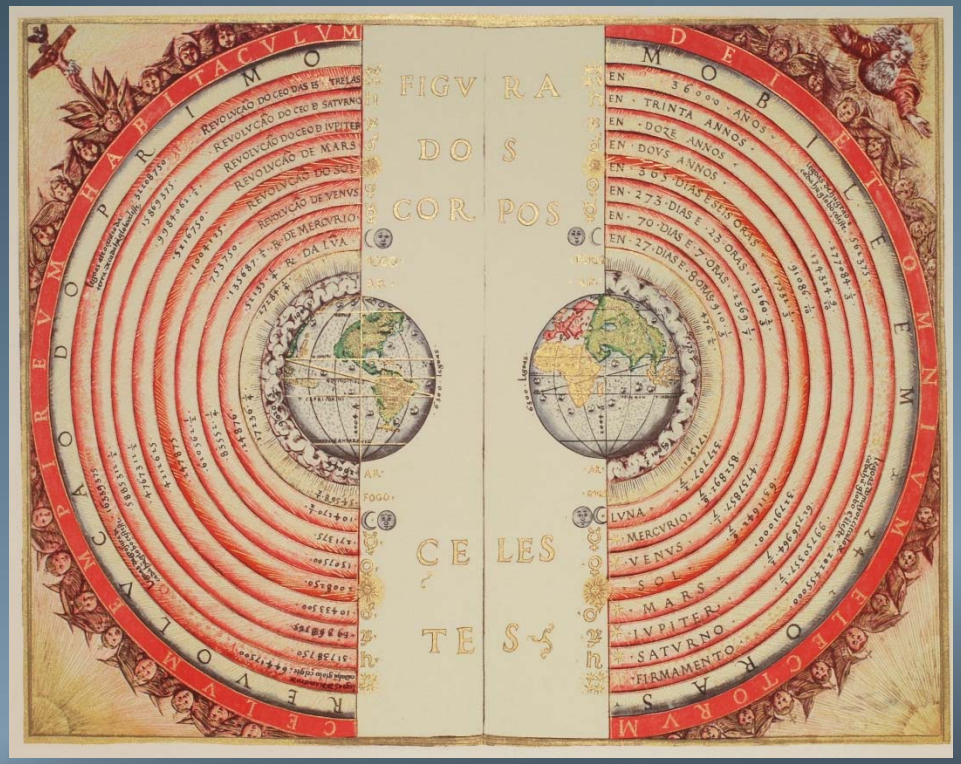
As simple as possible, but no simpler



Simplicity ≠ Accuracy

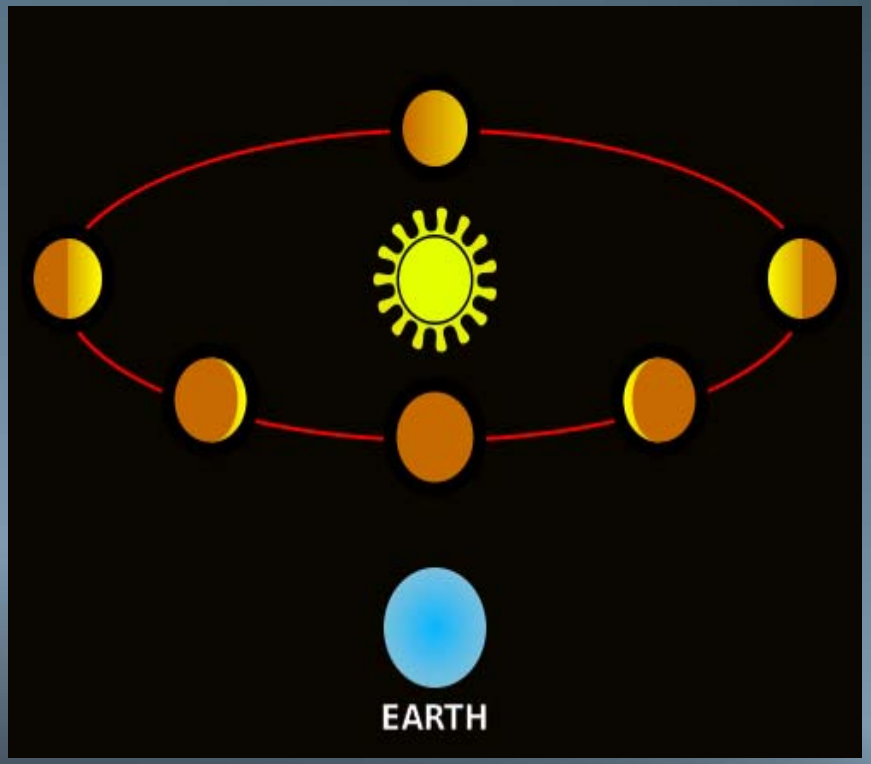
Geocentrism

6th century BC



Heliocentrism

17th century AD



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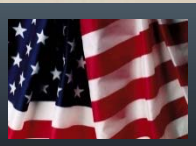

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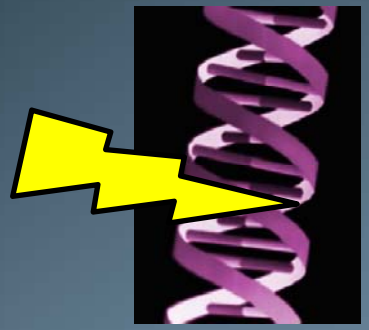
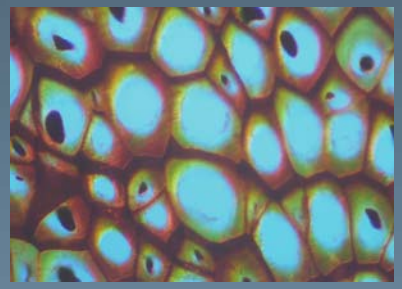
Straightening Up

"The number [of mutations] varies with the x-ray dosage, but it seems that the "degree" or nature of the individual mutations themselves does not vary with the dosage".

H.J. Muller, Proc. Nat Acad. Sci, 14(9), 1928

Microdosimetric Argument





Radiation energy is deposited linearly in cells, therefore DNA damage is linear with dose, and radiation carcinogenesis increases linearly with dose

Microdosimetric Argument

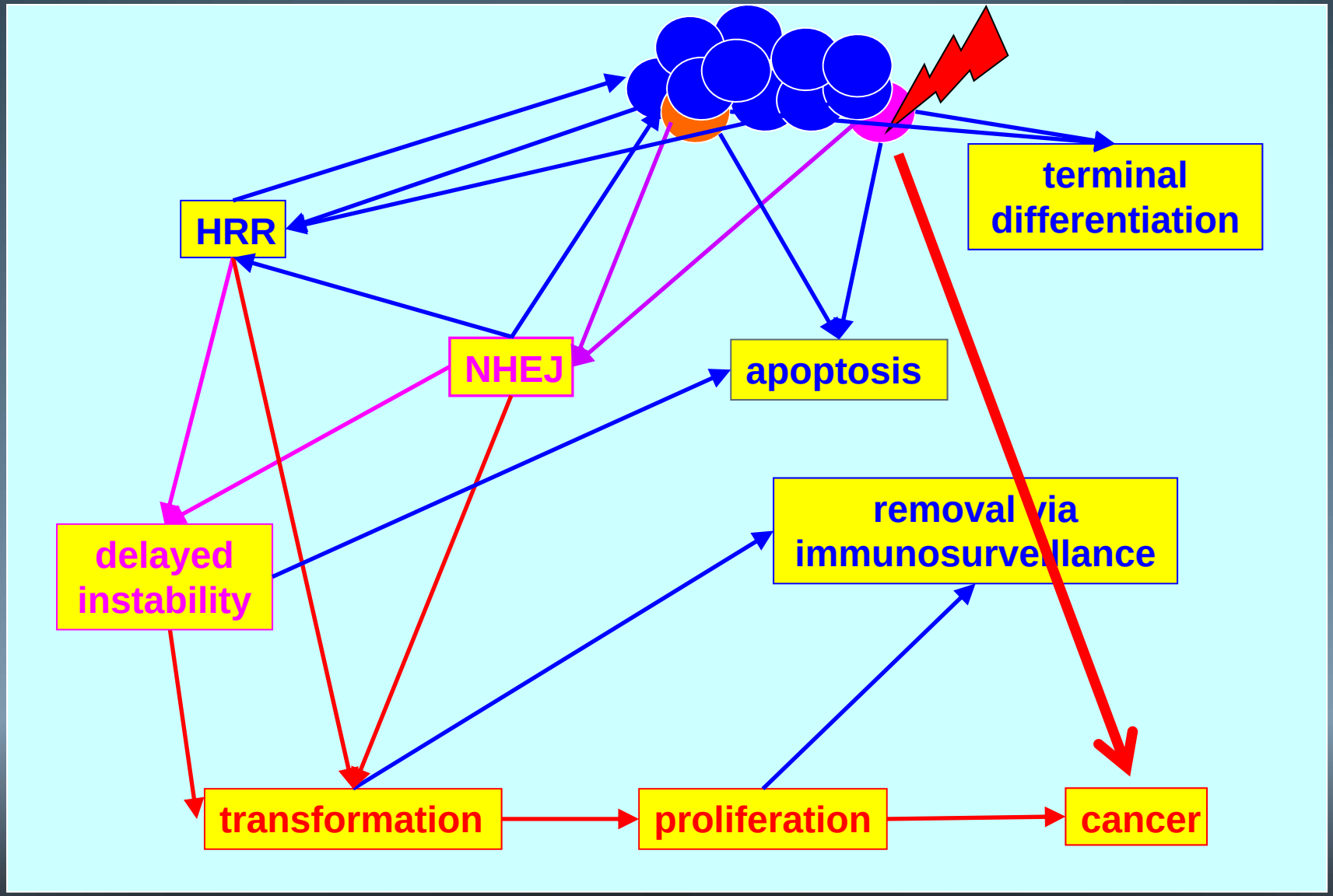
Assumptions

(NCRP 136, 2001)

1. **Cancer induction is causally related to radiation-induced damage in a single cell**

2. **The ways cells and cell systems modify the probability that a damaged cell becomes the origin of cancer do not vary with dose in a nonlinear fashion**

From Damage to Cancer



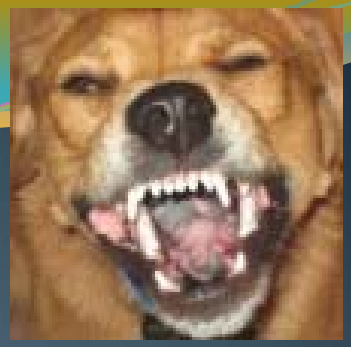
LNT Predictions

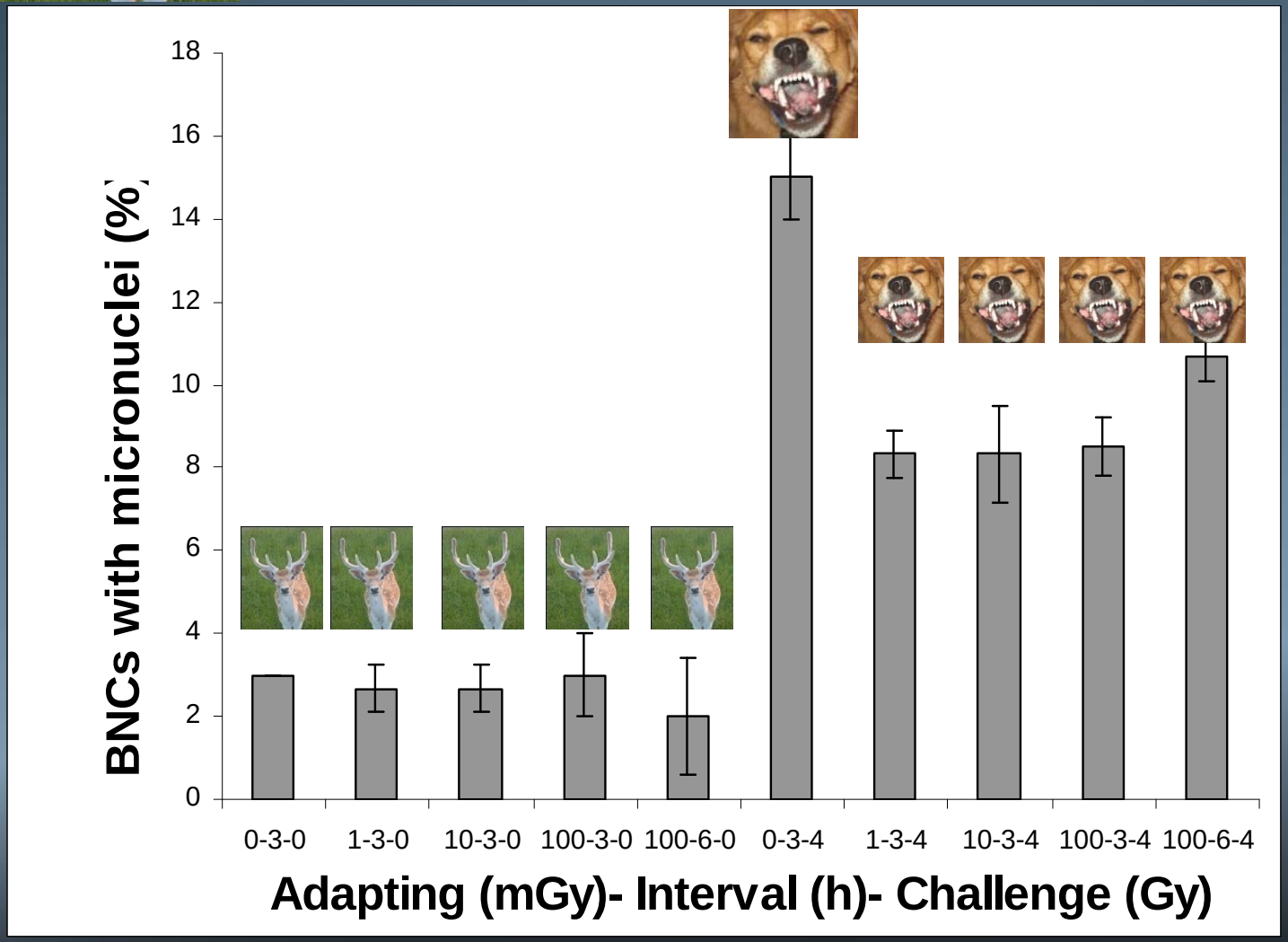
- Recall LNT says: $Y = aD + b$
- This means risk varies **quantitatively** with dose, but not **qualitatively**
- The same kinds of effects are observed at high and low doses, but they increase linearly

Gene Expression and Dose

- Damage response genes are activated by low dose, low dose-rate exposures
- Apoptosis and proliferation are activated by high dose, high dose-rate exposures
- Genes expression profiles *qualitatively* differ, depending on dose/dose-rate

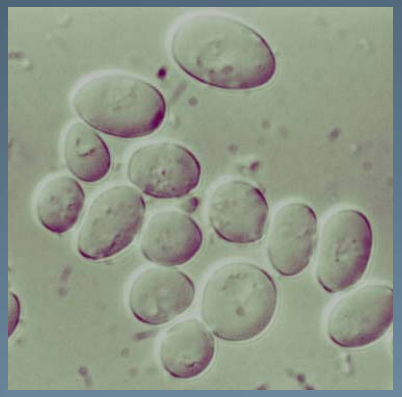
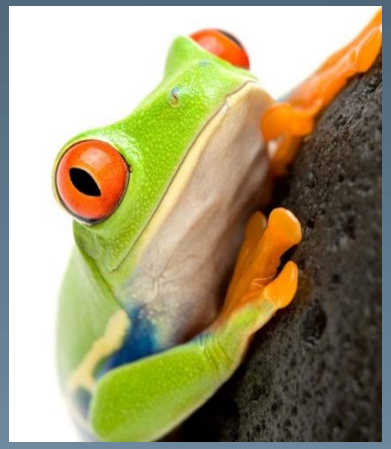
Bambi and the Beast

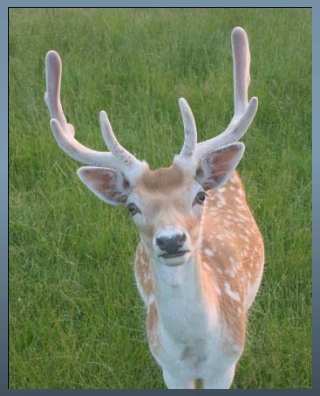




Ulsh et al, J. Environ Rad. 74: 73-81, 2004

Adaption or Extinction

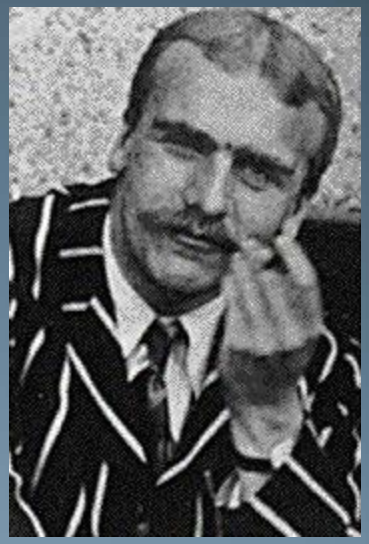
Neighborhood Watch

Bystander effects

- Dominant at low doses and saturates at intermediate doses
- Nonlinear
- Selective apoptosis of damaged cells = protective

Facing Facts

Stages of Acceptance:

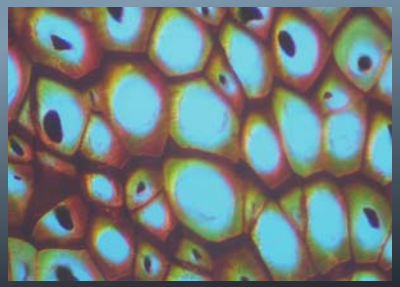


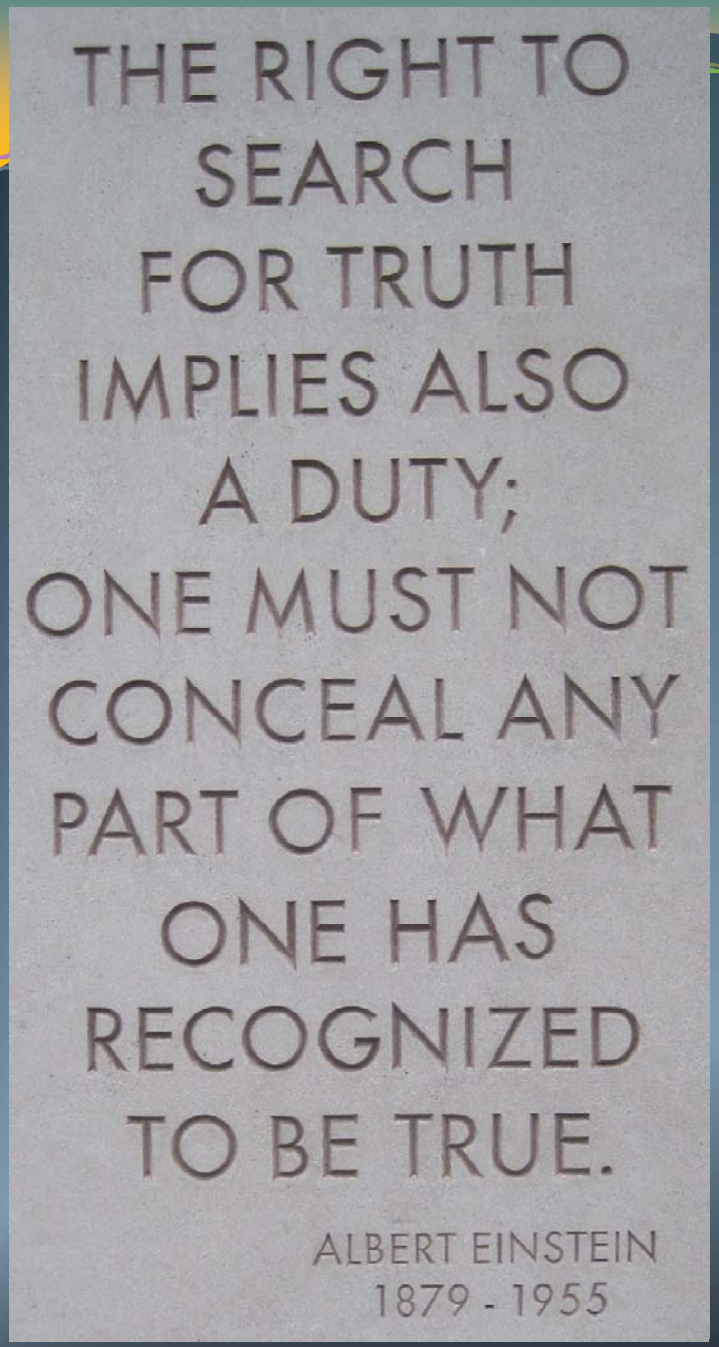
1. This is worthless nonsense
2. This is an interesting, but perverse point of view
3. This is true, but quite unimportant
4. I always said so

J.B.S. Haldane, J. Genetics, 58, p. 464, 1963

Bridging the Gap

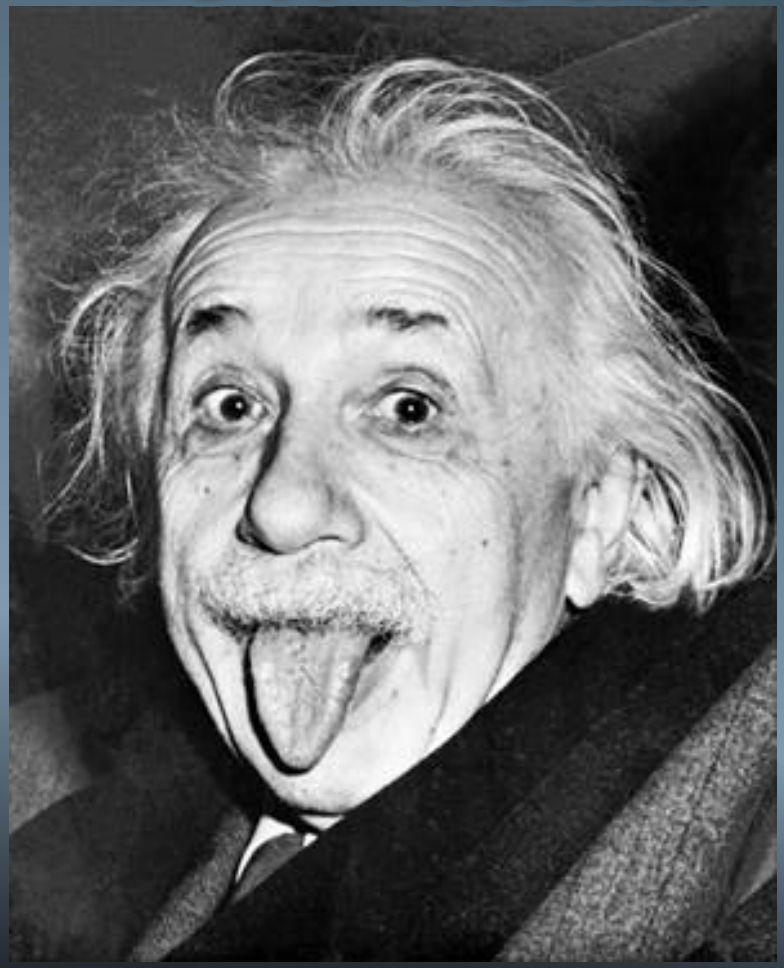
- Biologists
  - Demonstrate relevance of *in vitro* endpoints to *in vivo* effects
  - Focus on relevant doses
- Epidemiologists
  - Pay more attention to dose
  - Consider LNT alternatives





High Road

Low Road



Keep In Touch!

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