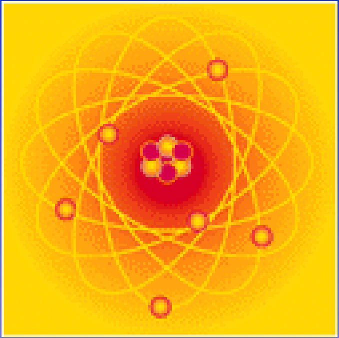


III. Biological Effects of Ionizing Radiation

Robert E. Reiman, MSPH, MD, Duke University Medical Center

Center for Medical Countermeasures Against Radiation

Objectives

- **Understand interaction of ionizing radiation with matter on the molecular level.**
- **Understand how molecular-level effects lead to damage at the cell and tissue levels.**
- **Identify major effects of radiation on humans.**

Interaction of Radiation With Matter

- **Ionizing radiation can interact with matter in three ways:**
  - **Photoelectric absorption (low photon energies)**
  - **Compton scatter (medium photon energies)**
  - **Pair production (photon energies > 1.02 MeV)**
  - **Particle collisions**

Photoelectric Absorption

- **Photon interacts with the electronic shells of an atom and is completely absorbed.**
- **An electron is ejected from atom, with kinetic energy equal to photon energy minus the binding energy.**
- **An ion pair results.**

Compton Scatter

- **A photon interacts with an outer-shell electron in material.**
- **Only part of photon energy is transferred to electron. The amount of energy transferred depends upon the direction of travel of scattered photon.**
- **An <u>ion</u> <u>pair</u> results.**

Compton Scatter

- **The scattered photon may in turn interact with another atom in the material by photoelectric absorption or Compton scatter.**
- **Multiple ion pairs may result as the energy from scattered photons is deposited in the material.**

Pair Production

- **A photon of energy greater than 1.022 MeV produces an electron-positron pair.**
- **The positron travels a short distance before interacting with an electron and producing two 511 KeV photons (annihilation photons).**
- **These photons can in turn interact with material to produce ion pairs via Compton scatter.**

Particle Collisions

- **Charged (betas, alphas) or uncharged particles (neutrons) can interact with nuclei and/or electron shells in material and lose energy.**
- **Particle may undergo hundreds of interactions before all energy is transferred to material.**
- **<u>Ion</u> <u>pairs</u> are formed along track.**

Linear Energy Transfer

- **Photons, charged particles and neutrons can leave multiple ion pairs along a “track” as they traverse material.**
- **The total deposited energy divided by the length of the “track” is the <u>linear energy transfer</u> of the radiation, or <u>LET</u>.**

Linear Energy Transfer

- Photons and beta particles are generally classified as “low LET” radiation, whereas alpha particles and neutrons are classified as “high LET” radiation.
- LET correlates with biological effect. The higher the LET, the greater the biological effect.

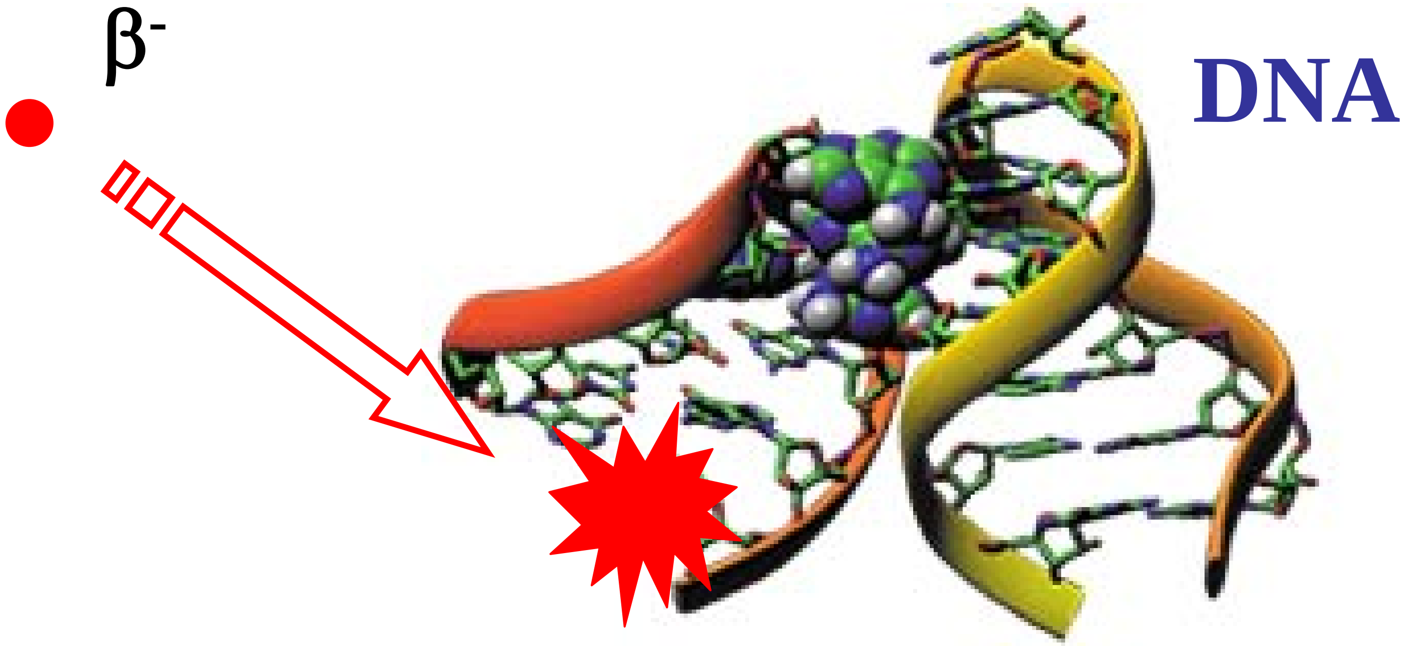
Mechanisms of Biological Damage by Ionizing Radiation

- **Direct damage to DNA**
- **Indirect damage via formation of reactive chemical species**
- **End Result: disruption cell membrane integrity, cellular chemistry and DNA replication.**

Biological Damage by Direct Mechanisms

- **Ionizing event that occurs in nuclear DNA can break single or double strands.**
- **Damage may be (a) irreparable, or may be (b) incorrectly repaired.**
- **Can result in (a) cell death at next mitosis or (b) point mutation.**

Direct Radiation Damage



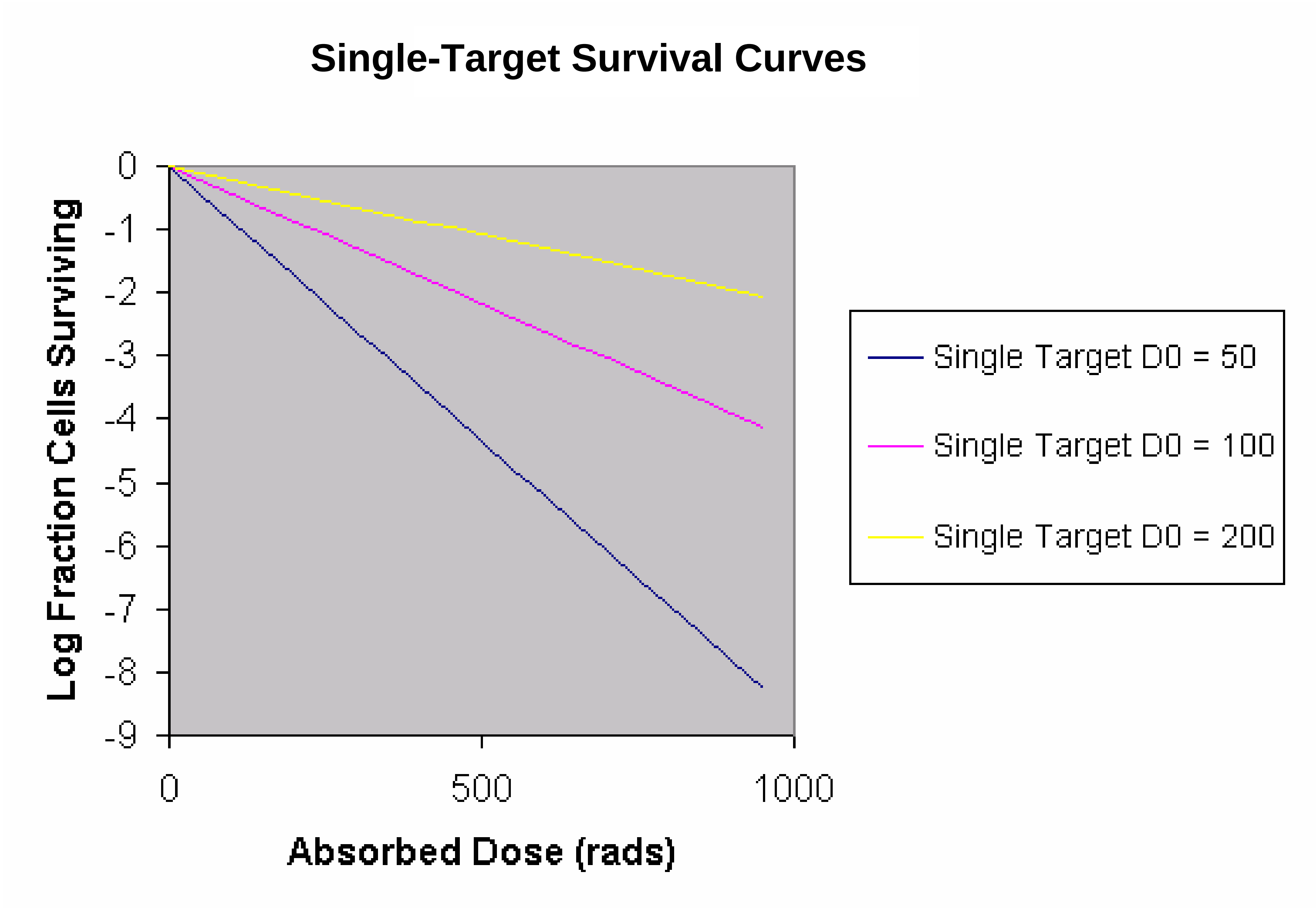
Particle or EMR hits the DNA in the nucleus of a replicating cell, either causing the cell to <u>die</u> during mitosis, or inducing a <u>mutation</u>.

"Target" Theory

Think of ionizing radiation photons as a hail of "bullets". The higher the exposure, the more bullets. The smaller the cell, the smaller the "target" it presents to the hail of "bullets", and the more difficult it is to "hit".

Single Target, Multi-Hit Theory

- **Assumes that a cell requires a certain number of hits to inactivate a single target. Then $S = \exp(-D / D_o)$, where S is the surviving fraction at dose D, and D_o is the "mean lethal dose."**
- **Accurately describes survival curves of viruses and simple bacteria.**

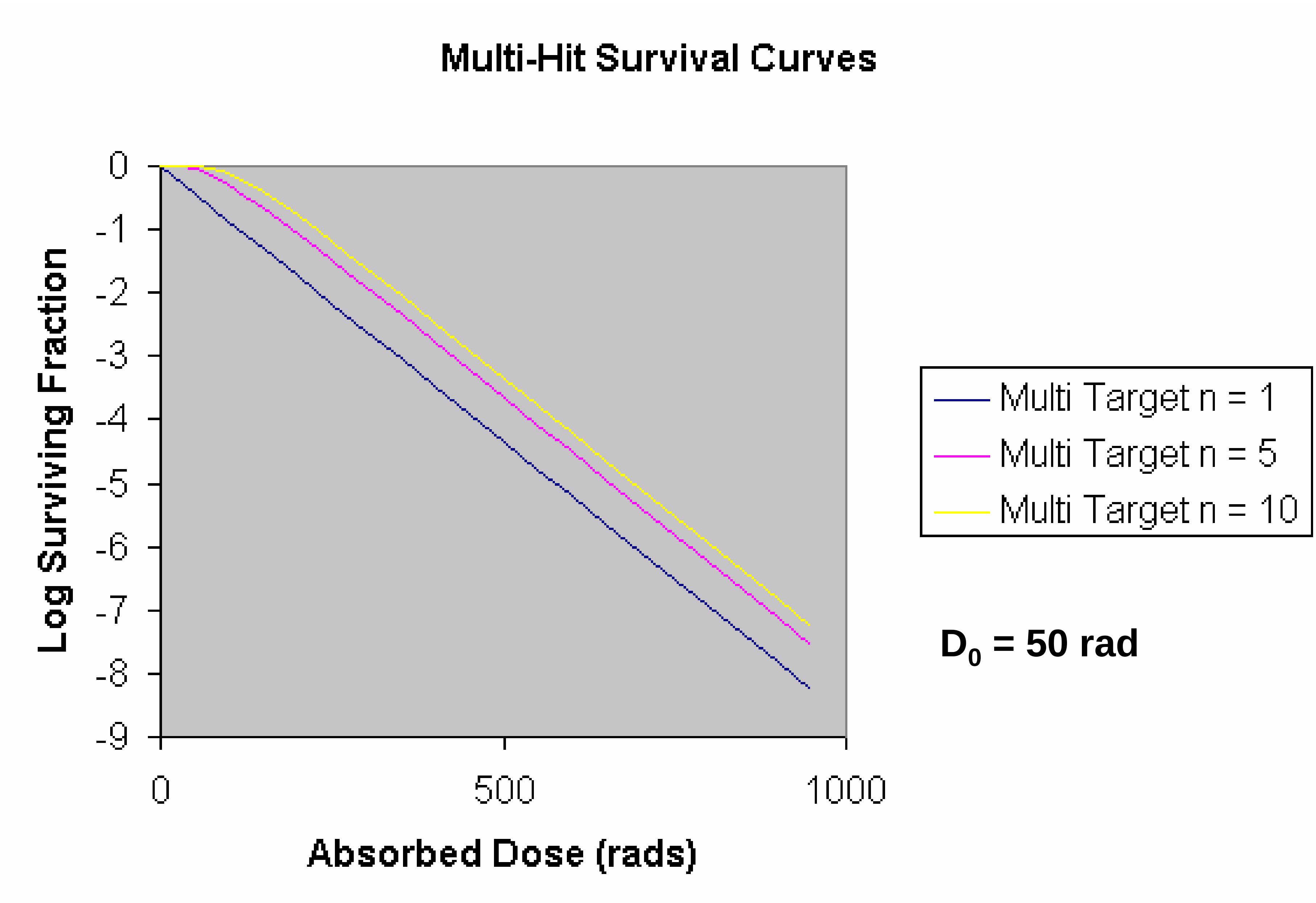

Single-Target Survival Curves
Log Fraction Cells Surviving
0
-1
-2
-3
-4
-5
-6
-7
-8
-9
0
500
1000
Absorbed Dose (rads)
Single Target D0 = 50
Single Target D0 = 100
Single Target D0 = 200

Multi-Target, Multi-Hit Theory

- **Assumes that a cell requires multiple hits to inactivate "n" targets. Then**

  $$S = 1 - (1 - \exp(-D / D_o))^n$$

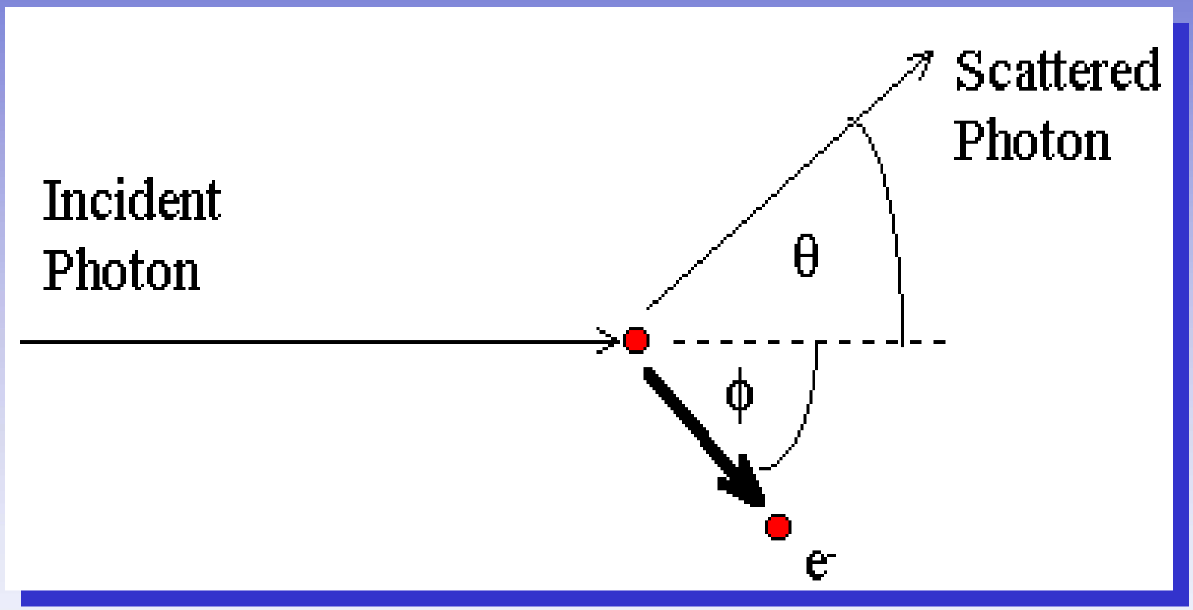
- **This reduces to the simple multi-hit theory for n = 1.**
- **Produces a "shoulder" in the survival curve for complex eukaryotes (increased survival at low doses).**


Multi-Hit Survival Curves
Log Surviving Fraction
0
-1
-2
-3
-4
-5
-6
-7
-8
-9
0
500
1000
Absorbed Dose (rads)
Multi Target n = 1
Multi Target n = 5
Multi Target n = 10
D0 = 50 rad

Biological Damage by Indirect Mechanisms

- **Ionizing radiation produces free electrons in materials, and thus ion pairs.**
- **Ion pairs combine to form reactive chemical species.**
- **Reactive chemical species disrupt cell membrane integrity, cellular chemistry and DNA replication.**

Indirect Radiation Damage



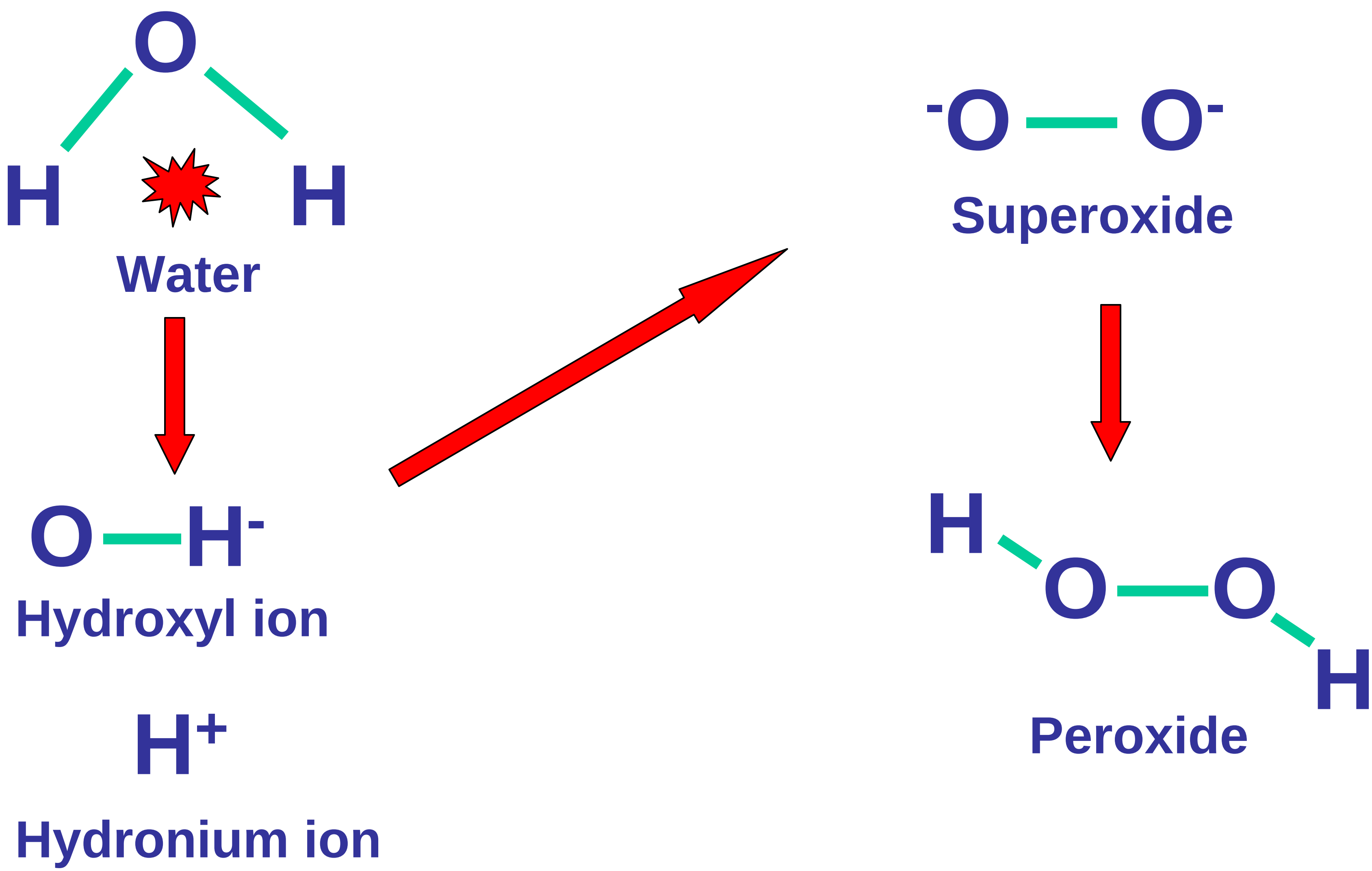
H^+

$+$

OH^-

Formation of hydronium and hydroxyl <u>ion pairs</u> in <u>water</u> lead to the formation of <u>reactive species</u>.

Free Radical Production



Damage at the Tissue Level

- **Disruption of vascular endothelium and its underlying stroma leads to erythema (in skin), edema, and necrosis.**
- **Cell death leads to variable degrees of tissue dysfunction, which can in turn effect the whole organism.**

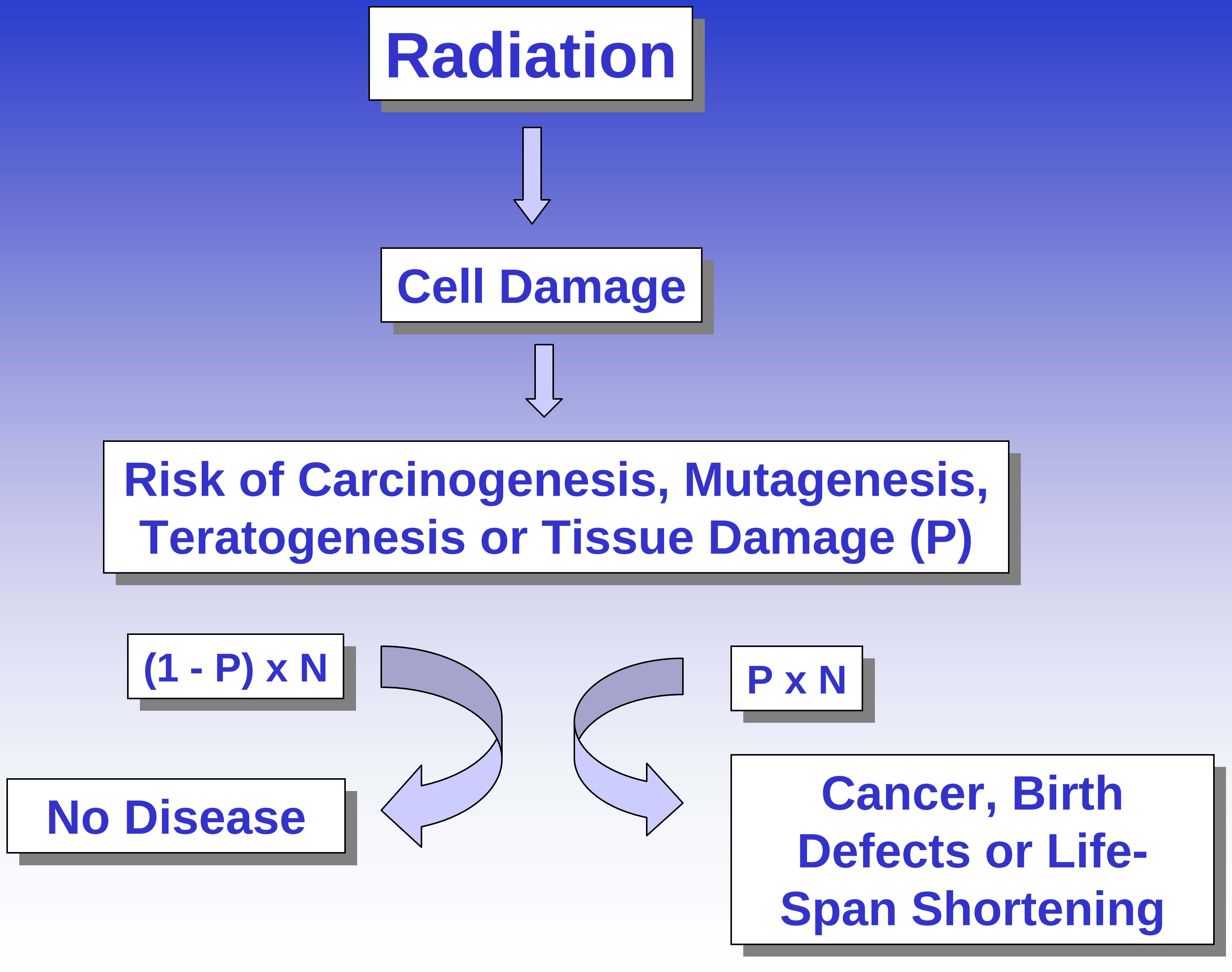
The Law of Bergonié and Tribondeau (1906)

"Those tissues that are the most sensitive to radiation are the tissues that are most rapidly proliferating."

- **In the human, these would include the red marrow, GI tract and sperm cells.**
- **Slowly proliferating tissues such as nerve cells are relatively radioresistant.**

Damage to the Organism

- **Interactions of radiation with living material may result in damage at the <u>molecular</u> or <u>cellular</u> levels.**
- **May be a result of mutation or cell death.**
- **Translates into <u>disease</u> in the organism or its offspring.**


Radiation
Cell Damage
Risk of Carcinogenesis, Mutagenesis, Teratogenesis or Tissue Damage (P)
(1 - P) x N
P x N
No Disease
Cancer, Birth Defects or Life-Span Shortening

Factors Related to Risk of Disease ("P")

- **Magnitude of Radiation Dose**
- **Type of Radiation ("Quality Factor")**
- **Duration of Accumulation Period and Ability to Repair Damaged DNA**
- **Sensitivity of Specific Tissues**
- **Stochastic versus "Dose-Related" Effects**

Deterministic versus Stochastic Effects

- **Deterministic (Non-stochastic): Severity is dose-related, and there is a threshold below which effect is not seen. Tend to occur at whole-body doses > 100 rem.**
- **Stochastic: Probability of occurrence is dose-related. Type or severity of effect is not related to dose. No threshold is assumed for stochastic effects but are documented only at doses > 10 rem.**

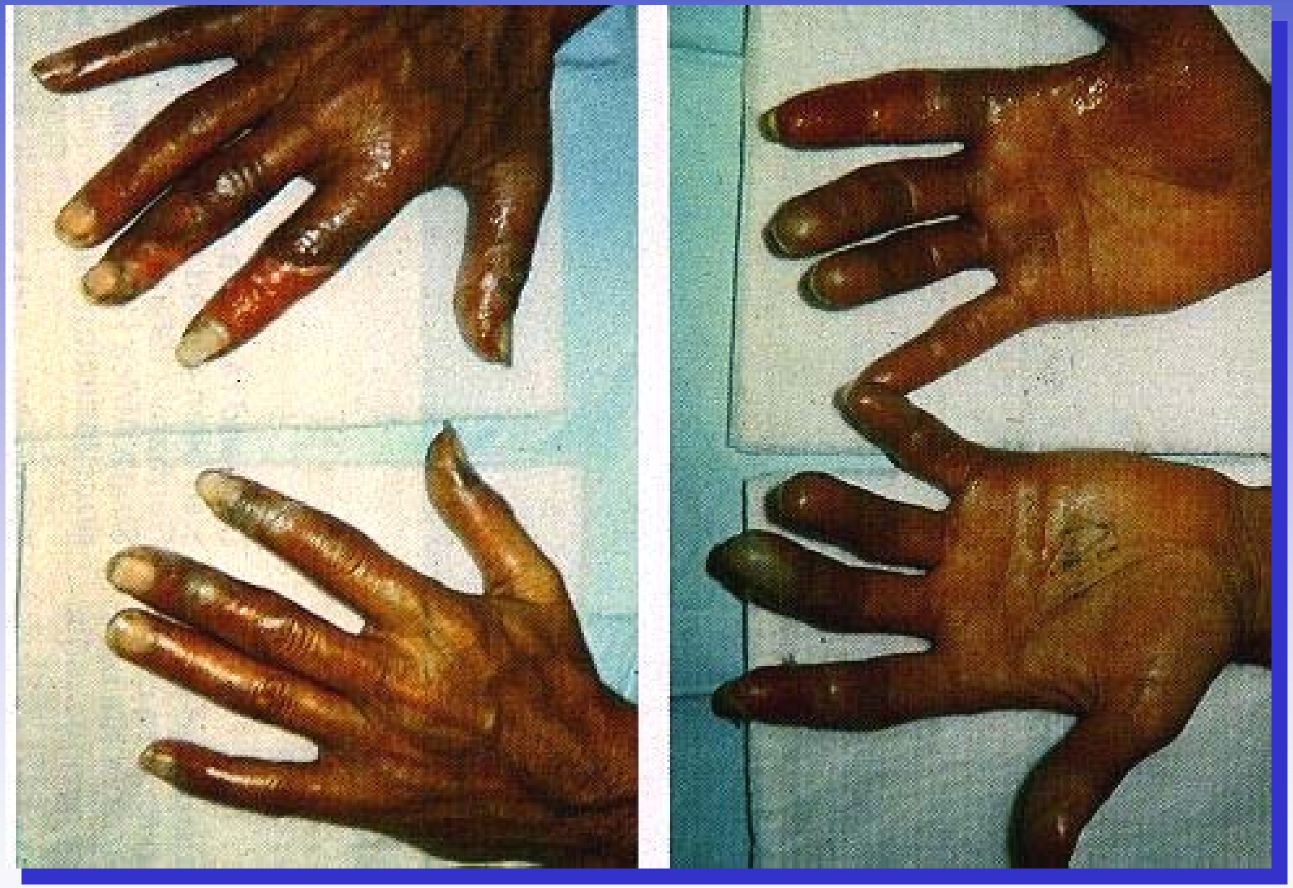
Examples of Deterministic and Stochastic Effects

- **Deterministic: erythema, cataracts, decreased sperm count, bone marrow depression, GI symptoms.**
- **Stochastic: life-shortening, cancer induction, mutagenesis.**

Skin Damage: A Deterministic Effect

- **Transient Erythema: > 200 rads. Appears 24 to 48 hours following exposure and is self-limiting. Epilation occurs > 300 rads.**
- **Main Erythema: 600 – 800 rads: Permanent pigmentation changes.**
- **Ulceration/Necrosis: > 1500 rads. Injuries do not heal without skin grafting, free flaps, and other measures.**

Skin Injuries



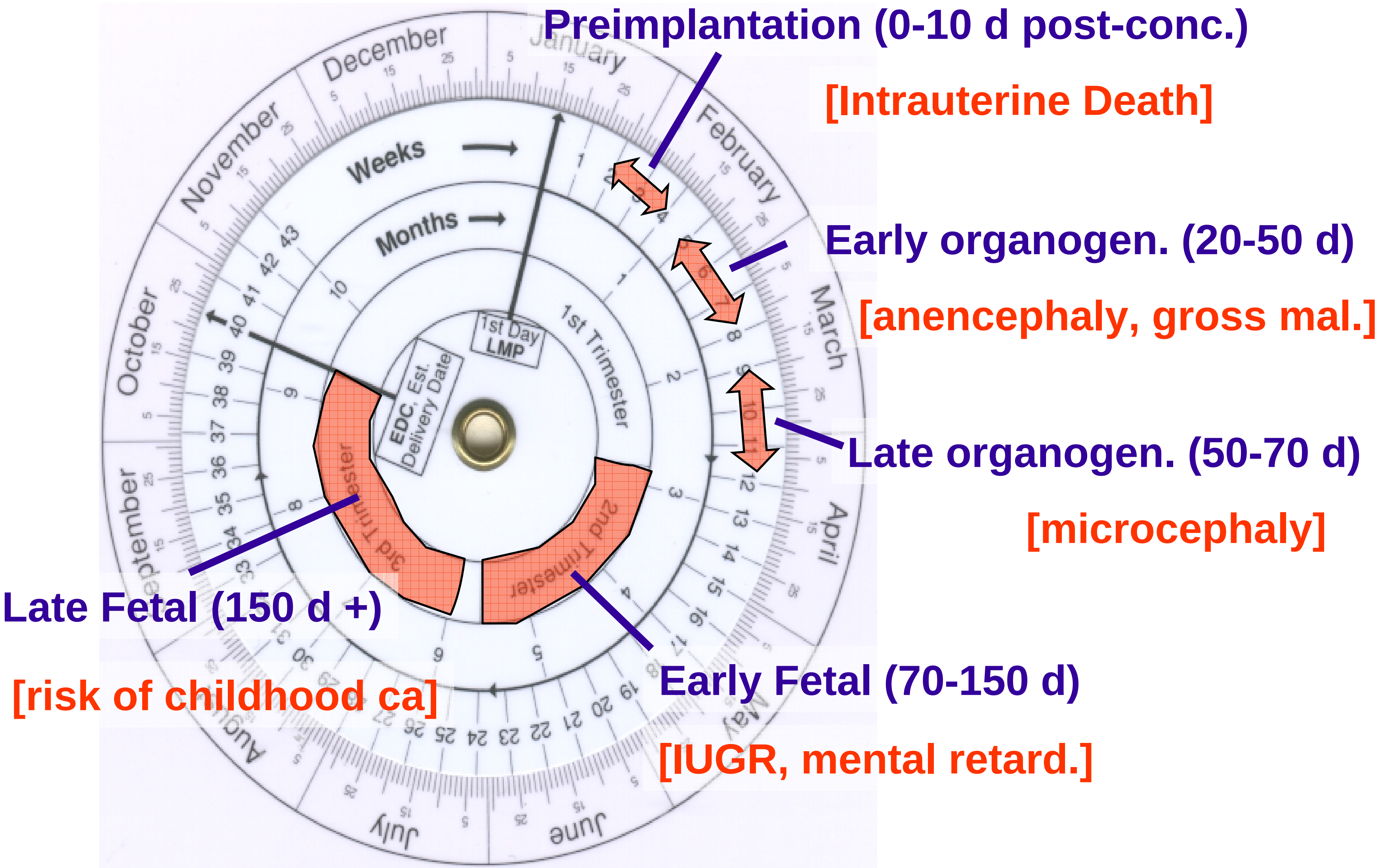
“Radiation burns” of hands secondary to inadvertent handling of an industrial radiography source.

Skin Injuries

Extensive necrosis of skin and underlying soft tissues in an individual who carried an iridium-192 industrial radiography source in his back pocket for several days.

Congenital Defects: A Deterministic Effect

- **Narrow spectrum of defects observed in humans: mental retardation, microcephaly, reduced IQ / school performance, intrauterine growth retardation.**
- **Type of effect depends upon stage of gestation when irradiated.**
- **Threshold dose > 25 rads**

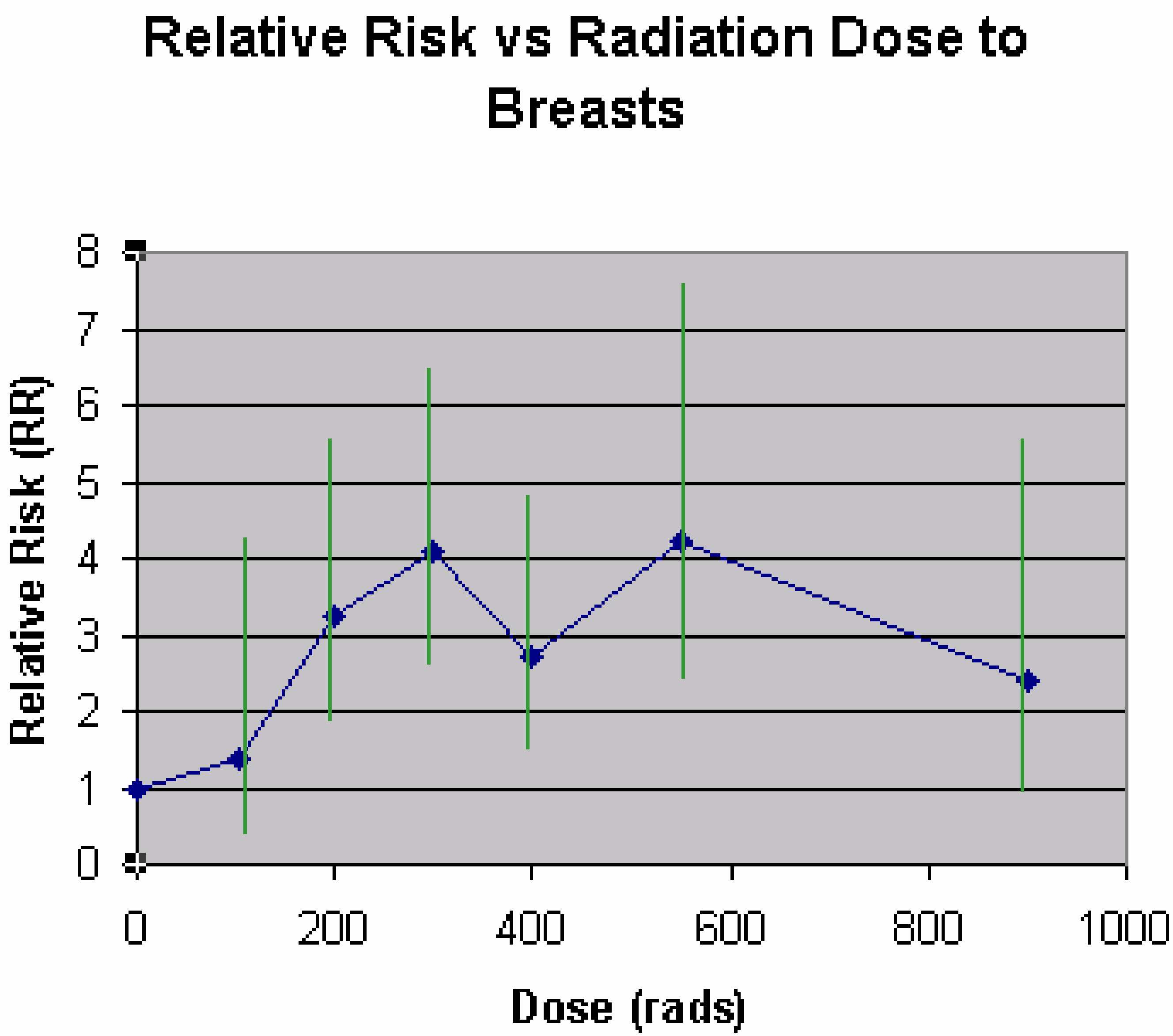

Preimplantation (0-10 d post-conc.)
[Intrauterine Death]
Early organogen. (20-50 d)
[anencephaly, gross mal.]
Late organogen. (50-70 d)
[microcephaly]
Early Fetal (70-150 d)
[IUGR, mental retard.]
Late Fetal (150 d +)
[risk of childhood ca]
Weeks
Months
1st Day LMP
EDC, Est. Delivery Date
1st Trimester
2nd Trimester
3rd Trimester
December
January
February
March
April
May
June
July
August
September
October
November

Cancer Induction: A Stochastic Effect

- **Skin cancer, osteogenic sarcoma, breast cancer, thyroid cancer and leukemia have all been associated with exposure to ionizing radiation.**
- **May be a <u>latency period</u> of years from exposure to detection.**

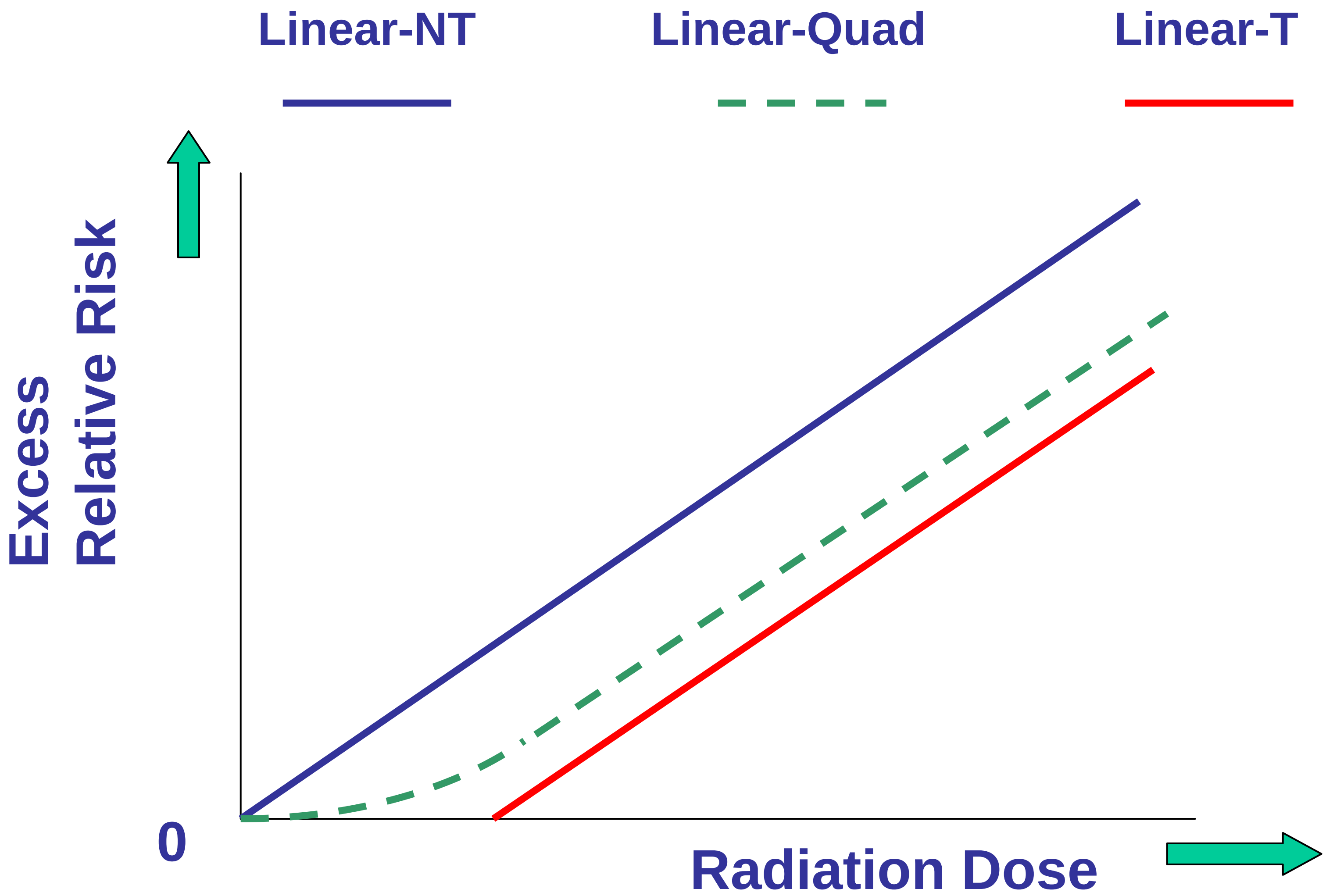
Cancer and Radiation: At-Risk Populations

- **Fluoroscopy for TB: <u>Breast Cancer</u>**
- **Radium Dial Painters: <u>Osteosarcoma</u>**
- **XRT for Ankylosing Spondylitis: <u>Leukemi</u>a**
- **XRT for Tinea Capitis: <u>Thyroid Cancer</u>**
- **XRT for PP Mastitis: <u>Breast Cancer</u>**



Computed from Shore et al.

Models of Radiation Risk



Linear No-Threshold Model

- **Adverse biological effects of ionizing radiation are produced in amounts directly proportional to absorbed dose.**
- **Any radiation dose greater than zero will result in adverse biological effects.**
- **Conservative, so is used as the basis for regulatory practice.**

Types of "Radiation Death"

- **Neurological Death:** occurs in minutes to hours. Characterized by stupor or coma. Requires about 10,000 rem.
- **Gastrointestinal Death:** days to weeks. Characterized by diarrhea, hematochezia and dehydration. Requires 500 - 1000 rem.

Types of "Radiation Death"

- <u>**Hematopoietic Death:**</u> **occurs in weeks to months. Characterized by anemia, bleeding, immune suppression. Requires several hundred rem.**
- <u>**LD-50/30:**</u> **radiation dose required to cause death in 50% of the population within 30 days. About 400 - 600 rem for humans.**

Acute Radiation Syndrome

- **Prodrome: Nausea, vomiting, diarrhea, fever, apathy, anxiety, headache and other non-specific symptoms.**
- **Latent Phase: May see a brief recovery from prodrome.**
- **Illness Phase: Hematopoietic, gastrointestinal and neurological effects may be seen depending upon dose.**

End of Module III

- **This is the end of Module III.**
- **Please Proceed to Module IV: “Standard Protective Measures Against Ionizing Radiation”.**