Radiation Epidemiology Course

Division of Cancer Epidemiology & Genetics
National Cancer Institute
National Institutes of Health
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Introduction and Overview

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Course Overview

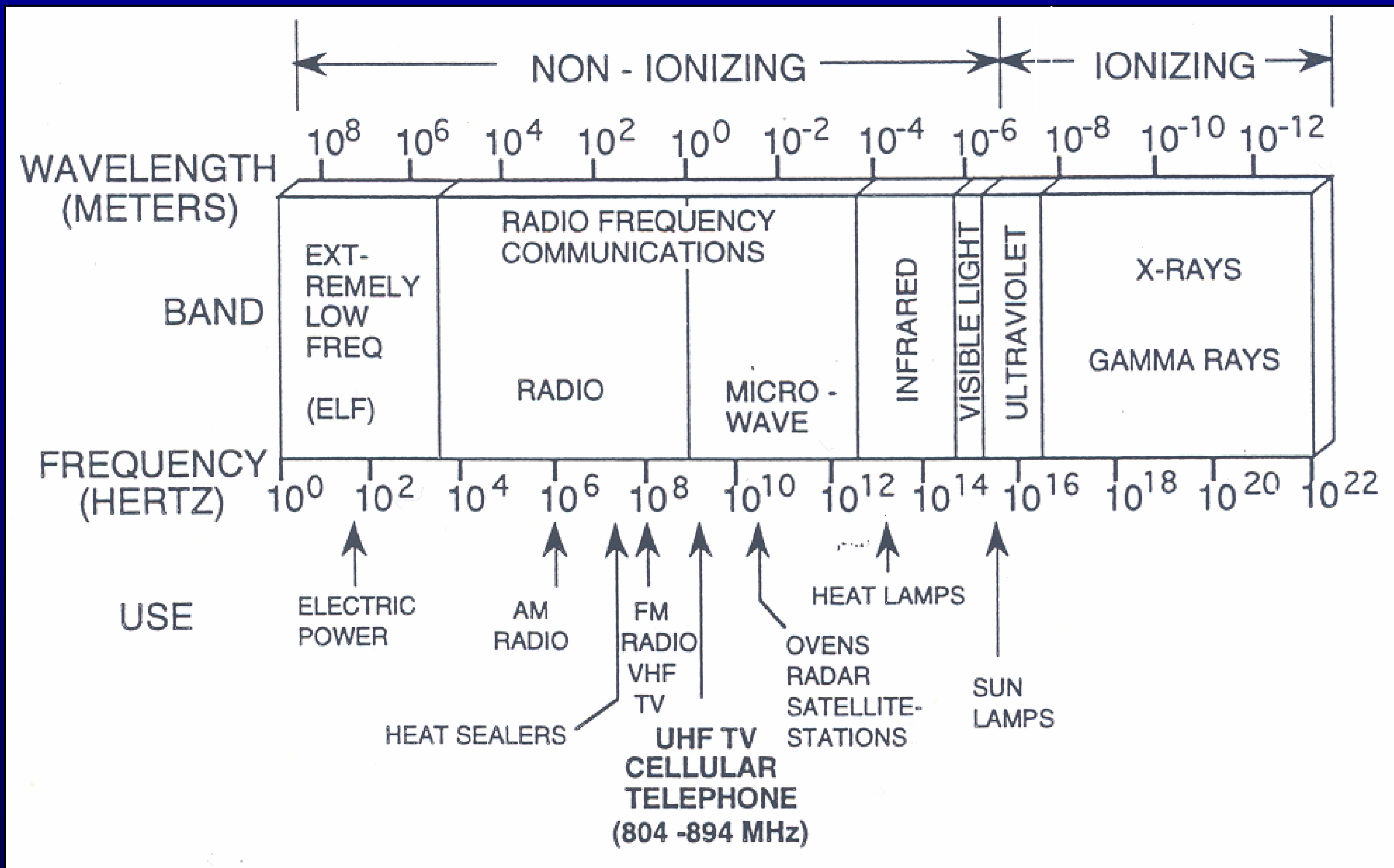
- Types and characteristics of radiation
- Interaction of radiation with living tissue
- Acute and delayed biological effects
  - Focus on cancer
- Sources of human exposure (past, present and future)

Course Overview (cont'd)

- Epidemiologic studies & risk estimation
  - Major theme: importance of dosimetry
  - Challenges to the study of low-dose effects
- Use of epidemiologic & experimental data for radiation protection
- Risk communication & radiation risks in perspective

“Radiation” = radiant energy

Electromagnetic Spectrum



From: Rothman *et al.*; *Epidemiology* 1996;7:291

Photon Energy

- "Photon" = packet of energy
- Energy directly proportional to frequency and inversely proportional to wavelength
- Photon energy (keV) = 12.4 ÷ wavelength (angstroms)

(I keV=1.6 x 10^{-9} ergs)

Characteristics of Ionizing Radiation

- Energetic
  - 10-15 electron volts required to eject electron
- Penetrating

  … to a varying extent, depending on radiation type and energy (less so for alpha-particles)
  - Unaffected by cellular boundaries; all parts of cell equally vulnerable
- Energy deposition occurs randomly in tissue
- Capable of causing most types of cancer, and variety of other effects, immediate & delayed

Characteristics of UV Radiation

- Non-penetrating
- Insufficient energy per quantum (photon) to cause ionization (except for very short λ)
- Chemical change may result from molecular *excitations*
- Known skin carcinogen
- Also: erythema, cataracts, eye injury, possible effects on immune system

Long-wavelength Radiations (e.g., Microwaves, ELF)

- Penetrate tissue (extent inversely-associated with frequency)
- Biological effects primarily due to heating and induced fields and currents
- Direct genotoxic effects unlikely
- No clear evidence of carcinogenicity

Microwave Radiation

From: National Radiological Protection Board. 1998. *Living with radiation*

Radiation vs. Chemical Toxins

- Radiation deposits energy at random within tissues
- Mechanisms operating for chemical agents absent with (external) radiation
  - Absorption, excretion, receptors, membranes, metabolic activation/deactivation

Radiation vs. Chemical Carcinogens

- Radiation is more easily measurable & “dose” has precise meaning
  - Have much more quantitative information for radiation than for chemical carcinogens
- Mechanisms of cancer induction by radiation & some chemical carcinogens may be similar
- Radiation as a model for action of chemical carcinogens and mutagens at level of DNA?
  - e.g., free radicals

Types of Ionizing Radiation

- Electromagnetic
  - X-rays and gamma-rays
  - Identical as to type but differ as to source
  - Gamma-rays generally of higher energy
- Particulate
  - Alpha-particles: positive charge (helium nucleus)
  - Beta-particles: negative charge (electron)
  - Neutrons: uncharged
  - Protons: positive charge

Interaction of Ionizing Radiation with Tissue

charged particles

↓

electrical interactions

↓

ionization

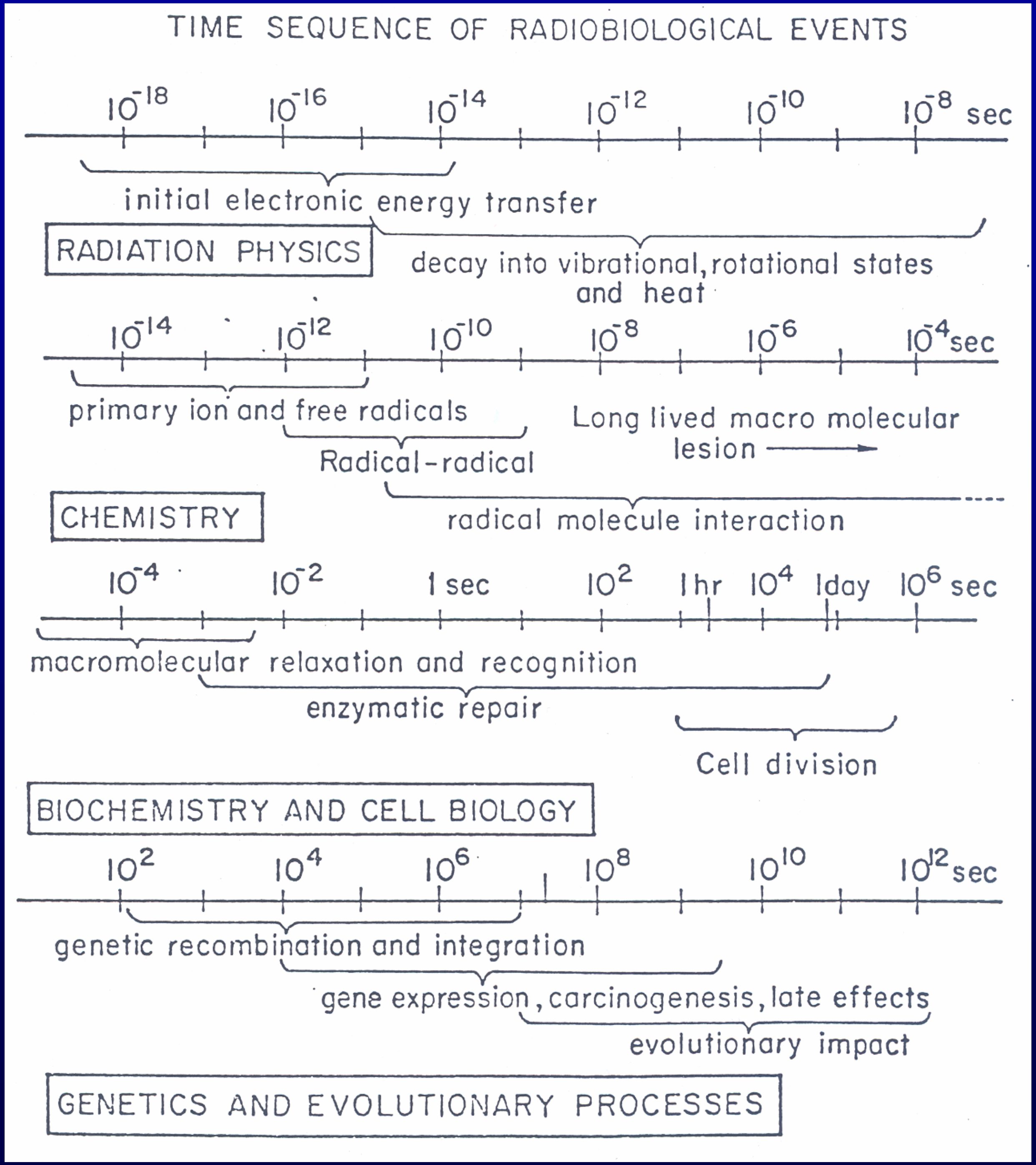
↓

chemical changes

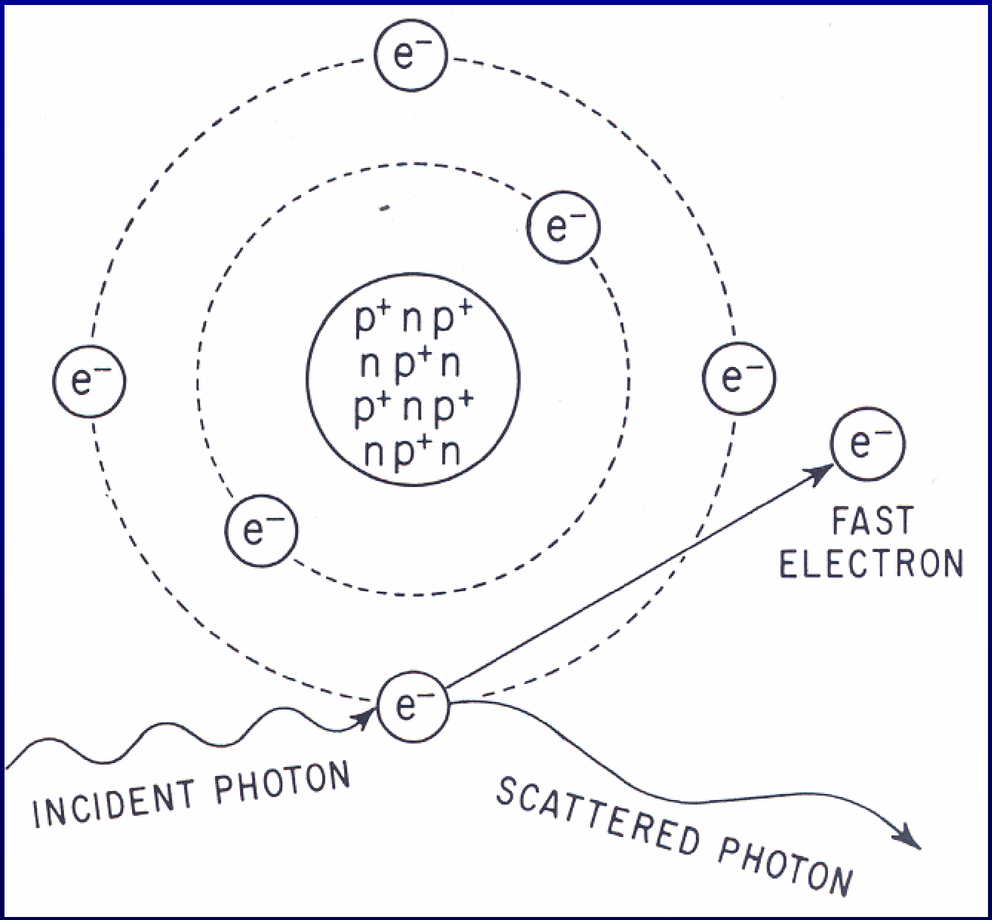
↓

biological effects

From: National Radiological Protection Board. 1998. *Living with radiation*

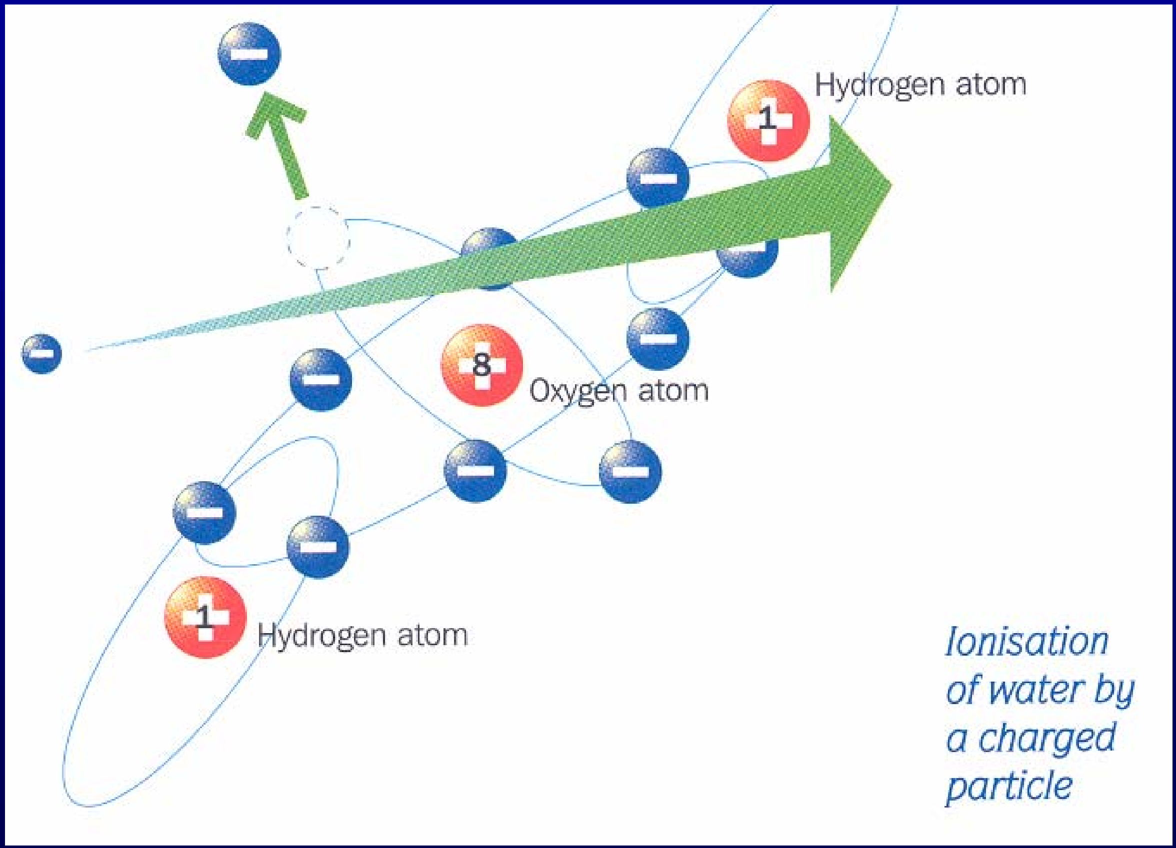

TIME SEQUENCE OF RADIOBIOLOGICAL EVENTS
10^{-18} 10^{-16} 10^{-14} 10^{-12} 10^{-10} 10^{-8} sec
initial electronic energy transfer
RADIATION PHYSICS
decay into vibrational, rotational states and heat
10^{-14} 10^{-12} 10^{-10} 10^{-8} 10^{-6} 10^{-4} sec
primary ion and free radicals
Long lived macro molecular lesion
Radical-radical
CHEMISTRY
radical molecule interaction
10^{-4} 10^{-2} 1 sec 10^{2} 1 hr 10^{4} 1 day 10^{6} sec
macromolecular relaxation and recognition
enzymatic repair
Cell division
BIOCHEMISTRY AND CELL BIOLOGY
10^{2} 10^{4} 10^{6} 10^{8} 10^{10} 10^{12} sec
genetic recombination and integration
gene expression, carcinogenesis, late effects
evolutionary impact
GENETICS AND EVOLUTIONARY PROCESSES

Ionization by X-rays or γ-rays



Hall (1994)

Ionization of Water By Charged Particle



From: National Radiological Protection Board. 1998. *Living with radiation*

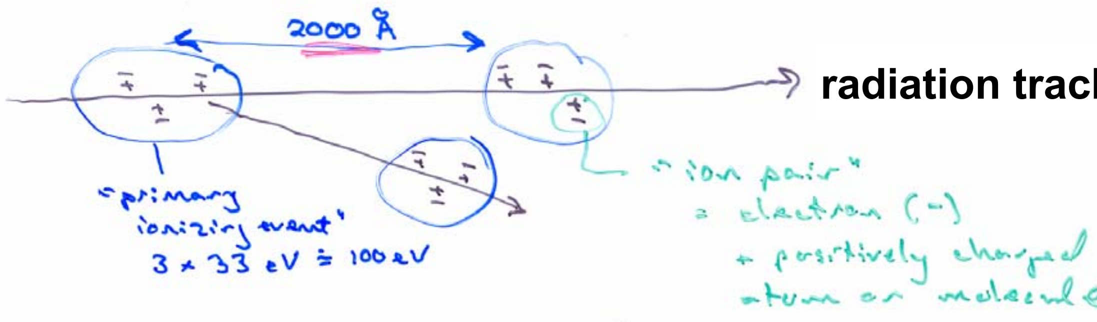
Energy Deposition

- Distributed randomly in discrete packets ("primary ionizing events")
- Average of three ion pairs (e.g., e^- and H_2O^+) produced per primary event
- Ionizing radiation causes molecular excitations as well as ionizations + some energy lost as heat
- → average of 32-34 eV of energy deposited for each ionized atom or molecule, even though only 10-15 eV required to eject single electron

- Physics of energy deposition different for neutrons and alpha-particles, but biological effects still mediated through charged particles, electrical interactions and resultant ionizations
- Radiations differ as to the density of ionizations produced and the degree of penetration of tissue
- Accounts for differences in biological effects

Ionization Density

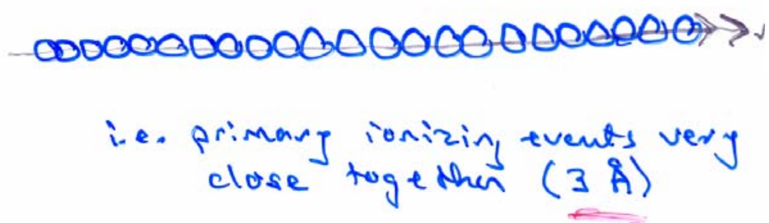
Low density
e.g., cobalt-60
γ-rays



radiation track

Sparsely-ionizing radiation
(low ionization density)
(low linear energy transfer, LET)

High density
e.g., α-particles



radiation track

High ionization density
(high LET)

Linear Energy Transfer (LET)

- Measure of density of ionizations along path of ionizing particle or wave
- Dimensionality: energy per unit distance (keV/μ)
- Only <u>physical</u> difference among radiation types that influences biological damage produced

Linear Energy Transfer (LET)

Low-LET radiations

X-rays, γ-rays, β-particles

High-LET radiations

α-particles, neutrons, protons

- Each ionization event involves loss of energy

→ high ionization density is associated with rapid loss of energy & lesser penetration

Penetration, By Radiation Type

Radiation Type	Penetration	Extent of Exposure
Alpha (α)	0.05 mm	confined to specific cells in organ
Beta (β)	1-2 cm	confined to particular tissue
Gamma (γ)	10-20 cm	less localized, potentially whole-body

Radiation Chemistry

- Cells > 80% water $\rightarrow$ > 80% of energy will be deposited in water
- Radiation chemistry of water is important
- Radiation + water $\longrightarrow$ free radicals
- Enhanced by presence of O_2

Radiation Chemistry of Water

$$\text{x-rays} + H_2O \longrightarrow H_2O^{+} + e^{-}$$

$$e^{-} + H_2O \longrightarrow H_2O^{-}$$

$$H_2O^{+} \longrightarrow H^{+} + OH\bullet$$

$$H_2O^{-} \longrightarrow OH^{-} + H\bullet$$

$$H^{+} + OH^{-} \longrightarrow H_2O$$

Net Reaction: $\text{x-rays} + H_2O \longrightarrow H\bullet + OH\bullet$

Radiation Chemistry (cont'd)

- Ionizing radiation is potent inducer of free radicals
- Free radicals can attack cellular macromolecules, including DNA
  – Important mediators of radiation damage
- Modifiers of free radical formation or removal can modify radiation effects

Energy Deposition Relative to Lethal Radiation Dose

- *Local* energy levels around primary ionization events very high, BUT …
- Temperature rise for cell very small for lethal dose
- If all energy were converted to heat, would increase temperature of cell by 0.001° C

Example from Hall (1994):

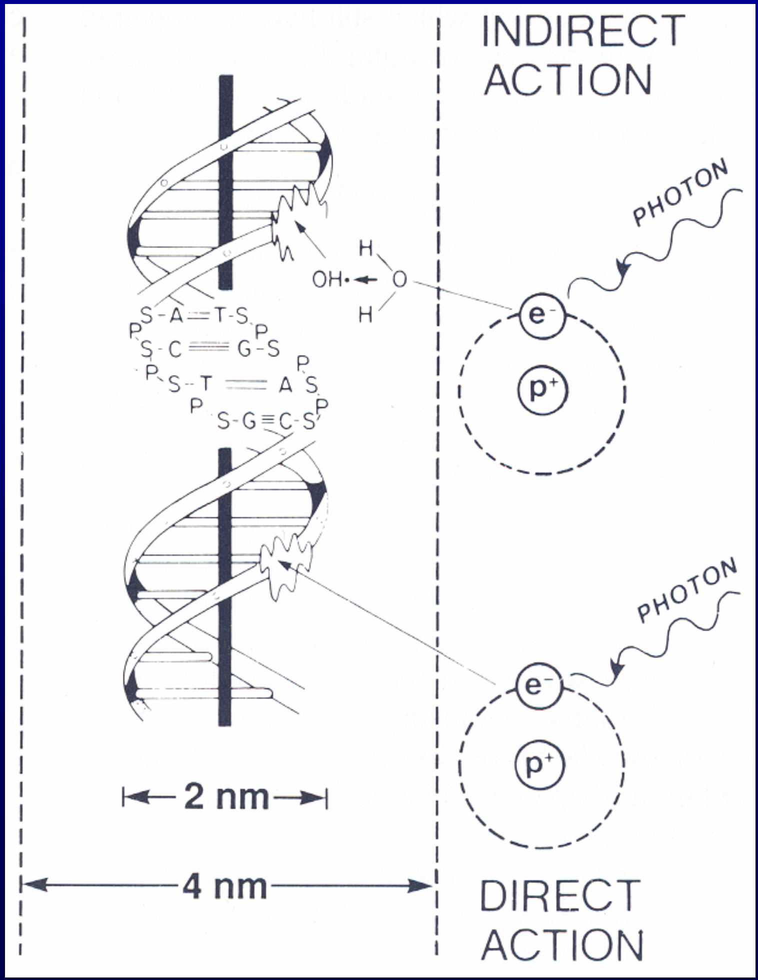
- Total energy absorbed in 70 kg human exposed to LD_{50} of 4 Gy of X-rays = 67 calories
- Equal to energy absorbed from drinking 1 sip of hot coffee
- i.e., *biological effect of radiation does not depend on amount of energy absorbed, but on the photon ("packet") size of the energy*

Energy Deposition Relative to Lethal Radiation Dose

- Proportion of ionized molecules in cell at lethal radiation doses is very small
  $\longrightarrow$ affected macromolecules must be very important

- DNA as a likely essential target

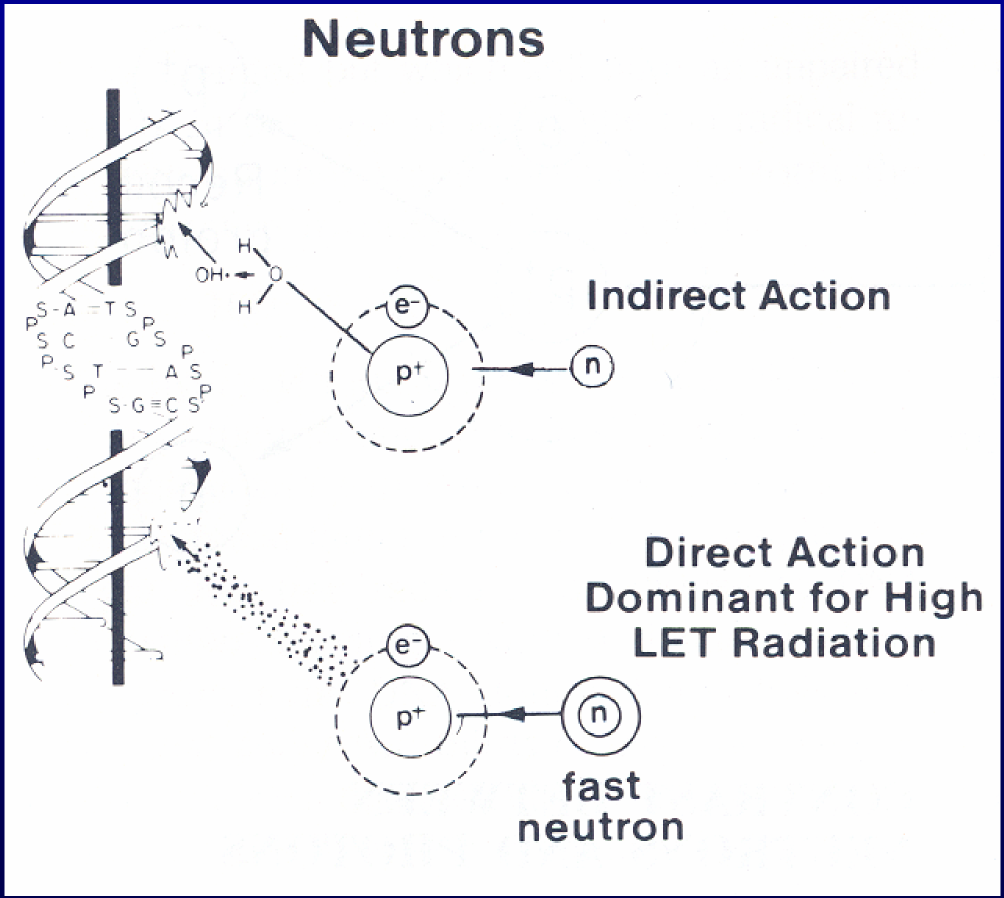
Direct versus Indirect Effects of Radiation On DNA: γ- or x-rays



Indirect action dominant for low LET radiation

Hall (1994)

Direct versus Indirect Effects of Radiation On DNA: neutrons



Hall (1994)

Exposure Parameters Influencing Biological Events

- Dose
- Linear energy transfer (LET)
- Anatomic distribution of dose
  - Whole-body (e.g., atomic bomb explosions)
  - Partial-body (e.g., radiotherapy)
- Dose-rate
  - Instantaneous vs. protracted or fractionated exposures
  - Effect depends on radiation type and endpoint

(Ionizing) Radiation Dose

- Absorbed dose (energy per unit mass)
  - I Gray (Gy) = I joule per kg = 100 cGy (rad)
- Equivalent dose
  - ≈ Absorbed dose x quality factor (QF)
  - takes account of differences in effectiveness (harmfulness) of different types of radiation
  - 1 Sievert (Sv) = 100 rems
  - QF = 1 for x-rays, γ-rays and β-particles
  - QF ≈ 10 for neutrons & 20 for α-particles

Radiation Exposure

- Dose in air (energy imparted per gram of air) ≈ exposure dose to skin
- Unit = Roentgen (R)
- 1 R of exposure $\longrightarrow$ absorbed dose in soft tissue of 0.97 cGy
- No longer widely used

Exposure Parameters Influencing Biological Events

- Dose
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Linear Energy Transfer (LET)

- Only <u>physical</u> difference among radiation types that influences biological damage produced
- i.e., density of ionizations along path of radiation as critical determinant of biological effect

Relative Biological Effectiveness (RBE)

Definition (from BEIR V): "Biological potency of one radiation as compared to another to produce the same biological endpoint"

- Equals inverse of ratio of absorbed doses required to produce equal effect
- Varies with the endpoint
- Generally higher for high-LET radiation
- Common reference: 200-kV x-rays
  - e.g. an RBE=20 implies the radiation is 20-fold more effective than 200 kV x-rays

Exposure Parameters Influencing Biological Events

- Dose
- Linear energy transfer (LET)
- Anatomic distribution of dose
  - Whole-body (e.g., atomic bomb explosions)
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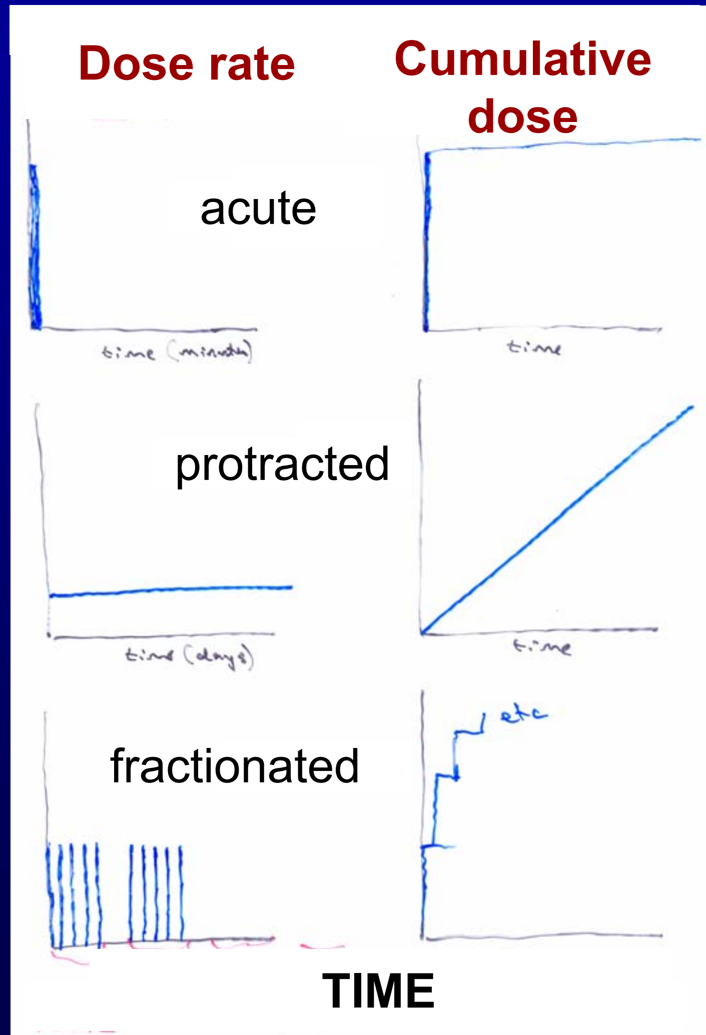
Dose-Time Relationships

Dose rate or Dose



“Radioactivity”

- To say that a material is radioactive is to say that it includes unstable atoms
- Stability is determined by relative number of neutrons and protons
- When instability is present, nucleus ‘tries” to achieve stability by altering relative number of neutrons and protons
- Conversion of mass to energy in nucleus

  $\longrightarrow$ high-energy emissions (e.g., α, β, γ)

Definitions

- Nuclide: species of atom characterized by its number of protons, number of neutrons & energy content (e.g., carbon-12)
- Radionuclide: unstable nuclide that emits ionizing radiation (e.g., carbon-14)
- Isotopes: nuclides with same number of protons (atomic number) but different numbers of neutrons

Radionuclides

Activity

Decay rate (rate of transformations) in a radionuclide

Unit = becquerel (Bq) = 1 transformation per second

1 Curie (Ci) = 3.7×10^{10} Bq

Half-life of radionuclide

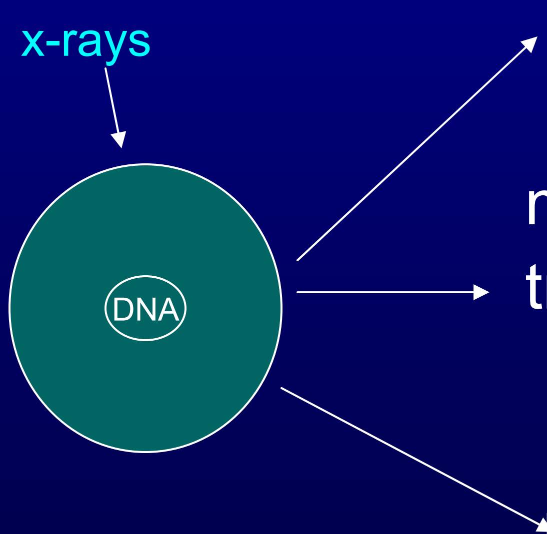
Time for half of the nuclei in the sample to decay

Examples:		
	Iodine-131	8 days
	Cesium-137	30 years
	Carbon-14	5,730 years
	Plutonium-239	24,000 years
	Uranium-238	4,470 million years

Biological Effects of Ionizing Radiation

Biological Effects of Ionizing Radiation

	Cellular Effects		Organismal Effects
	cell-killing	→	acute (& delayed) somatic effects, developmental effects
	malignant transformation	→	carcinogenesis
	↑		
	mutations	→	genetic (hereditary) effects



Biological Effects of Ionizing Radiation: Cell-Killing

- Immediate ("interphase") death
  - uncommon; typically only at very high doses
- Reproductive (proliferative) failure
  - Mitotic inhibition
  - Leads to acute somatic effects (& some late effects)
  - No cytologic damage immediately after irradiation
  - Cell may undergo several divisions before failure occurs
  - No effect in nonproliferating cells ("radioresistance")
- *Proliferative failure is the primary effect of radiation on cells*

Acute Somatic Effects of Radiation

- Due to killing of cells, generally in tissues where cells are rapidly proliferating
- Radiosensitivity
  - Proportional to reproductive activity and dividing future
  - Inversely proportional to degree of differentiation

Types of Cell Populations

- Static
  - No mitotic activity
  - Examples: neurons, striated muscle
- Expanding
  - Mitotic activity adjusted to increase in cell number during growth; eventually becomes static
- Renewing (cell renewal systems)
- Conditional cell renewal systems

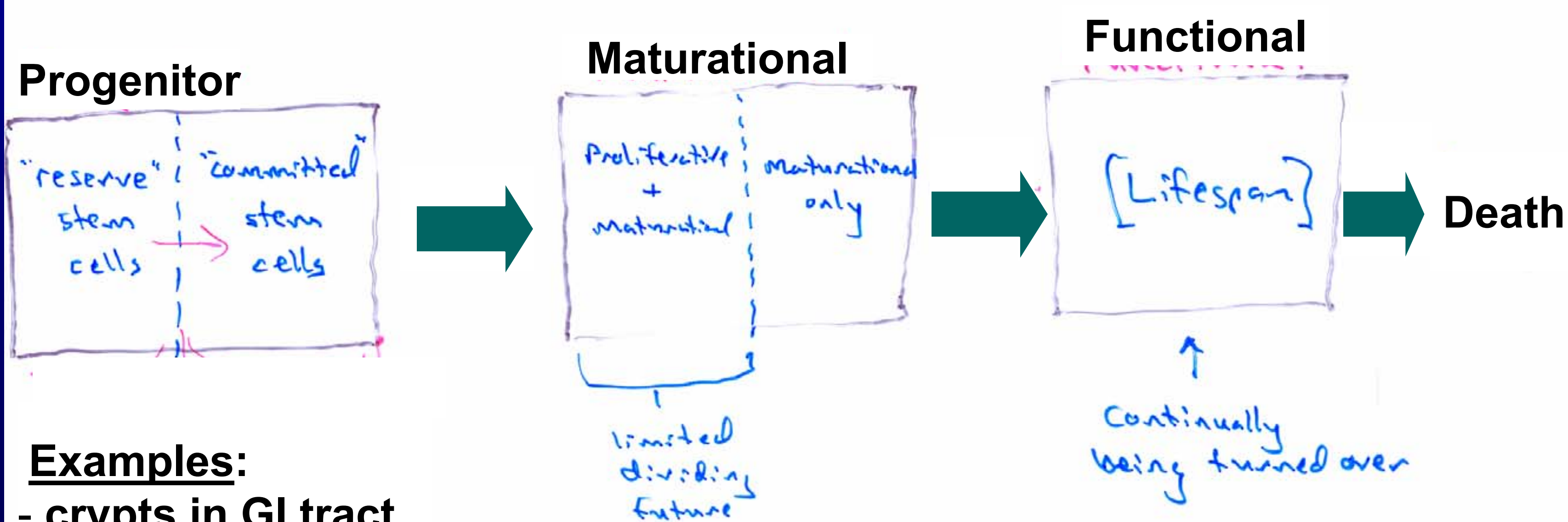
Cell Renewal Systems

- Mitotic activity exceeds that required to sustain growth
- Mature cells lost
- Examples: most cell types

< 1%/day new cells: liver, kidneys, blood vessels, connective tissue

>1%/day: e.g., blood-forming tissue, GI tract

Compartments in Cell Renewal Systems



<u>Examples</u>:
- **crypts in GI tract**
- **marrow stem cells**

Approximate Turnover Times in Functional Cell Compartments

Blood:	RBCs	120 days
	Granulocytes	10 hours
	Lymphocytes	up to many years
	Platelets	10 days
GI tract:	Oral cavity	5 days
	Stomach	3-9 days
	Small intestine	1.5 days
	Colon	10 days

Based mostly on animal data

General Radiation Effects in Cell Renewal Systems

- Killing of stem cells → eventual depletion of functional cells (loss w/o replacement)
- Timing of appearance of somatic effects depends on lifespan of functional cells
- *Understanding of kinetics of cell renewal systems is central to understanding of radiation effects*

Survival in Humans Following Acute, Whole-Body Exposure

< 1 Sv	rarely symptomatic
2 Sv	all persons show some symptoms
4-5 Sv	fatal in about 50% of previously healthy people (LD_{50})
≥ 8 Sv	almost universally fatal within 2 weeks
≥ 100 Sv	death within 1-2 days (CNS effects)

Acute Somatic Effects

- Effects on GI tract occur w/in few days, whereas effects on hematopoietic system occur over a few weeks
  - GI tract death = early death ("5-day death")
  - Bone marrow death = 25-28 day death
- GI tract stem cells more radio-resistant than bone marrow stem cells
- Higher dose required to see GI tract symptoms
- When you do, effects likely to be lethal (> 6-7 Gy)

Delayed Somatic Effects

- Radiation nephritis, pneumonitis
  - Months to years after exposure
  - Associated with radiation therapy
  - Mediated through damage to vascular system
- CNS syndrome
  - *Very* high doses
  - Death w/in 1-2 days
  - Probably due to vascular effects
- Cataracts, sterility
  - Due to mitotic inhibition

Radiation and Cancer

- Radiation causes <u>most</u> types of cancer
  - Radiation as “universal carcinogen”?
  - Not quite, but close
- Does not appear to cause CLL, Hodgkin’s disease, cervical cancer, prostate cancer
  - Why not?
- Risk varies by dose, dose rate, LET, age at exposure, time since exposure, gender, other exposures, genetic constitution

"Stochastic" and "Non-Stochastic" Effects

Stochastic: *random* events leading to effects; probability of effect, but not its severity, depends on dose

e.g., cancer, genetic effects

Non-stochastic: severity of effect varies with dose, and threshold often exists

e.g., cataract, loss of hair or skin reddening, bone marrow depletion, impaired fertility

Erythema
(example of non-stochastic effect)

From: National Radiological Protection Board. 1998. *Living with radiation*

Biological Effects of Ionizing Radiation: Induction of Mutations

- Damage to genetic material of cell insufficient to influence its ability to proliferate
  - In somatic cells → long-term somatic effects (e.g., cancer)
  - In germinal cells → heritable effects
- Ionizing radiation is a relatively weak mutagen (relative to its cytotoxicity)

DNA Damage Caused by Radiation

- Single-strand breaks
  - Efficiently produced by radiation
  - Most rapidly repaired
- Double-strand breaks
  - Most lethal
  - Repaired incompletely or slowly
  - High-LET radiation more effective than low-LET
- Base damage
  - Degradation of bases (<u>common</u>)
  - Pyrimidine dimers produced by UV radiation

Chromosomal Damage

- Ionizing radiation is an efficient inducer of chromosomal aberrations (but not of point mutations)
- Gross aberrations (e.g., dicentrics) generally → cell death
- Translocations tend to persist
  - Genes in new locations → altered gene expression, which can lead to cancer
  - Potential applications in biodosimetry

Repair and Recovery Processes

- Repair at tissue level
  - Due to replacement/repopulation by surviving cells
- Intracellular recovery
  - Phenomenological observation
  - Due to repair of sublethal or potentially lethal damage?
- Molecular repair
  - Restoration of damaged DNA
  - May be related to intracellular recovery & tissue repair

Development of Radiation Injury

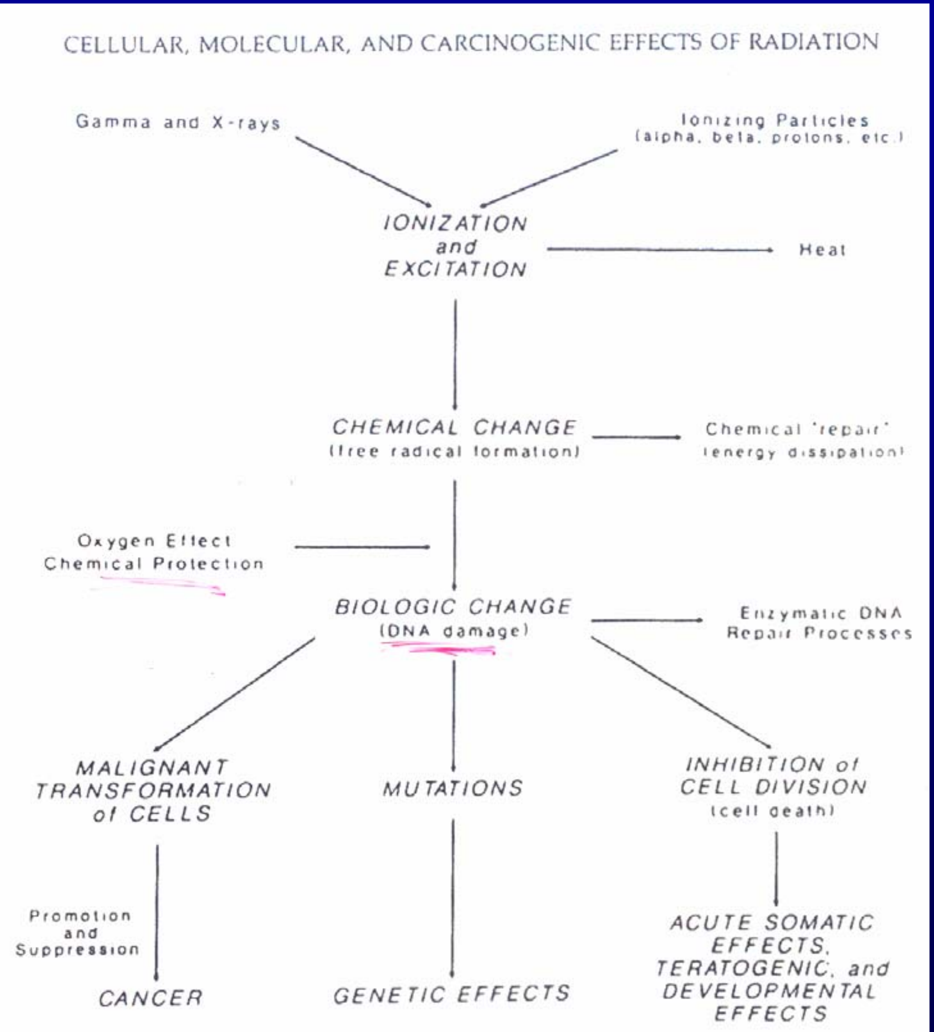


Figure 1. Development of radiation injury.

Little and Williams (1977)

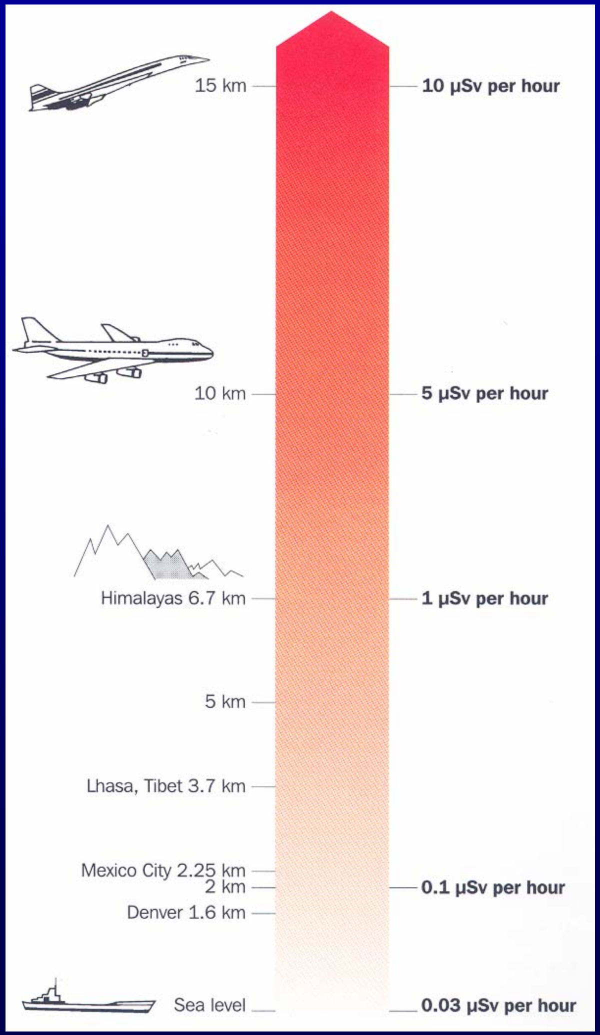
Sources of Human Exposure to Ionizing Radiation

- Natural background radiation
- Man-made sources
  - Medical
  - Occupational
  - Military
  - Environmental

Natural Background Radiation

- Cosmic radiation
  - Primarily neutrons and γ-radiation
  - Exposure varies with altitude
- External γ-radiation
  - Naturally-occurring isotopes of uranium series
  - Depends on local geology & type of building material
- Internal emitters
  - Radon gas

Cosmic Radiation, By Altitude



10 μSv/hr

1 μSv/hr

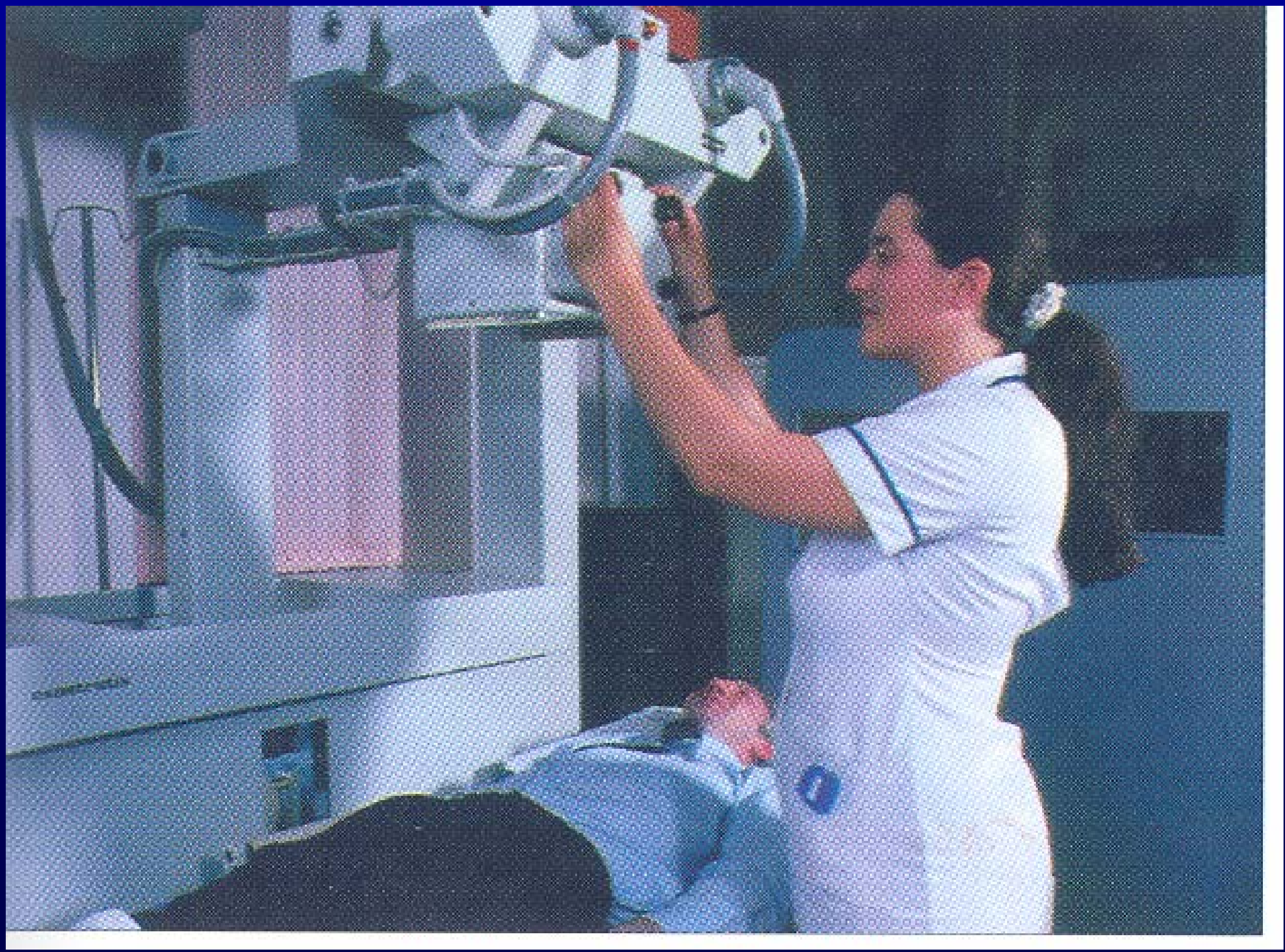
0.03 μSv/hr

From: National Radiological Protection Board. 1998. *Living with radiation*

Medical Radiation Exposures

- Diagnostic x-rays
  - High frequency of population exposure, but cancer risks likely small
- Radiation therapy
  - Opportunities for good radiation dosimetry
  - Interactions
- Nuclear medicine

Medical Radiography



From: National Radiological Protection Board. 1998. *Living with radiation*

Computed Tomography (CT) Scan

From: National Radiological Protection Board. 1998. *Living with radiation*

Doses From Conventional X-ray and Computed Tomography Exams

	Dose (mSv)	
Examination	X-ray	CT
Head	0.03	2
Teeth	<0.1	-
Chest	0.02	8
Abdomen	0.7	10
Pelvis	0.7	10
Lower spine	0.7	6
Lower GI	7	-

From: National Radiological Protection Board. 1998. *Living with radiation*

Occupational Radiation Exposures

- Nuclear industry
- Medical radiation workers
  - radiologists, x-ray technologists
- Increased exposure to background radiation for some occupations
  - e.g., miners, airline pilots & attendants
- Radium dial painters (historical)

Typical Doses on Flights from London

Flight No.	Destination	Flight Time (h)	Dose (mSv)
NR14	Paris	1	0.004
RP15	Madrid	2	0.010
NR23	Rome	3	0.014
RP18	Kiev	4	0.018
PB71	New York	7	0.042
PB77	Los Angeles	13	0.069
PB93	Tokyo	14	0.078

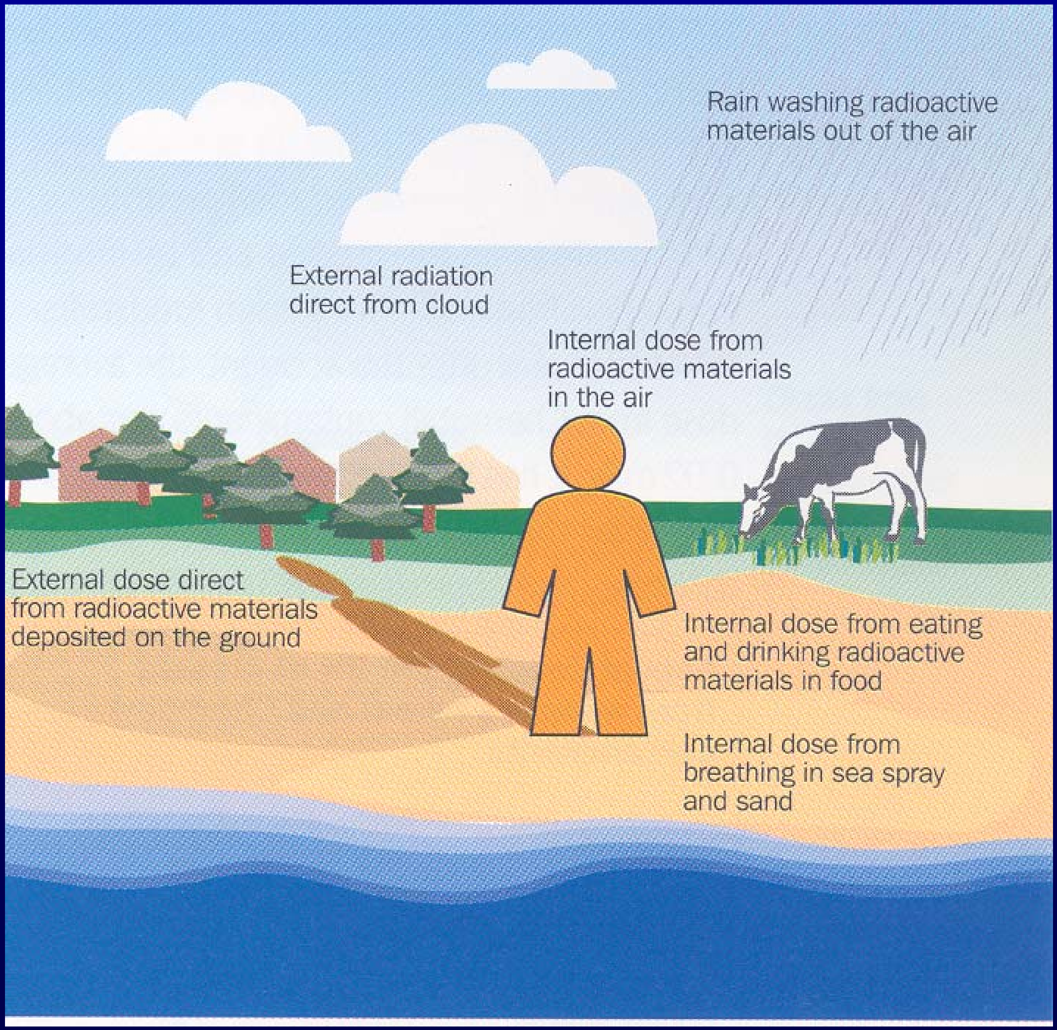
For comparison, 24 hours on the ground would result in a dose of 0.002 mSv from cosmic and terrestrial sources.

From: National Radiological Protection Board. 1998. *Living with radiation*

Military & Environmental Exposures

- Atomic bomb explosions in Japan
  - Single most important source of information on radiation effects
- Fallout from weapons tests
  - Estimate your thyroid dose & thyroid cancer risk (http://ntsi131.nci.nih.gov) from U.S. tests
- Nuclear reactor accidents
  - e.g., Chernobyl

Pathways of Environmental Exposure

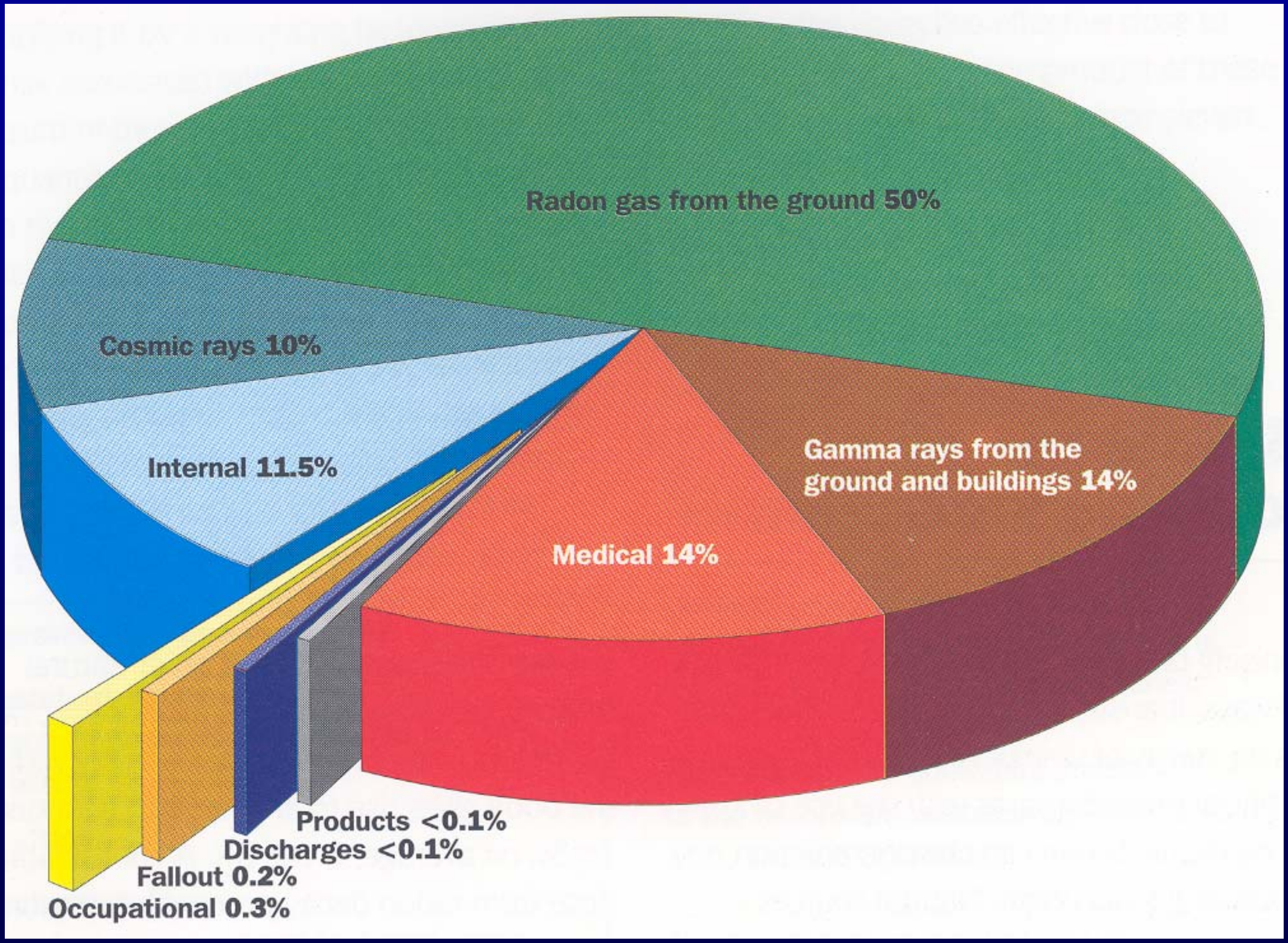


From: National Radiological Protection Board. 1998. *Living with radiation*

Internal Radiation Exposures

- Organ- or tissue-specific concentration of radionuclides
  - e.g., radioiodines in thyroid gland
- Biological effect depends on dose to critical (target) cells within a specific tissue
- Contrast with external exposure, for which dose to tissue is more uniform

Sources of Radiation Exposure



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Average Annual Dose (all sources)

0.15 to 0.20 rem = 0.0015 to 0.0020 Sv
= 1.5 to 2.0 mSv

Over 80-year lifetime: 120 to 160 mSv
(12 to 16 rem)

Radiation Epidemiology

Radiation Epidemiology

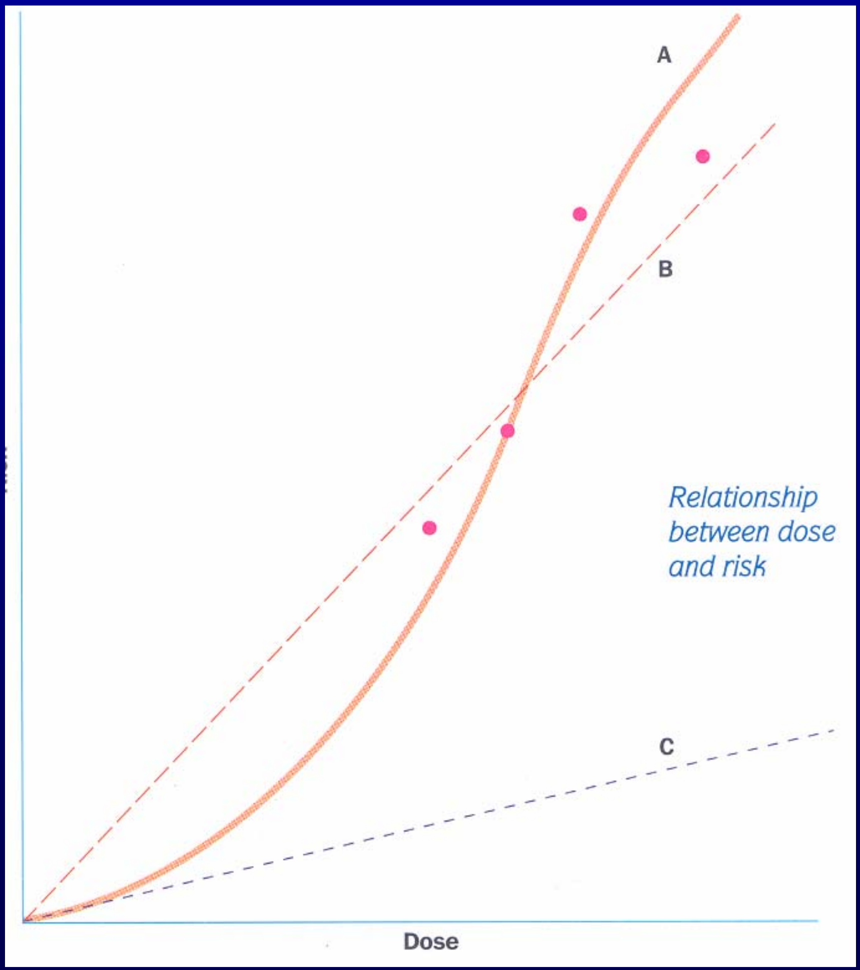
- Understanding of radiation effects in humans has come from epidemiology
  - A-bomb, medical, occupational, environmental, background
- Ionizing radiation is a well-established carcinogen
- Variation in organ/tissue sensitivity
  - Highly sensitive: bone marrow, thyroid gland, breast, lung

General Research Aims

- Dose-response
  - Quantitative estimates of risk
  - Risk at low doses & dose rates
- Influence of radiation type
- Expression of excess risk over time
  - Relation to background incidence
- Dependence on host characteristics
- Joint effects of radiation and other exposures
- Insights into mechanisms

Radiation Dose and Risk

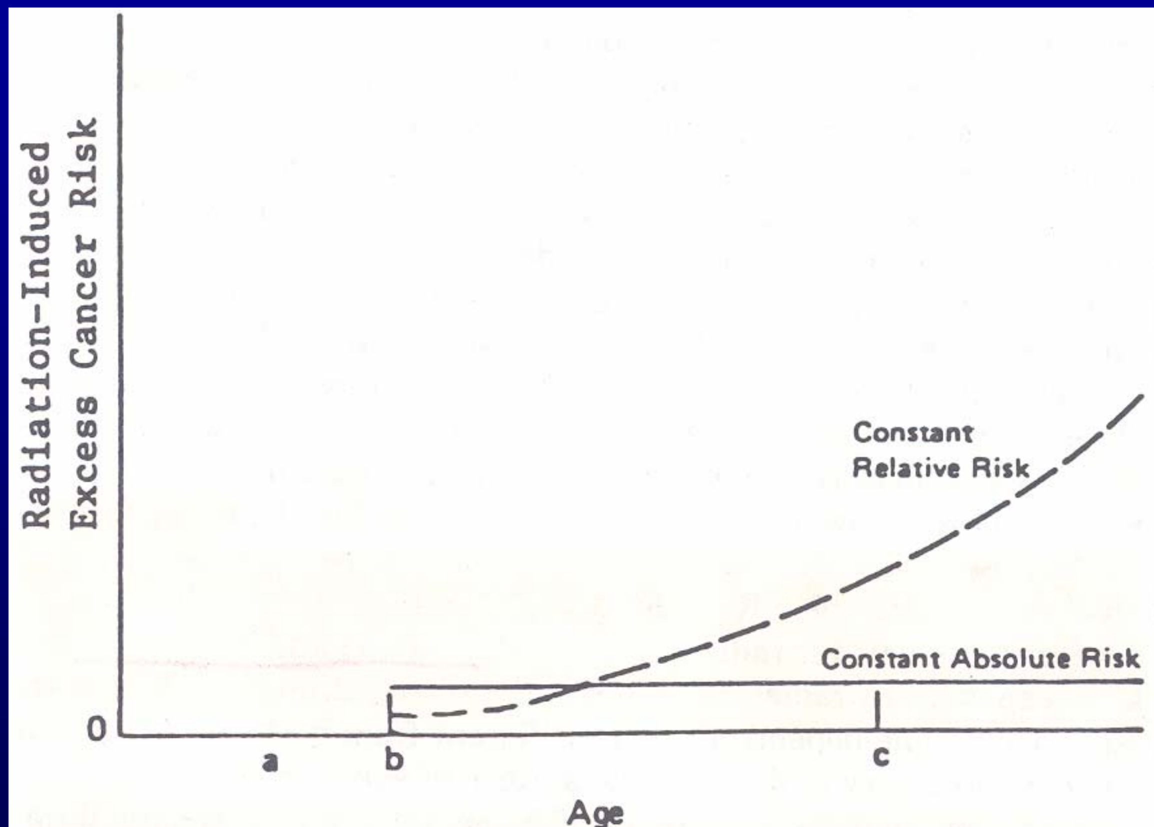
Risk



Dose

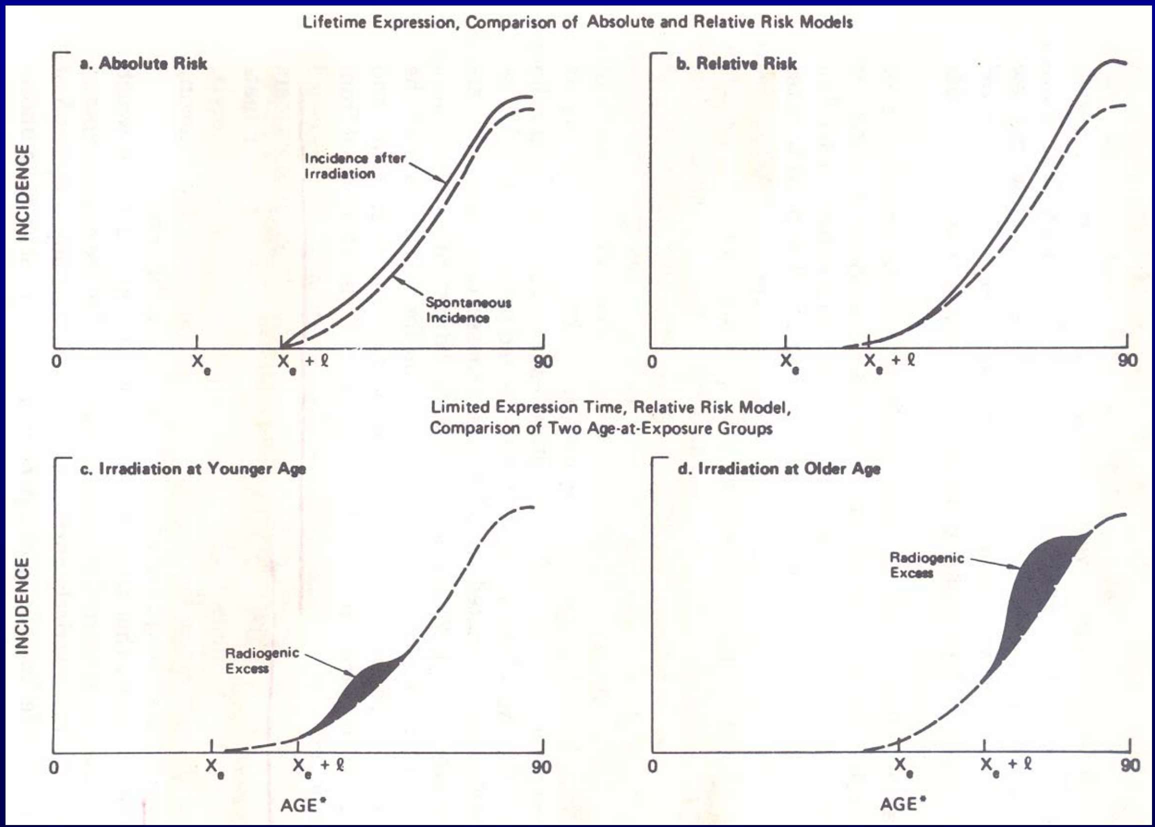
NRPB 1998

Time-Response Models for Radiogenic Cancer



From: Boice et al. (1985), after BEIR 1980

Possible Relations of Radiogenic Excess Cancer to Background



From: Boice et al. (1985), after BEIR (1980)

Importance of Radiation Relative to Other Causes of Cancer Mortality

	% Deaths in U.S.	
Due to:	Best Estimate	Range
Tobacco	30	25 – 40
Diet	35	10 – 70
Geophysical factors*	3**	2 - 4

* Includes UV and ionizing radiation;

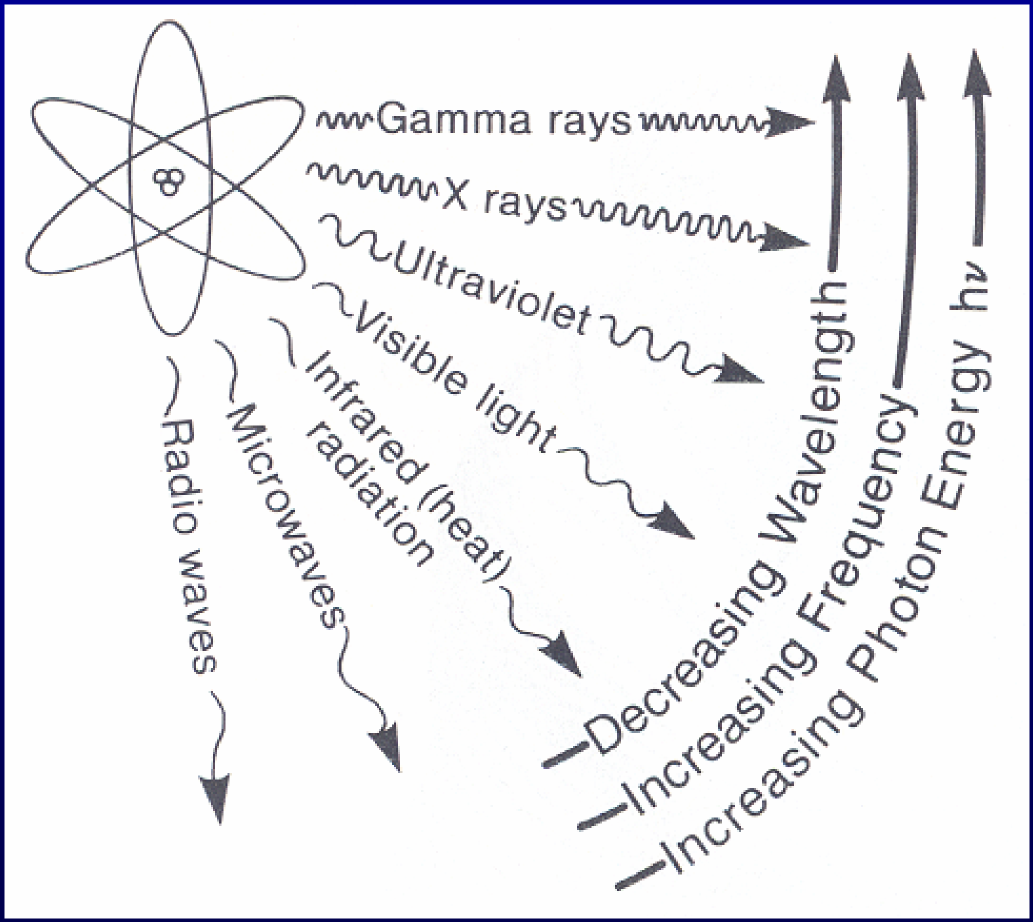
**Up to 30% of *non-fatal* cases, due to UV-induced skin cancers

From: Doll and Peto; *JNCI* 1981;66:1191

Applications of Radiation Epidemiology

- Inform radiation protection policy, risk assessment, decision-making
  - Some exposures are avoidable
  - Costs/benefits? (e.g., re: medical procedures)
- Legal proceedings, compensation
- Insights into radiobiology & cancer biology

Radiation Wavelength, Frequency & Energy

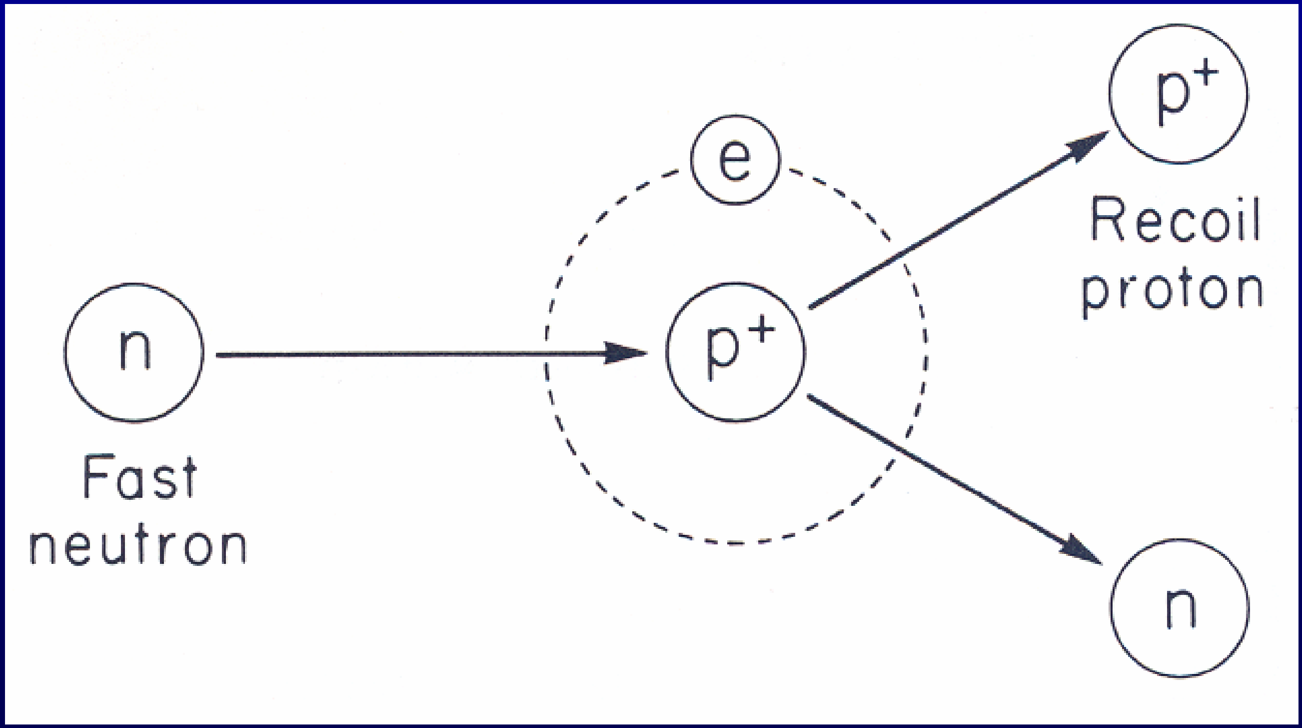


From: Hall EJ. *Radiobiology for the Radiologist*. 4th ed. Lippincott, Williams & Wilkins, 1994

Selected Issues in Study Design

- Magnitude and prevalence of exposure
- Statistical power/precision
  - low dose effects
  - Interactions
- Ability to estimate radiation doses for individuals
- Unbiased outcome ascertainment (e.g., cancer)
- Ability to control for confounding factors

Ionization By Neutrons



Hall (1994)

Radiation Risks in Perspective

Average annual risk of death in the UK from some common causes		
Smoking 10 cigarettes a day	5.0×10^{-3}	1 in 200
Heart disease	3.3×10^{-3}	1 in 300
All cancers	2.5×10^{-3}	1 in 400
All causes, 40 years old	1.4×10^{-3}	1 in 700
All radiation ($2.6\, mSv\, y^{-1}$)	1.3×10^{-4}	1 in 7 700
Accident in the home	6.9×10^{-5}	1 in 15 000
Accident on the road	5.9×10^{-5}	1 in 17 000
Homicide	1.0×10^{-5}	1 in 100 000
Nuclear discharges ($0.14\, mSv\, y^{-1}$)	7.0×10^{-6}	1 in 140 000
Pregnancy, for mother	6.0×10^{-6}	1 in 170 000

From: National Radiological Protection Board. 1998. *Living with radiation*

Future Issues in Radiation Epidemiology

- New medical exposures
- Possible application to radiological terrorism
- Interactions with host factors and environmental exposures
  - e.g. radiation & smoking
  - genetic susceptibility
- Insights to cancer mechanisms

Relationship Between Old and New Ionizing Radiation Units

Quantity	Old Unit	New Unit	Relationship
Activity	Curie (Ci)	becquerel (Bq)	1 Ci=3.7x10^{10} Bq
Absorbed dose	rad	gray (Gy)	1 rad=0.01 Gy
Equivalent dose	rem	sievert (Sv)	1 rem=0.01 Sv

From: National Radiological Protection Board. 1998. *Living with radiation*

Types of Cell Populations

- Static
  - No mitotic activity
  - Examples: neurons, striated muscle
- Expanding
  - Mitotic activity adjusted to increase in cell number during growth of animal
  - Eventually becomes static
  - Examples: glandular tissue

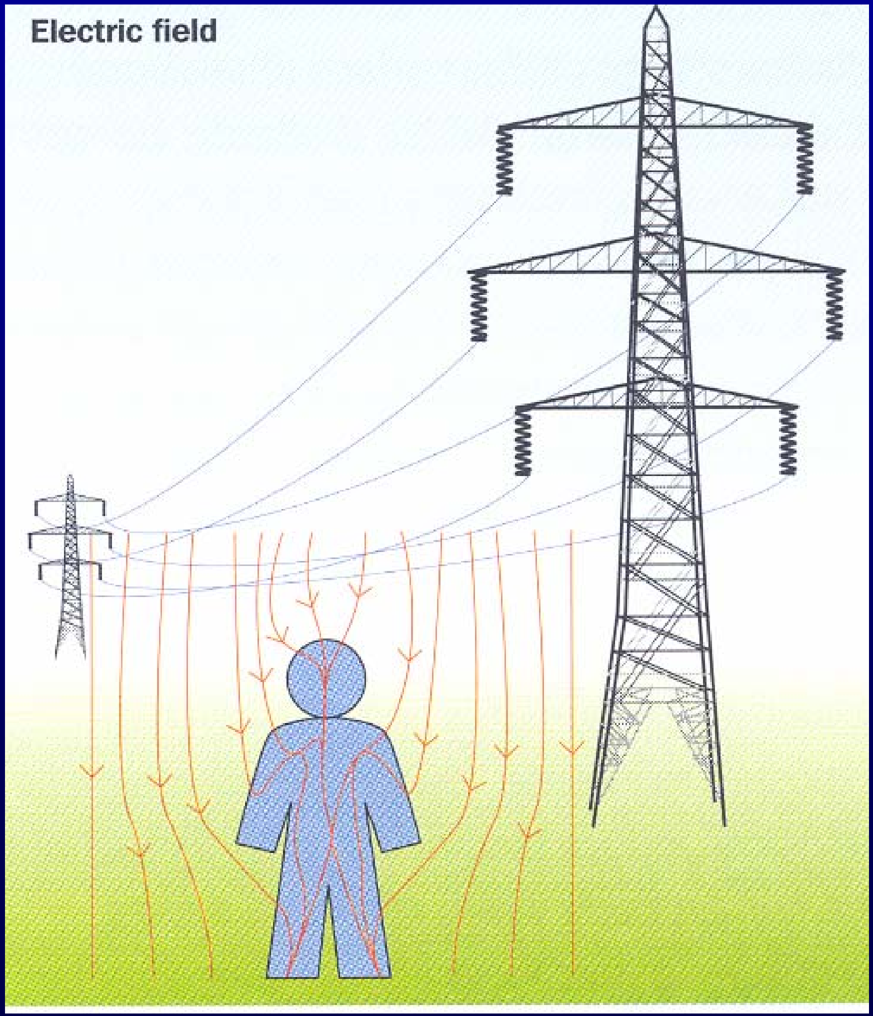
Stages in Radiation Interaction With Biologic Systems

- Physical stage (10^{-14} seconds)
- Chemical stage (10^{-7} to 10^{-4} seconds)
- Biological stage (seconds/lifetimes/generations)
  - Biochemical (seconds to hours)
  - Physiologic (hours to years)
  - Genetic & evolutionary (years to decades+)

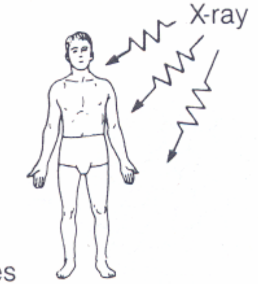
Types of Cell Populations

- Conditional cell renewal systems
  - Capable of renewal under special circumstances
  - Examples: liver, kidney

NRPB Dose by Airline Flights


Electric field

Total-Body Irradiation



Mass = 70 kg
LD/50/60 = 4 Gy
Energy absorbed =

$$70 \times 4 = 280 \text{ joules}$$
$$= \frac{280}{4.18} = 67 \text{ calories}$$

X-ray

A

Drinking Hot Coffee

Excess temperature (°C) = 60° − 37° = 23°
Volume of coffee consumed to
equal the energy in the LD/50/60 $= \frac{67}{23}$
= 3 mL
= 1 sip

B

Energy Deposition Relative to Lethal Radiation Dose

- Local energy levels around primary ionization events very high, BUT …
- Temperature rise for cell very small for lethal dose
  - If all energy were converted to heat, would increase temperature of cell by 0.001º C
- Proportion of ionized molecules in cell at lethal radiation doses is very small

→ affected macromolecules must be very important

→ DNA as a likely essential target

Course Objectives

Basic understanding of:

- Types and sources of radiation
- Interaction of radiation with living systems
- Acute and delayed effects of radiation exposure
- Radiation dosimetry & biodosimetry
- Major epidemiologic studies of cancer and radiation

Course Overview (cont'd)

- Issues in risk estimation and description
- Insights from experimental studies
- Application of findings to radiation protection
- New radiation exposures
- Risk communication

Course Overview

- Types & sources of radiation exposure
- Measurement of radiation exposures
- Interaction of radiation with living systems
  - Radiation physics, chemistry and biology
  - Biodosimetry
- Spectrum of health effects
  - Focus on cancer
- Major epidemiologic studies

Long-wavelength Radiations

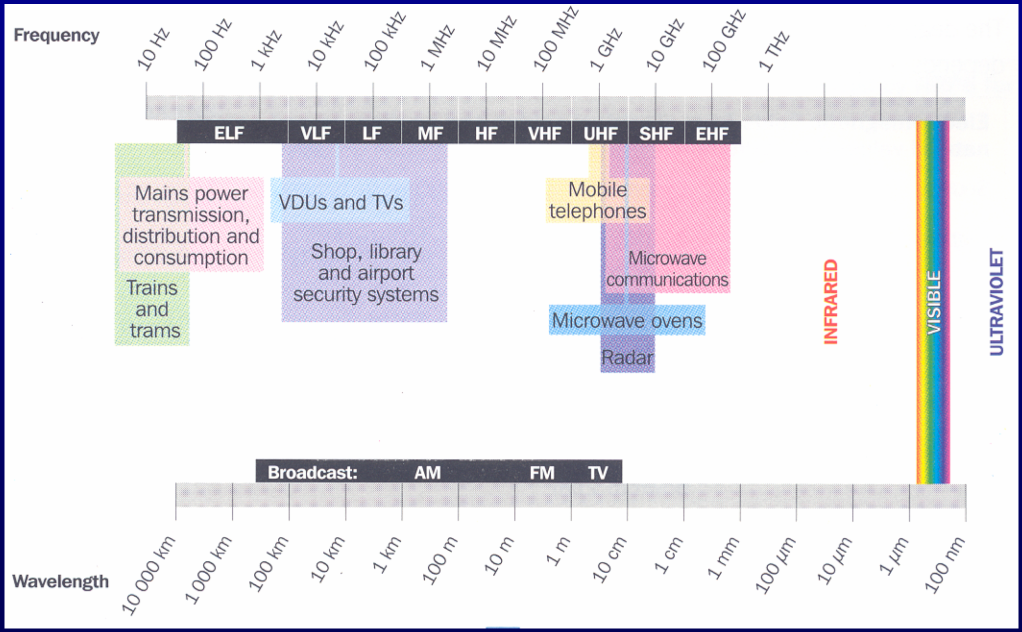
Optical Radiation

Photobiological divisions of the optical radiation spectrum with some early and late effects of overexposure

Spectral division	Wavelength range	Biological effects: On the eye	Biological effects: On the skin
UVC	100 nm – 280 nm		
UVB	280 nm – 315 nm	Photokeratitis	Erythema Tanning Cancers
UVA	315 nm – 400 nm	Photochemical cataract Lens yellowing	Photoageing Cancers
Visible	400 nm – 770 nm	Retinal injury	
IRA	770 nm – 1.4 μm	Thermal cataract Retinal injury (Lenticular lesions?)	Burns
IRB	1.4 μm – 3 μm	Corneal burn	
IRC	3 μm – 1 mm		

From: National Radiological Protection Board. 1998. *Living with radiation*

Electromagnetic Spectrum Non-ionizing Radiation



From: National Radiological Protection Board (NRPB).1998. *Living with radiation*

Radiation vs. Chemical Toxins

- Radiation has minor effects on cellular structures, metabolism or transport mechanisms, except at very high doses
- Under most circumstances, effects on DNA more important
- Environmental radiation can be easily detected and precisely measured
  - Have much more information re: cancer for radiation than for cancer
- Mechanisms of chemical carcinogens and radiation in induction of cancer may be similar
  - Radiation as a model for action of chemical carcinogens and mutagens at level of DNA?

How Does Radiation Cause Ionizations ?

- Ionization (damage) produced by electrical interaction with charged particles, whatever the nature of the incident radiation
- Radiations differ as to the density of ionizations produced and the degree of penetration of tissue
- Latter accounts for differences in biological effects

Cell Survival Curves

- Single-event curve (e.g. alpha particles)
- Multiple event curve (x- or gamma ray)

General Radiation Effects in Cell Renewal Systems

- Stem cells
  - Undergoing mitosis
  - Kinetics of killing similar to tissue culture cells *in vitro*
- Mature cells
  - No cell division
  - Interphase killing (rare)
  - Not affected by low to moderate doses (usually)

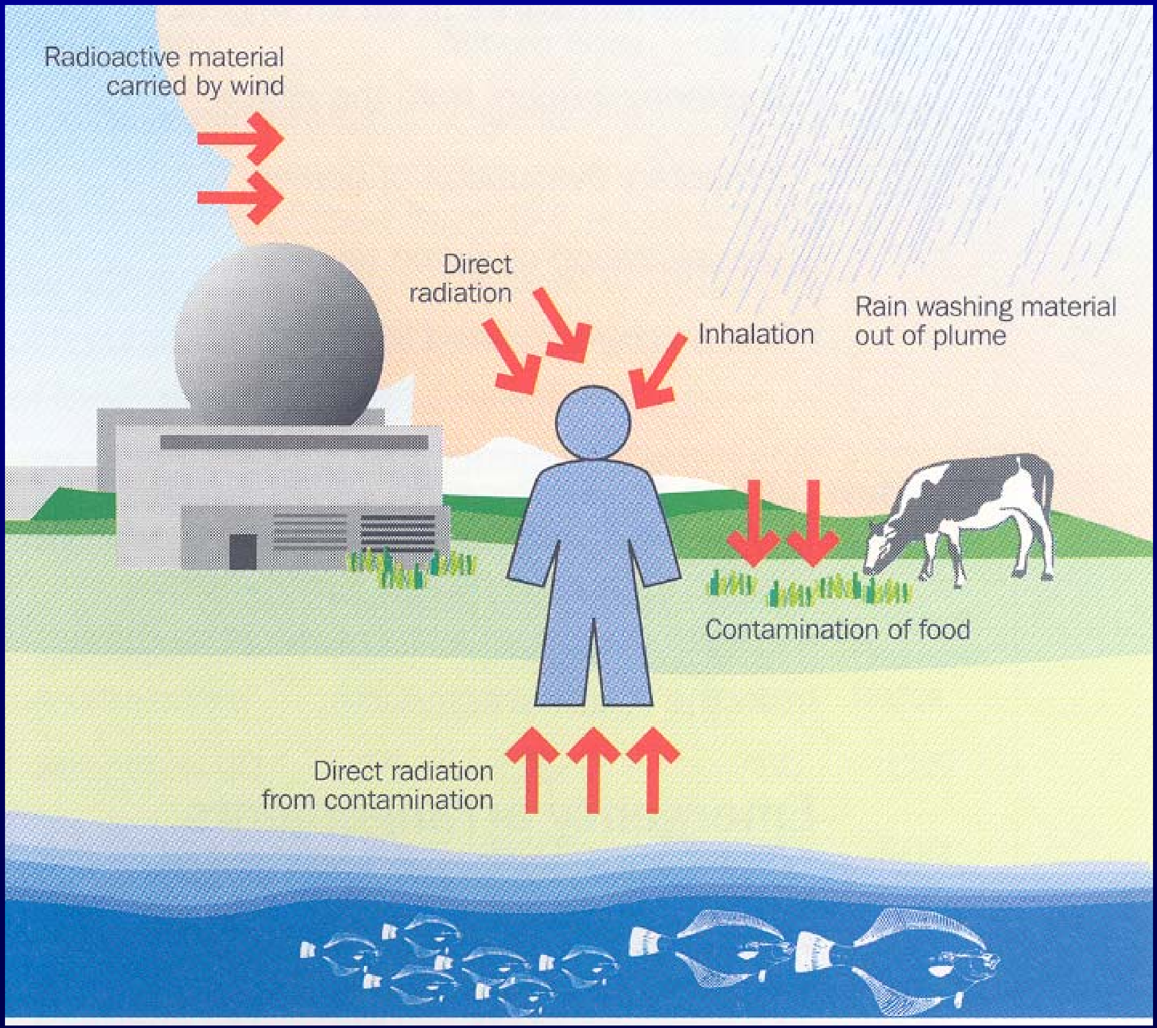
Early and Late Effects

Harmful radiation effects

Health consequences	Circumstances of exposure	Sources of information
Early effects		
	High dose and dose rate:	Human data from various sources
Death	to much of the body	
Erythema	to area of skin	
Sterility	to testes and ovaries	
Late effects		
Various cancers	Any dose or dose rate Risk depends on dose Appear years later	Risk factors for human beings estimated from high doses and dose rates in human health studies
Hereditary defects	Any dose or dose rate Risk depends on dose Appear in offspring	Risk factors for human beings inferrred from animal data and the absence of human evidence
Functional damage to organs and tissues	High dose at any rate Various times to appear	Human data from various sources
Mental retardation	Dose in the womb Appears in the child	Limited human data

From: National Radiological Protection Board. 1998. *Living with radiation*

Pathways of Environmental Exposure



From: National Radiological Protection Board. 1998. *Living with radiation*

Internal Radiation Exposures

Physical Factors

- Nature of radiation (LET) and range (penetration) in tissue
- Half-life of radionuclide

Chemical Factors

- chemical form – toxicity
- Solubility & other factors affecting transport, absorption and excretion

Biological Factors

- Absorption & excretion
- Localization or concentration within given organ or tissue

How Does Radiation Cause Ionizations?

- Example for gamma or beta particle and for neutrons (uncharged)
- Directly vs. indirectly ionizing radiations
- Compton effect vs. photoelectric effect

- Picture showing radioactive decay chain for U-238

From: National Radiological Protection Board. 1998. *Living with radiation*

Sources of Radiation Exposure
Natural Background Radiation

- Cosmic radiation
  - Primarily neutrons and γ-radiation
  - Exposure varies with altitude
- External γ-radiation
  - Naturally-occurring isotopes of uranium series
  - Depends on local geology & type of building material
- Internal emitters
  - Radon gas

Sources of Exposure to Ionizing Radiation

What Proportion of Human Cancer is Caused by Radiation?

- See Doll and Peto

Current Issues of Scientific and Public Interest

- Quantification of risk
  - Need for good dosimetry + consideration of uncertainties in dose estimates
- Effects of different types of radiation
- Risks at low doses and dose-rates
- Probability of causation
- New modalities of medical treatment and diagnosis

Current Issues of Scientific and Public Interest (cont'd)

- Environmental exposures
  - Reactor accidents
  - Weapons tests
  - Proximity to waste sites
- Radiological terrorism
- Indirect effects of radiation
- Nonionizing radiation

Current Issues of Scientific and Public Interest (cont'd)

- Joint effects of radiation & other factors
  - Host factors
  - Other known environmental carcinogens
  - Chemotherapy
  - Genetic susceptibility

References

- NRPB (National Radiological Protection Board). *Living with radiation*. NRPB, Chilton: United Kingdom, 1998.
- Hall EJ. *Radiobiology for the radiobiologist*. 4th ed. Philadelphia: Lippincott Williams & Wilkins,1994
- Boice JD Jr.
- Rothman KJ. Epidemiology 1996;7:291-8
- Doll R, Peto R.
- Little JB. Radiobiology course. Harvard School of Public Health, 1984.

Sources

- NRPB (National Radiological Protection Board). *Living with radiation*. NRPB, Chilton: United Kingdom, 1998.
- Hall EJ. *Radiobiology for the radiobiologist*. 4th ed. Philadelphia: Lippincott Williams & Wilkins,1994
- Boice JD
- Rothman KJ. Epidemiology 1996;7:291-8
- Doll & Peto
- Course notes for radiobiology class: Jack Little 1984

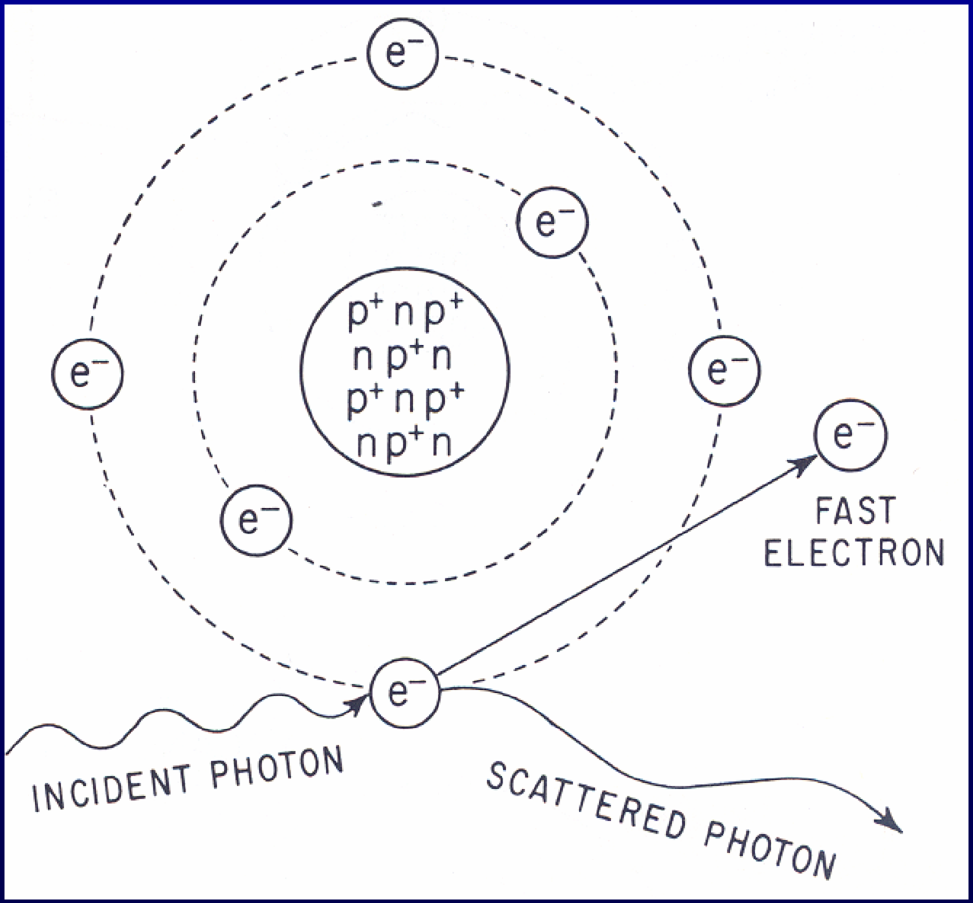
Compute Your Own Dose - Handout

Insert A-bomb Picture

Interaction of Radiation with Matter

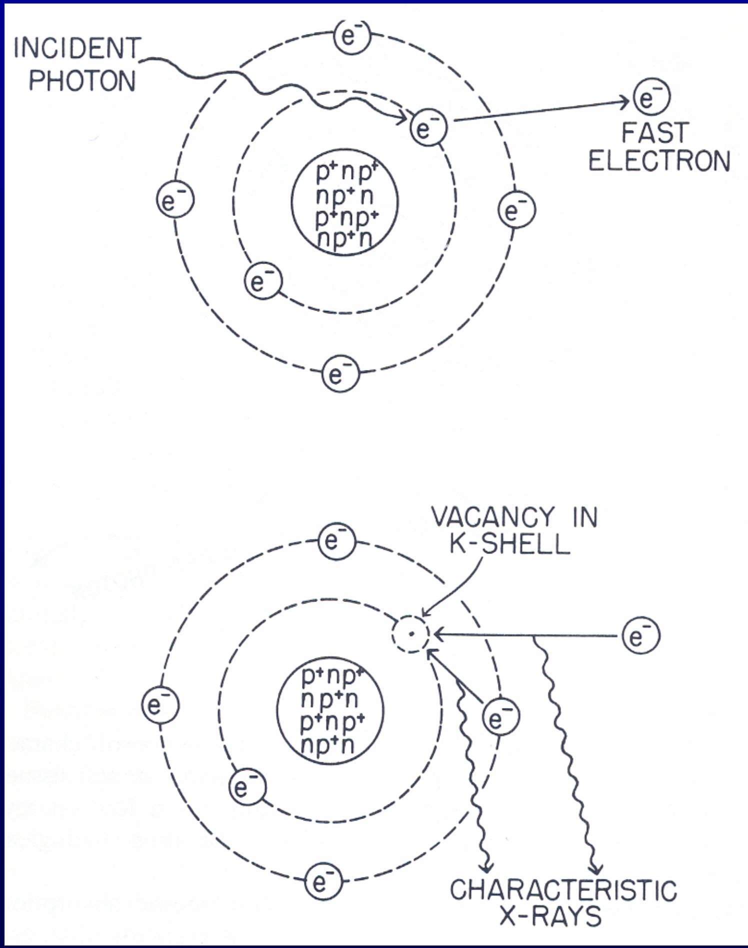
- Initial event involves deposition of energy in the form of ionization (ejection of electron (e^-)
- Ionized molecules then give up energy through a variety of mechanisms, which may or may not involve chemical change
- Biological damage results from these downstream processes

How Does Radiation Cause Ionizations?



Hall (1994)

How Does Radiation Cause Ionizations?



Hall (1994)

Ionizing Radiation and Tissue

charged particles

↓

electrical interactions

↓

ionization

↓

chemical changes

↓

biological effects

How Does Radiation Cause Ionizations?

- Ionization (damage) produced by electrical interaction with charged particles, whatever the nature of the incident radiation
- Radiations differ as to the density of ionizations produced and the degree of penetration of tissue
- Latter accounts for differences in biological effects

Linear Energy Transfer (LET)

- Measure of density of ionizations along path of ionizing particle or wave
- Dimensionality: energy per unit distance (keV/μ)
- Proportional to square of charge and inversely proportional to velocity of particle

Energy Dissipation

- Chemical change
  - results mostly from ionizations

- No chemical change

  e.g., heat, fluorescence, phosphorescence

Radiation Epidemiology in Context

- Radiation physics, chemistry & biology
- Epidemiologic studies
  - Dosimetry & biodosimetry
  - Risk estimation & description
- Experimental studies
- Radiation protection
- New radiation exposures
- Risk communication

ASIDE: UV Radiation "Dose"

- Non-penetrating
- Measured in terms of incident dose (exposure)
- Units: energy per unit area of exposed surface (e.g., joules/m^2)

O_2 as Sensitizing Agent

Oxygen highly reactive in systems with free radicals

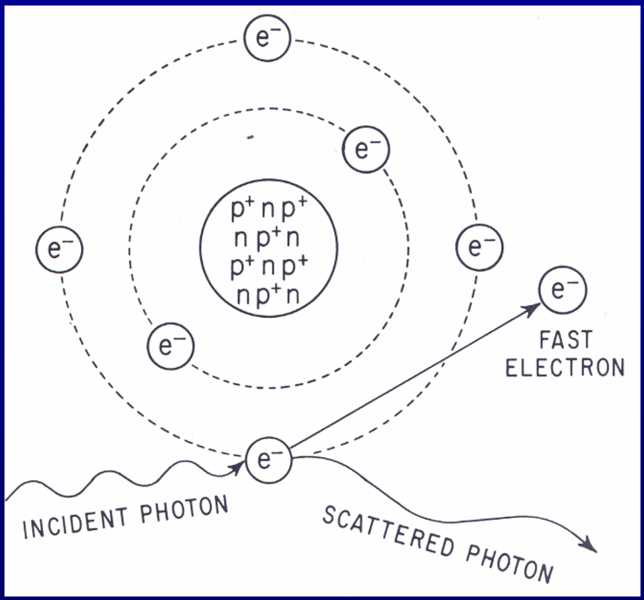
$H\bullet + O_2 \longrightarrow HO_2\bullet$ peroxy radical

$e^- + O_2 \longrightarrow O_2^-\bullet$ superoxide radical

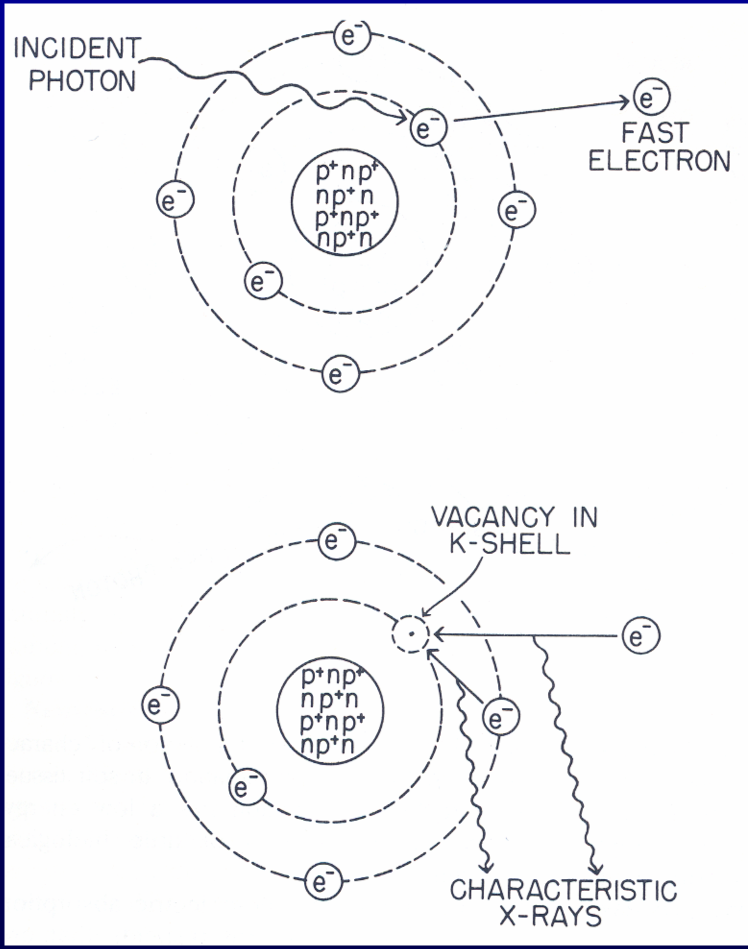
Radiation Risks in Perspective (Risks of 1 Part in 1 million)

Exposure		Outcome
10 mrem	x-rays	cancer
1.4	cigarettes	cancer, heart disease
1 hour	in coal mine	black lung disease
1000 miles	jet flying	accident
3000 mile	jet flying	cancer, from cosmic rays
2 months	in Denver	cancer, from cosmic rays

Ionization by X-rays or γ-rays



Compton Process



Hall (1994)

Photoelectric Process

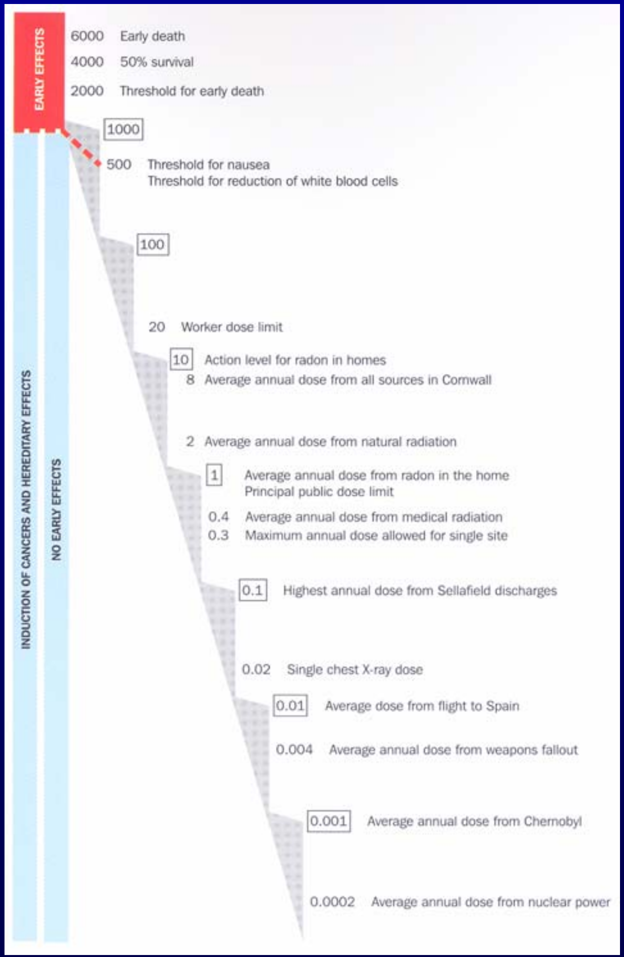
“Radiation” ≡ radiant energy

Photon energy <u>inversely</u> proportional to wavelength and <u>directly</u> proportional to frequency

Why Study Radiation and Cancer?

- Some exposures avoidable
  - Relative costs & benefits (e.g., dx X-rays)
- Mechanisms of cancer induction by radiation & some chemical carcinogens may be similar, but radiation more easily measured
  - Radiation as a model for action of chemical carcinogens and mutagens at level of DNA?
  - e.g., free radicals

Radiation Doses, Limits & Effects



From: National Radiological Protection Board. 1998. *Living with radiation*

Development of Radiation Injury

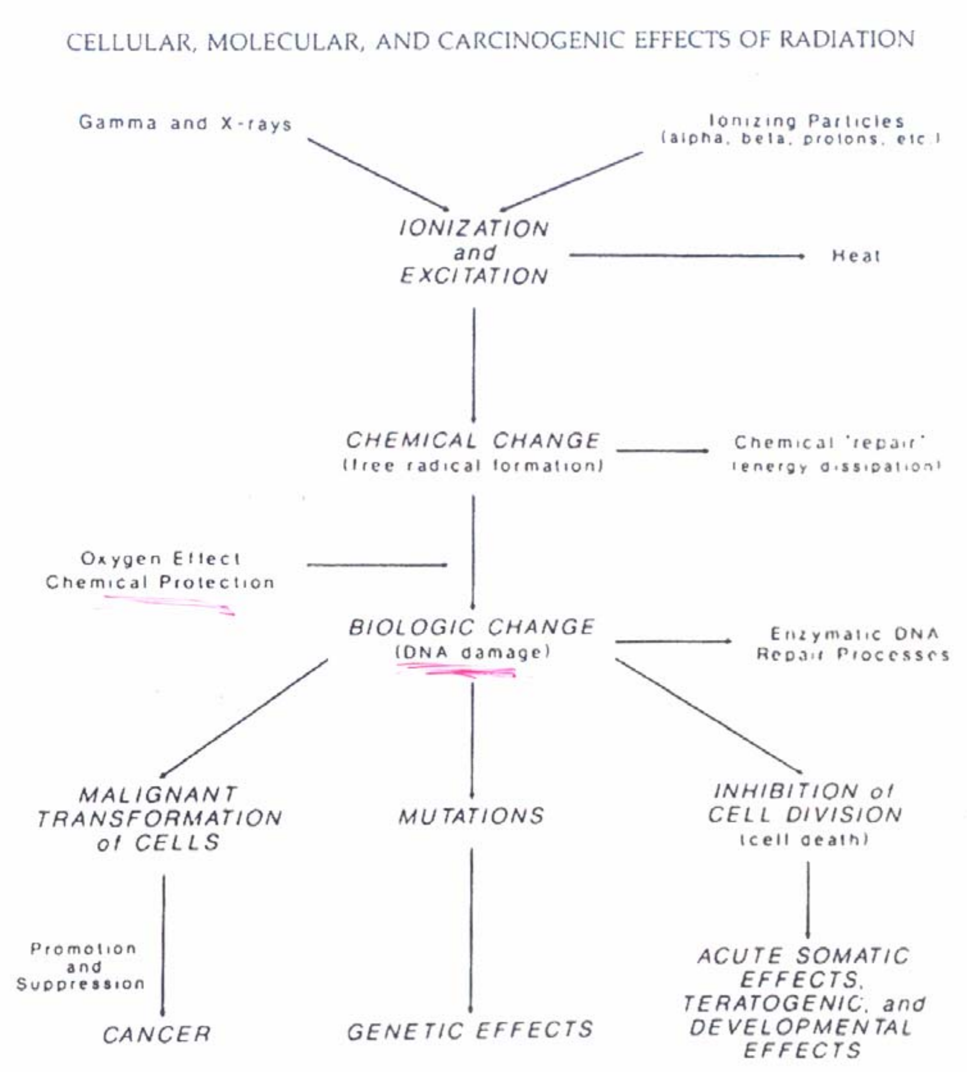
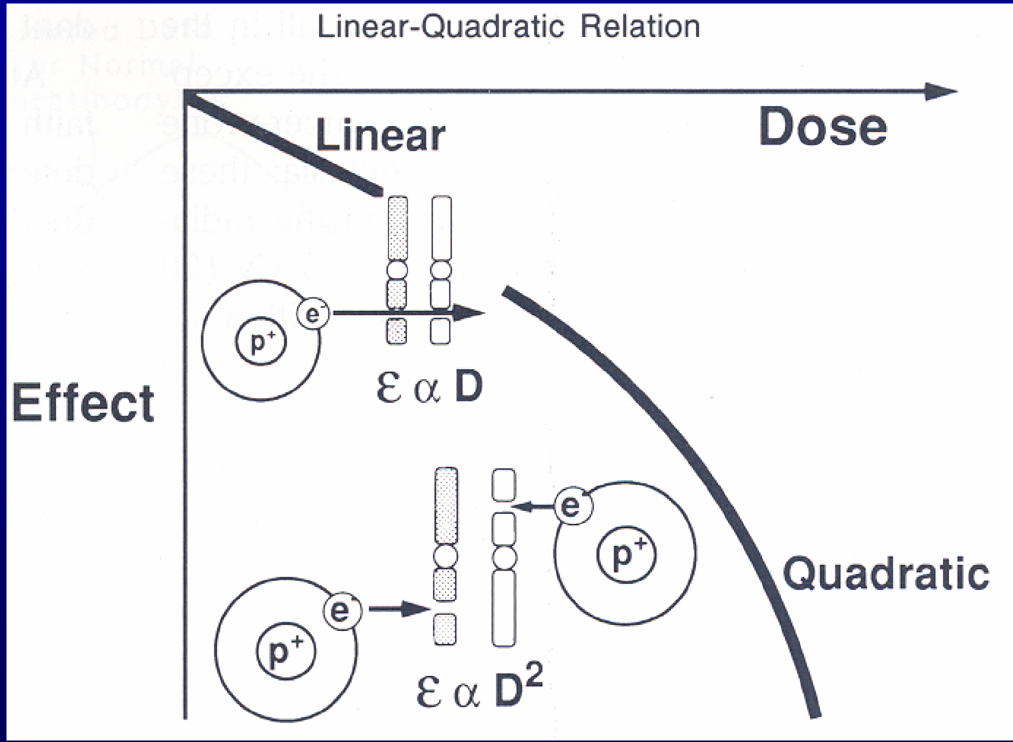


Figure 1. Development of radiation injury.


Linear-Quadratic Relation
Dose
Linear
Effect
p+
e-
ε α D
Quadratic
ε α D2

Hall (1994)

Cell Survival Curves

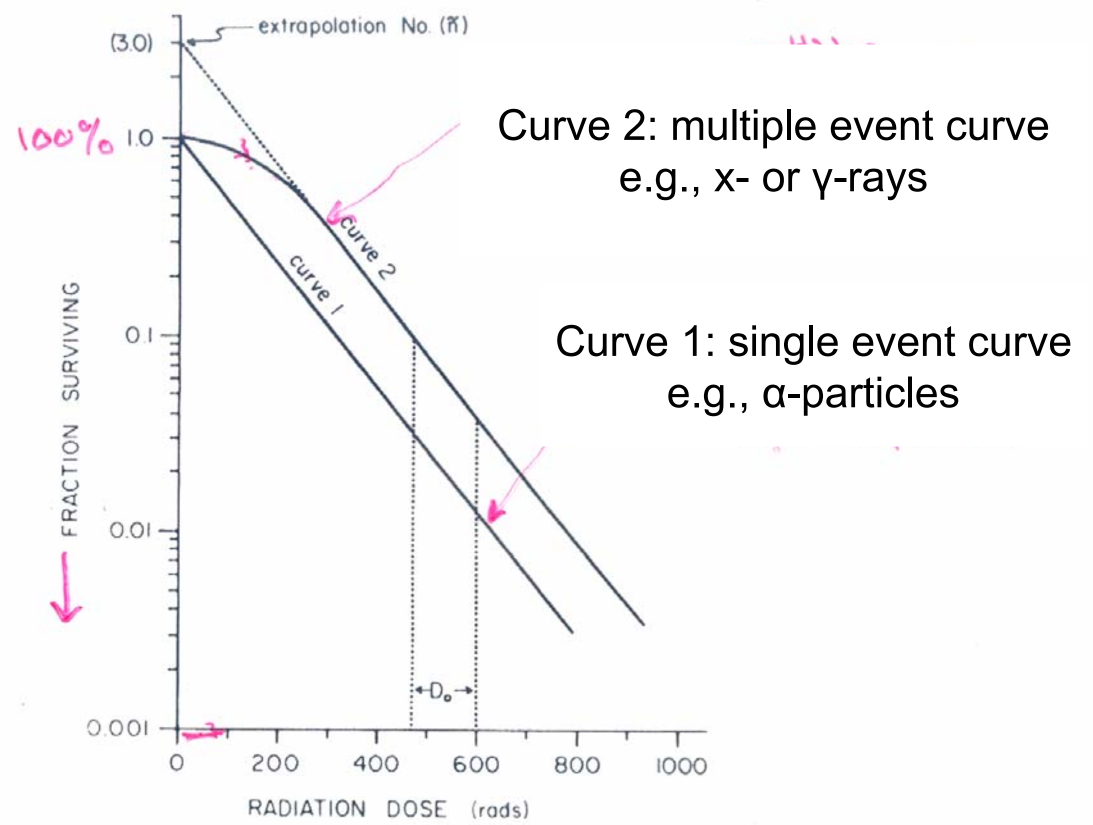


FIG. 2. Hypothetical dose-response curves for radiation-induced reproductive failure in cells. *Curve 1* is often referred to as a single-event and *curve 2* a multiple-event survival curve. The latter is the type associated with the killing of mammalian cells by gamma or X-irradiation, and its shape can be described by two parameters: the extrapolation number $\bar{n}$, which indicates the magnitude of the shoulder on the curve, and the D_0 or dose necessary to reduce survival to 37% on the linear portion of the curve, which determines its slope. Mathematically the D_0 is the inverse of the slope.

Little and Williams (1977)

Biological Change Due to Electromagnetic Ionizing Radiation

incident photon

↓

fast electron (e^-)

↓

ion radical

↓

free radical

↓

chemical changes from breakage of bonds

↓

biological effects

From: Hall (1994)

Internal Radiation Exposures

- Organ- or tissue-specific concentration of radionuclides
  - e.g., radioiodines in thyroid gland
- Biological effect depends on dose to critical (target) cells within a specific tissue
  - Many factors determine ultimate dose from internally emitting radionuclides
  - Unlike the case with external exposure, where dose to tissue is more uniform

Orientation/Housekeeping

- Introductions & Contacts (me, Ursula, Michele, Martha)/ my office
- IDs
- Restrooms
- Meals/map
- Metro shuttle
- Taxis
- Parking stickers (3-hour and all-day)
- Handouts (schedule, references, glossary, slides, map)
- Social events/dinner sign-up (Dutch-treat)
- Web site
- Message board, phones
- Don't leave valuables
- Mention NRPB book