

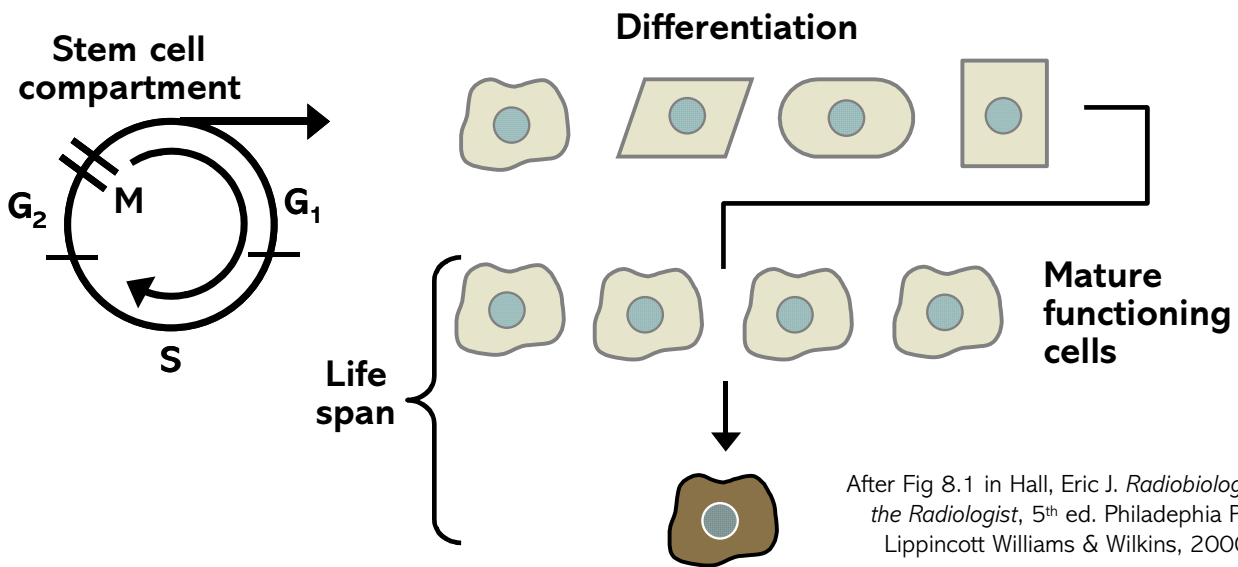
Health Effects of Radiation

Tissue organization

- Effects of radiation on tissues are related to the functional organization of each tissue.
- Tissues are often organized into specialized cell types with limited ability to divide.
- This tissue unit is supplied and regenerated by a population of “immortal” stem cells.

Tissue effects depend on

- Inherent sensitivity of the cells
- Kinetics of the cell populations: “acute” vs “late” effects.
- Stem cells much more radiosensitive than mature functioning cells.
- Cell death occurs as the cell tries to divide.
- Very large doses required to kill (stop the function) of a non-dividing cell.



Timing of onset of symptoms correlates with the lifespan of the functional cells.

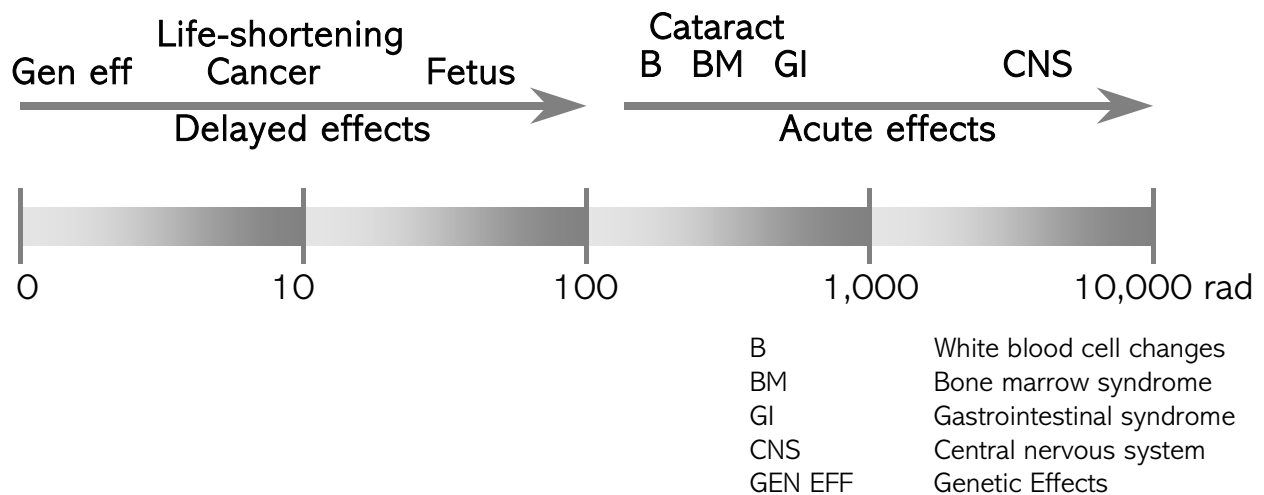
Early Effects: stem cells are the “target”

- Effects occur in a few days to weeks
- Rapidly dividing cell populations
- Examples: skin epidermis, gastrointestinal tract, hematopoietic system
- Damage can be repaired. Stem cells repopulate rapidly.

Late Effects:

- Effects occur in months to years.
- Slowly proliferating tissues: lung, kidney, liver, CNS
- Damage never repaired completely
- Vascular damage or mature functional cells as the “target”?

Dose scales for manifestation of radiation effects



Chronic effects of radiation exposure

Cells not killed, but damaged.....

- **Cataract formation**
- **Genetic (hereditary) effects**
- **Effects on the fetus**
- **Carcinogenic effects (cancer)**

Human Radiation Exposure Data

Japanese A-bomb survivors

- 93,000 survivors
- 27,000 non-exposed comparable individuals as controls
- Location at the time of the blast must be accounted for in the dosimetry.

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RERF: Radiation Effects Research Foundation

Joint US-Japan research foundation following all of the survivors for life.

www.rerf.or.jp

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Whole-body radiation exposure: Acute effects

Prodromial syndrome

- Nausea, vomiting
- Dose dependent
- Signs appear in minutes at very high doses

Central nervous syndrome (only at very high doses)

- Doses > 100 Gy
- Death in hours
- Cause not clear (**cerebrovascular syndrome**)

Gastrointestinal syndrome

- Doses above ~ 5 Gy
- Death in ~ 3 -10 days
- Nausea, vomiting, diarrhea

Bone marrow syndrome

- Doses above ~ 2 Gy
- Death in several weeks
- Immune system failure

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Intestinal epithelium

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- Stem cells located in “crypts” at the base of the finger-like villi.
- Maturing cells migrate to the tip of the villus.
- Transit time: crypt to tip, ~ 5-10 days.
- Doses >10 Gy will sterilize most of the stem cells in the crypts.
- Death in 3-10 days, villi, denuded and flat.
- If some crypt cells survive, they will regenerate functional crypts and repopulate the villi.

Hematopoietic System

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Stem cells located mostly in the bone marrow.

Stem cells very radiosensitive

Survival curve shows little or no shoulder

$$D_0 < 1 \text{ Gy}$$

Little sparing from fractionation or low dose rate

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Lymphocytes most sensitive (~0.3 Gy will deplete)

Timing and extent of cell population decline is dose dependent.

Total body dose of 3-4 Gy will suppress the immune system.

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- Dogs irradiated uniformly with 250 kVp x rays
- Doses are in roentgens (\sim cGy)
- Blood cell responses are very similar before recovery in survivors and non-survivors.

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- There is only a narrow range of doses where bone marrow transplant might be expected to help.
- Doses $< \sim 8$ Gy : most persons would survive with intensive hospital care.
- Doses > 10 Gy : most persons will die of the gastrointestinal syndrome.
- Death in 3-5 days from GI syndrome if $D > 10$ Gy.
- Dosimetry must be estimated.
- If dose $\sim 7-10$ Gy, bone marrow transplant may help.

Skin

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Epidermis: site of early reactions

- ~ 100 μm thick (30-300 μm)
- Basal stem cell layer
- Non-dividing differentiated cell layers (10-20 layers) migrating to the surface
- Keratinized cells at the surface
- Desquamation: loss of cells from the surface
- Transit time, stem cell to loss at the surface ~ 14 days (12-48).

Dermis: site of late reactions

- ~ 1,200 μm thick (1000-3000 μm)
- vascular network is in the dermis (no blood vessels in the epidermis)
- fibrous connective tissue

Two waves of skin reactions observed as a function of time after irradiation.

- **Early:** moist desquamation, ~ 10 days, stem cell damage, depletion of differentiated cells. (~20 Gy single fraction)
- **Late:** dermal necrosis ~ months to occur, vascular damage and breakdown of the skin.

Erythema and hair loss

Cells in the hair follicle are sensitive.

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Hair Loss: Relation between the proportion of people with severe epilation (loss of more than 2/3 of hair) and estimated radiation dose. Data from the Japanese atomic bomb survivors (www.rerf.or.jp).

Threshold doses for skin reactions

3 Gy **temporary hair loss**

6 Gy **erythema:** reddening of the skin, occurs within hours to a few days.

15–20 Gy **moist desquamation** and **dermal necrosis**

Hereditary Effects: effects on the offspring

- **Radiation does not produce “new mutations”.**
- **Radiation increases the incidence of mutations that occur spontaneously in the population.**

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Fig. 11.1 in Hall, Eric J. *Radiobiology for the Radiologist*, 5th ed. Philadelphia PA: Lippincott Williams & Wilkins, 2000.

Doubling dose: increases the natural background frequency by a factor of 2.

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Table 11.2 in [Hall].

Background mutation rate ~ 1-6%

Radiation-induced risk of hereditary disorder estimated at $0.6 \times 10^{-2}/\text{Sv}/\text{per person}$

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Fig. 11.3 in [Hall].

Dose rate effect data from the “Mega mouse” Experiments at Oak Ridge National Laboratory.

Fetal Effects

- Lethal effects
- Malformations
- Growth disturbances

Principal factors

- Dose
- Gestation age at time of irradiation

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Data from rats given 200 rads at various time post-fertilization.

Japanese atomic bomb survivors irradiated *in utero*.

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Growth retardation: height, weight and head diameter

Mental retardation: observed in children irradiated at 8-15 weeks (only) of pregnancy.

Effects observed at doses as low as 0.06 Gy.

Cataracts: any detectable change in the normally transparent lens of the eye.

Deterministic response

- Cells are produced by mitosis in the germination zone (GZ) of the epithelium.
- Differentiate into lens fibers in the meridional rows (MR).
- Cells in the central zone (CZ) do not normally divide.

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- No blood supply.
- No mechanism for removal of dead or damaged cells.
- Abnormal fibers migrate towards the posterior pole, the beginning of a cataract.
- Single doses > 2 Gy will cause cataracts.
- Fractionation and low dose rate increase the threshold to 4-5 Gy.

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See Preston, Dale J., Yukiko Shimizu, Donald A. Pierce, Akihiko Suyama and Kiyohiko Mabuchi. "Studies of Mortality of Atomic Bomb Survivors. Report 13: Solid Cancer and Noncancer Disease Mortality: 1950-1997." Radiation Research 160 (2003): 381-407.

Estimation of risk from radiation exposure

Excess risk: the excess cases of a particular health effect associated with exposure to radiation. Excess risk can be described in various ways:

- **Absolute Risk:** the difference in the rate of occurrence of a particular health effect in an exposed population and an equivalent population with no radiation exposure. (units: excess number of cases per person-year-sievert).
- **Relative Risk:** the ratio of the rates in exposed and unexposed populations (dimensionless)
- **Excess Relative Risk (ERR):** the ratio of the rate difference to the rate in an unexposed population (N.B., $ERR = \text{relative risk} - 1$)

Excess risks depend on:

- radiation dose
- age at exposure
- time since exposure
- current age
- gender

Risk estimates are usually reported for a specific dose (often 1 gray or 1 sievert).

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Graph of Radiation dose of the uterus vs. Relative risk

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Figure 2.

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Figure 1.

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Plot of Excess Relative Risk (ERR) for different forms of cancer.

Estimates based on a model that accounts for age at exposure and gender.
The vertical dotted line represents no excess risk.
The solid vertical line represents the excess relative risk for all cancers.

Cancer deaths between 1950 and 1990 among Life Span Study -
Survivors with significant exposures (> 0.005 Sv)

Dose Range	Number of Cancer Deaths	Estimated Excess Deaths	Attributable Fraction (excess lifetime risk)
0.005-0.2 Sv	3391	63	2% (=100 x 63/3391)
0.2 – 0.5 Sv	646	76	12%
0.5 – 1 Sv	342	79	23%
> 1 Sv	308	121	39%
All	4687	339	7%

Excess Lifetime Risk

- Based on observed cancer incidence to date
- Depends on dose, age at exposure, sex.

Lifetime cancer risks for atomic bomb survivors who received an acute dose of 0.2 Sv

Age at exposure (years)	Excess lifetime risk	Background lifetime risk	Excess relative risk (ERR)
MEN			
10	0.03	0.26	12% (= 100 x 0.03/0.26)
30	0.02	0.28	7%
50	0.01	0.18	6%
WOMEN			
10	0.05	0.19	26%
30	0.03	0.20	15%
50	0.01	0.15	7%

(Data from <http://www.rerf.or.jp>)

Numbers of cancer deaths by cancer type and strength of evidence for a radiation effect

SITE	TOTAL DEATHS	ESTIMATED EXCESS	EVIDENCE FOR EFFECT
Stomach	2529	65	strong
Lung	939	67	strong
Liver	753	30	strong
Uterus	476	9	moderate
Colon	347	23	strong
Rectum	298	7	weak
Pancreas	297	3	weak
Esophagus	234	14	strong
Gallbladder	228	12	moderate
F. Breast	211	37	strong
Ovary	120	10	strong
Bladder	118	10	strong
Prostate	80	2	weak
Bone	32	3	moderate
Other solid	948	47	strong
Lymphoma	162	1	weak
Myeloma	51	6	strong

- Statistical significance may vary, but excess risks are seen for all types of cancer.
- Supports the notion that radiation increases the risk for ALL types of cancer.

Radiation in Medicine: therapy and diagnosis

- a) thyroid cancer: 1930s and 1940s use of x-rays to shrink enlarged thymus in children.
- b) Ringworm of the scalp: 1940s and 1950s x rays used to cause temporary hair loss (several Gy), treat hair follicles more effectively. Increases in thyroid cancer, leukemia, brain tumors (10,000 patients in Israel, 2215 in New York).
- c) In Britain, ~14,000 patients with a congenital spinal cord problem known as ankylosing spondylitis were irradiated to relieve pain. Increased incidence of leukemia.
- d) Female tuberculosis patients undergoing repeated fluoroscopy procedures showed an increase in breast cancer.

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Fig. 10.5 in [Hall].

Radium dial painters

- Practice continued up to 1925. Ingestion of ^{226}Ra (bone seeker) caused an increased incidence of bone cancer.
- At autopsy, bone was analyzed for radium content.
- Note, that there appears to be a threshold below which no effects are seen.

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Fig. 10.6 in [Hall].

What are the risks from low-doses of radiation?

All human data are relatively high dose and delivered at high dose rates.....

.....and extrapolated down to the low dose region at low dose rates.

This is a source of significant and continuing controversy.

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Risk Estimation Models

- **linear no-threshold**
- **threshold**
- **linear-quadratic**

The choice of model, and the estimated risk, has serious implications for radiation protection.

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Data from high dose rate exposures is extrapolated to low doses and low dose rates.

Low dose rate exposure is significantly less damaging.

Is there a 4th curve??

Hormesis

a term coined to describe the behavior of an agent that is lethal at high doses but *beneficial* at low doses.

(e.g., nickel, chromium, hormones, ultraviolet light)

The radiation effects paradigm:

- Radiation exposure is harmful.
- Radiation exposure is harmful at all doses.
- There are no effects at low doses that cannot be predicted from the effects at high-dose levels.

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Graph: "Mortality risk from leukemia in Hiroshima and Nagasaki and dose-response curve. After UNSCEAR (1994).

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b. LNT Quote:

“The lung-cancer risk estimates for radon-daughter exposure derived by the committee in this report are based solely on epidemiological evidence.” BEIR IV, p.6, 1988

Hormesis Response:

Reducing radon in homes increases lung cancer and progeny reduce lung cancer deaths. The EPA limit of 4 pCi/l has no reasonable basis. Extrapolation from animals & miners is fallacious.

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Attitude of the General Public Towards “Risk”

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Refer to Sandman, Peter. *Explaining Environmental Risk: “Important If True.”* Originally published by EPA’s Office of Toxic Substances, Nov. 1986. [updated 10 Nov 2001, cited 29 March 2004]. <http://www.psandman.com/articles/explain1.htm>