Chapter 6: Radiobiology

NPRE441:Principles of Radiation Protection Spring 2024
MW 12-1:50 pm 2018 Campus Instructional Facility
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Slides retrieved and adapted from:

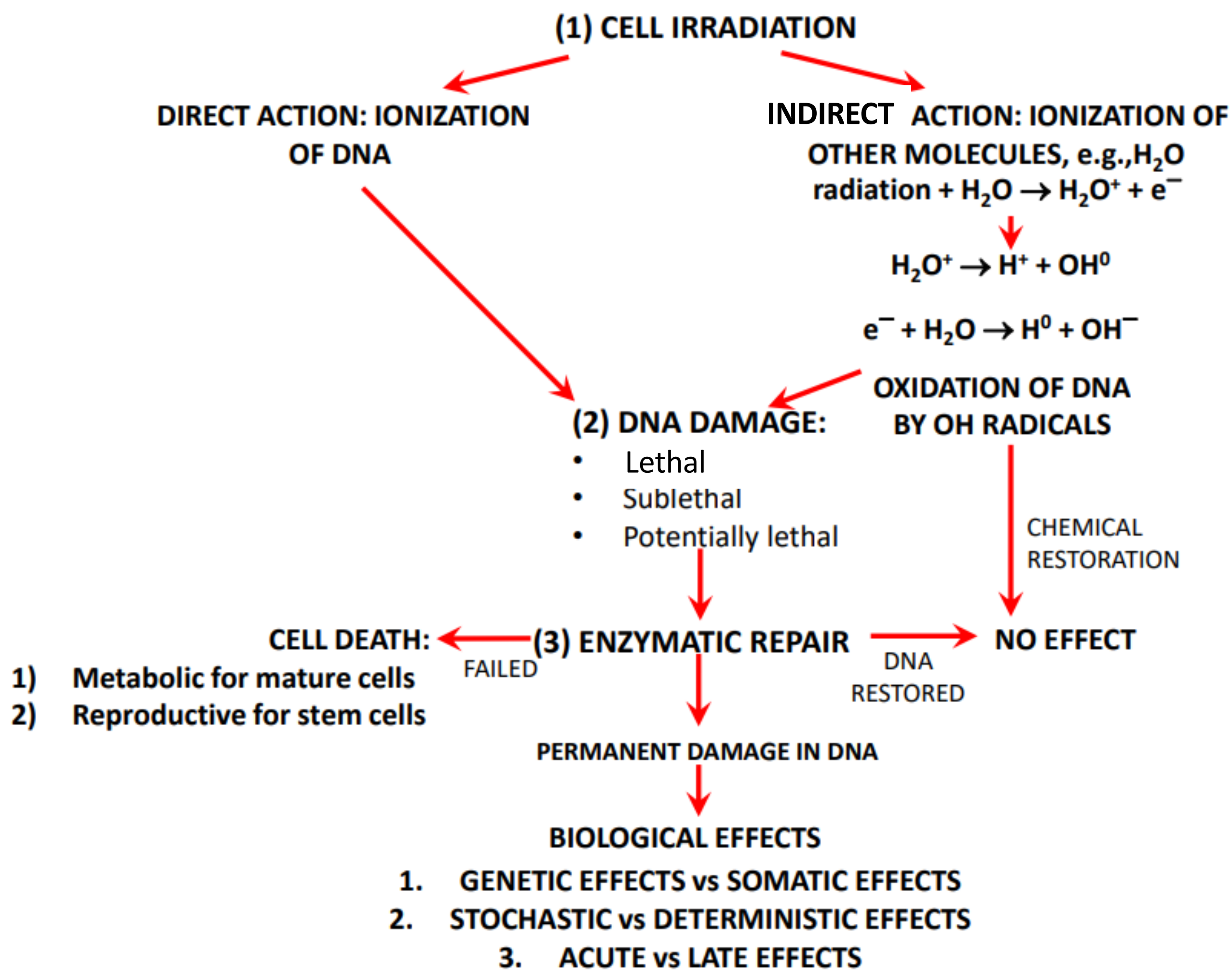
- Slide deck NPRE441 Spring 2023 by Dr. Elena Zannoni (UIUC, USA)
- Slide deck NPRE441 Spring 2021 by Prof.L.J. Meng (UIUC, USA)
- Slide deck prepared in 2015 by Dr.M. Cremonesi (IEO European Institute of Oncology, Milano, Italy)
- Slide deck prepared by Dr.E.Okuno (Institute of Physics of S. Paulo University, S. Paulo, Brazil)
- Slide deck prepared in 2006 by Dr.E.B. Podgorsak (McGill University, Montreal)

IAEA
International Atomic Energy Agency

OBJECTIVE: TO FAMILIARIZE THE STUDENTS WITH THE BASIC PRINCIPLES OF RADIOBIOLOGY

Primary reading resource:
J. Turner, "Atoms, Radiation, and Radiation Protection", Third Edition, Wiley-VHC, Inc. 2007

Radiation Effect on Biological Systems



Review of radiobiology from first lecture

- Groups of atoms make molecules (elements)
- Groups of molecules make subcellular structures (proteins, DNA, membranes)
- Groups of subcellular structures make cells
- DNA bases plus sugar phosphate backbone make nucleotide
- Nucleotides combine to make DNA strands (double helix)
- DNA is **transcribed** to mRNA which exits the nucleus and is **translated** to proteins on the endoplasmic reticulum
- DNA methylation can silence genes (no transcription)

CHAPTER 6.3

3. Type of radiation damage

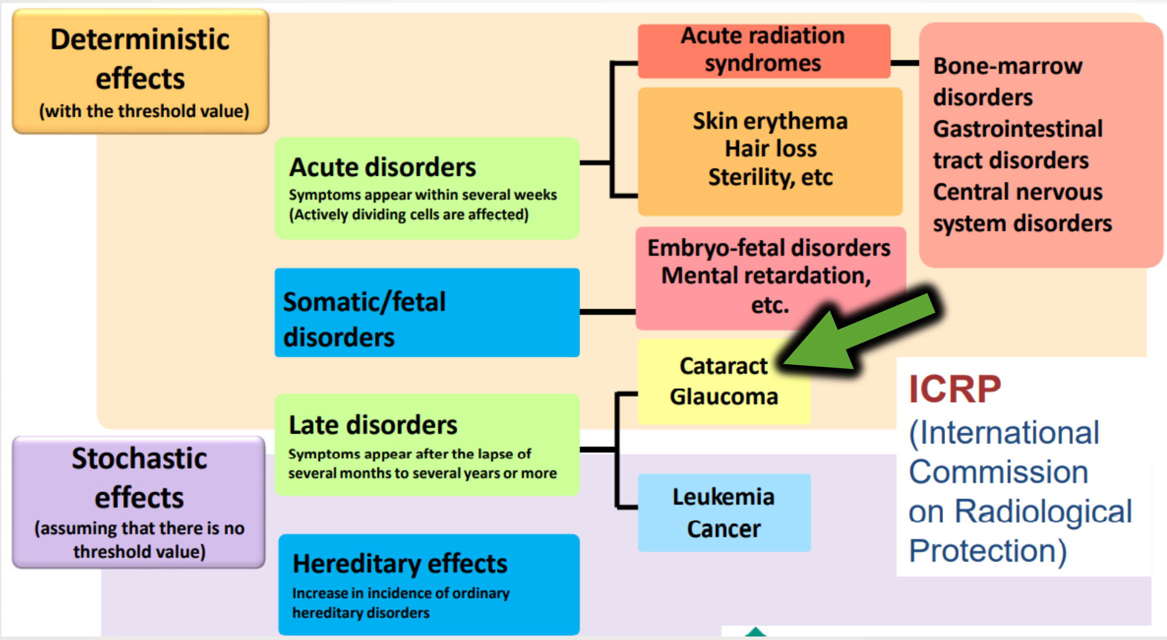
Classification/ overview

- A. Stochastic and deterministic (non-stochastic) effects
- B. Somatic and genetic/hereditary effects
- C. Acute vs late tissue or organ effects
- D. Total body irradiation and Acute Radiation Syndrome
- E. Equivalent and Effective Dose

Specific effects

- F. Carcinogenesis (Thyroid cancer)
- G. Cataractogenesis
- H. Skin effects
- I. Infertility
- J. Fetal Irradiation

TYPES OF RADIATION EFFECTS

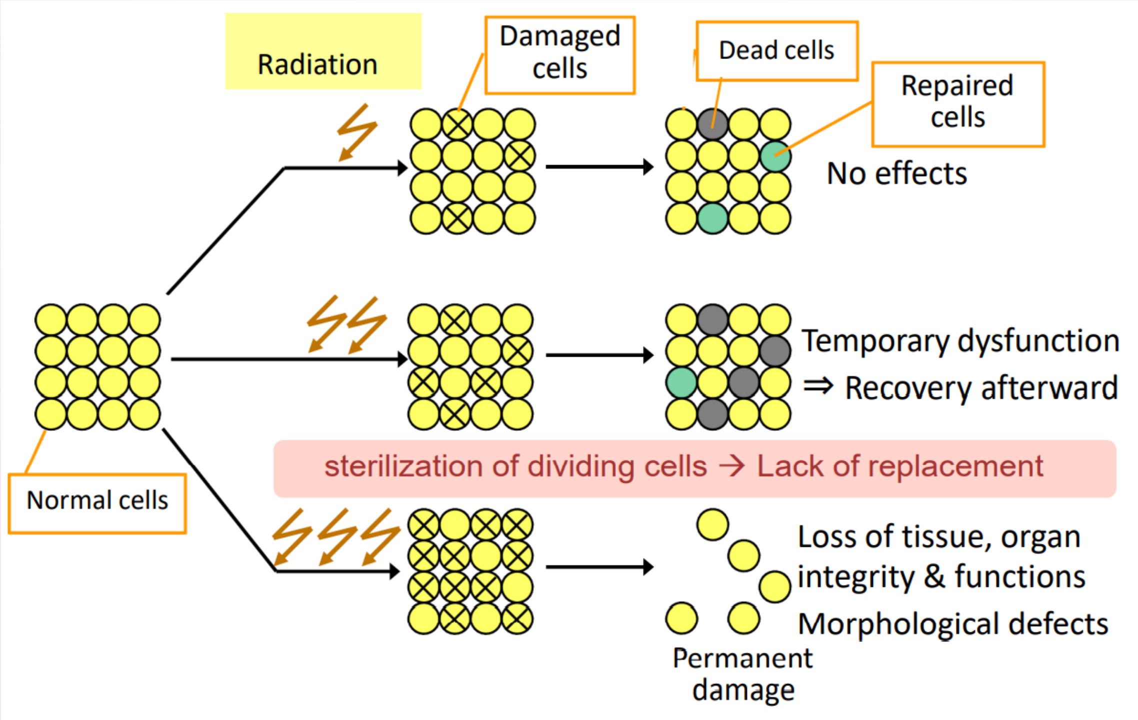


- Health effects can arise after radiation exposure
- Factors that impact what effects are seen include: the amount of radiation, parts exposed to radiation (whole-body exposure or local exposure), and exposure modes (acute, chronic or fractionated exposure).

6.3.A TYPE OF RADIATION DAMAGE
Stochastic vs. deterministic (non-stochastic) effects

- **Deterministic (non-stochastic) effect** is caused by damage to a large population of cells (e.g., organ dysfunction, fibrosis, lens opacification, blood changes, decrease in sperm count).
  - Above a **threshold** dose, the **severity** of the effect necessarily **increases with increasing dose**. This threshold varies from one effect to another
- May occur:
  - A few hours, days, or weeks after exposure (i.e. early skin reaction)
  - Months or years before expression (i.e. cataract of the eye lens)

DETERMINISTIC EFFECTS



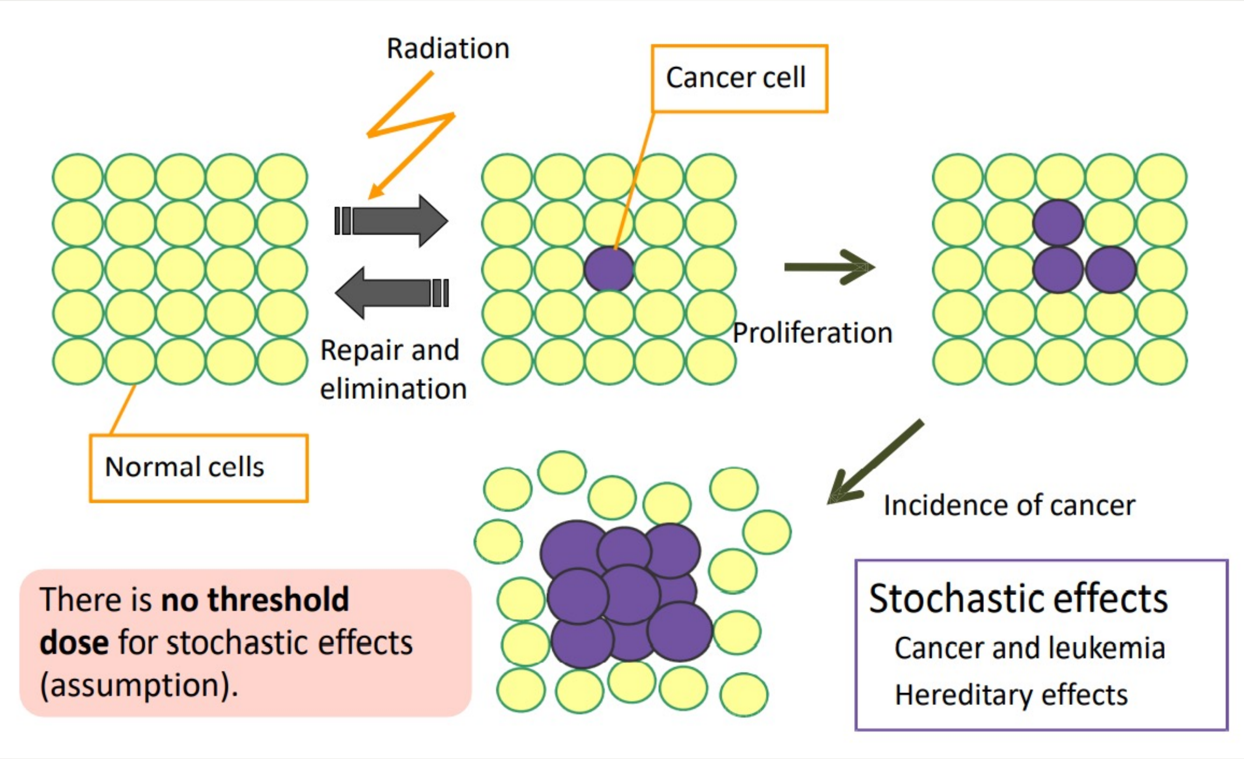
6.3.A TYPE OF RADIATION DAMAGE
Stochastic vs. deterministic (non-stochastic) effects

- In many tissues and organs, but not all, the rate of death of differentiated cells is balanced by renewal from a “pool” of tissue stem cells in order to maintain a healthy state and function
- Since radiation may lead to sterilization of dividing cells, in particular tissue stem cells, terminally differentiated (mature) cells can no longer be replaced
- Lack of replacement can eventually result in a loss of sufficient numbers of functioning cells and as a consequence a loss of tissue and/or organ integrity and function
- **Normal tissue tolerance** is defined by the dose above which there are unacceptable late effects in normal tissue in 1-5% of treated patients.

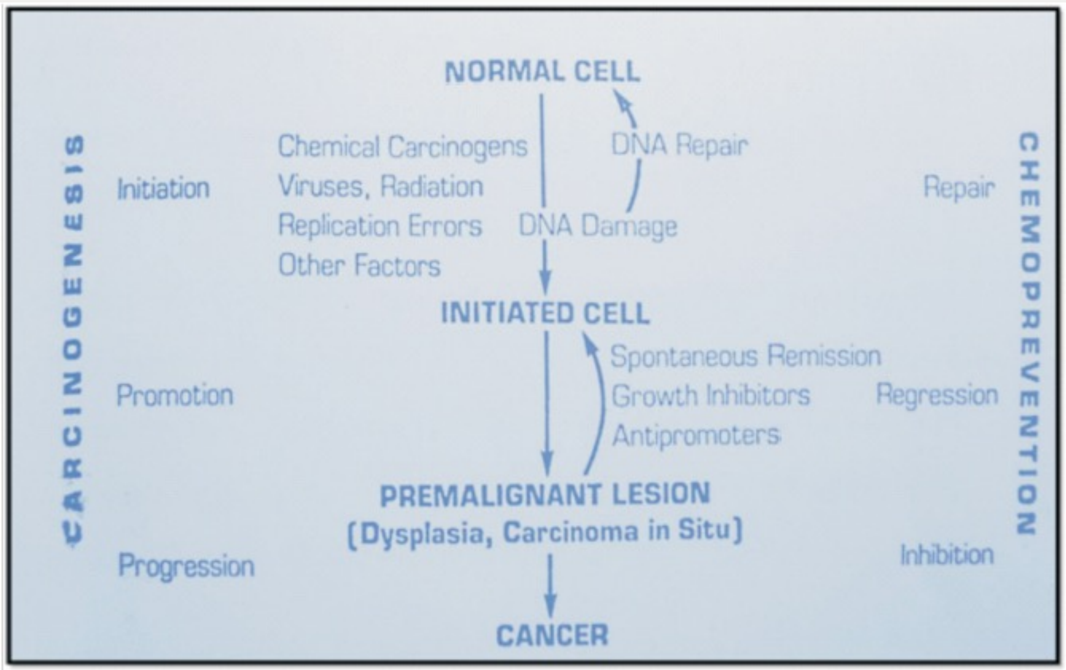
6.3.A TYPE OF RADIATION DAMAGE
Stochastic vs. deterministic (non-stochastic) effects

- **Stochastic effect** is one in which the probability of occurrence increases with increasing dose the severity of the effect is not function of the dose (e.g., induction of **cancer and genetic effects**).
  - There is no threshold dose for effects that are truly stochastic and arise in single cells.
  - They are **exclusively late effects** because they do not appear until **years after** radiation exposures.
- These are **random**. Stochastic is from the Greek word stokhastikos, meaning "able to guess," with the root stokhos meaning "a target."

STOCHASTIC EFFECTS



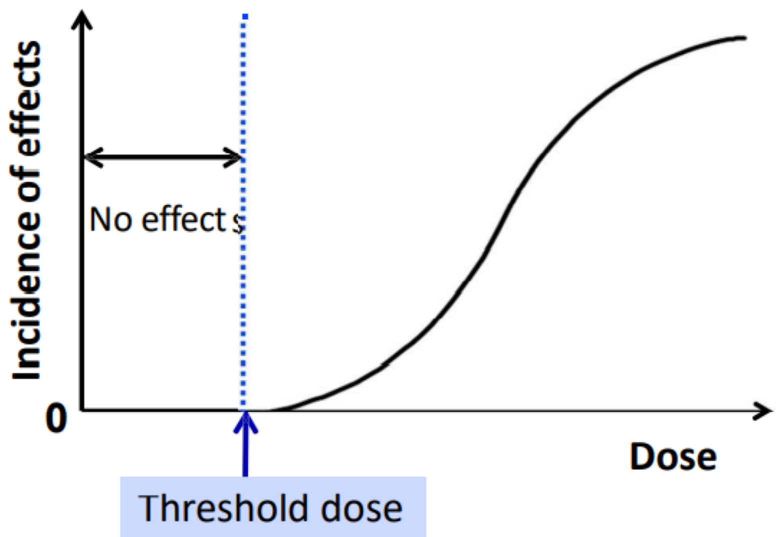
Multistage carcinogenesis



Deterministic effects

(Hair loss, cataract, skin injury, etc.)

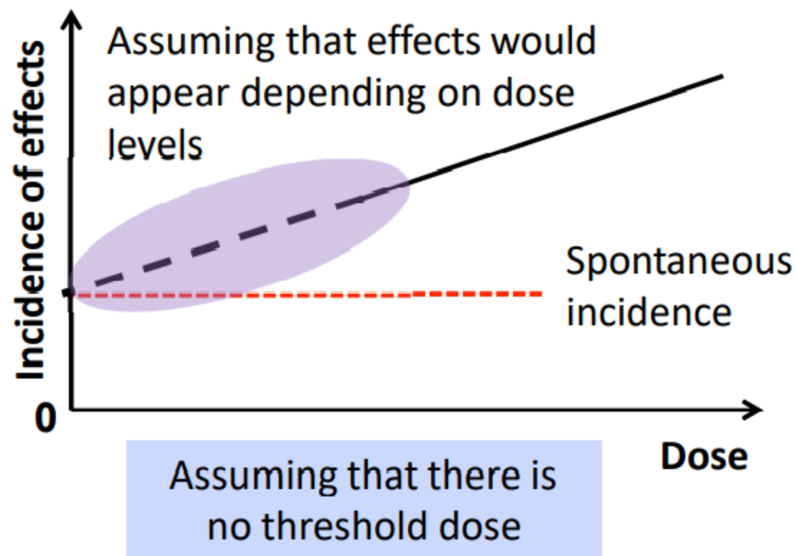
When a number of people were exposed to the same dose of radiation and **certain symptoms appear in 1% of them**, said dose is considered to be the **threshold dose.**
(2007 Recommendations of the International Commission on Radiological Protection (ICRP))



Stochastic effects

(Cancer, leukemia, hereditary effects, etc.)

Effects of radiation exposure under certain doses are not clear because effects of other cancer-promoting factors such as smoking and drinking habits are too large. However, the ICRP specifies the standards for radiological protection for such low-dose exposures, assuming that they may have some effects as well.



DETERMINISTIC: Threshold absorbed dose values for various effects

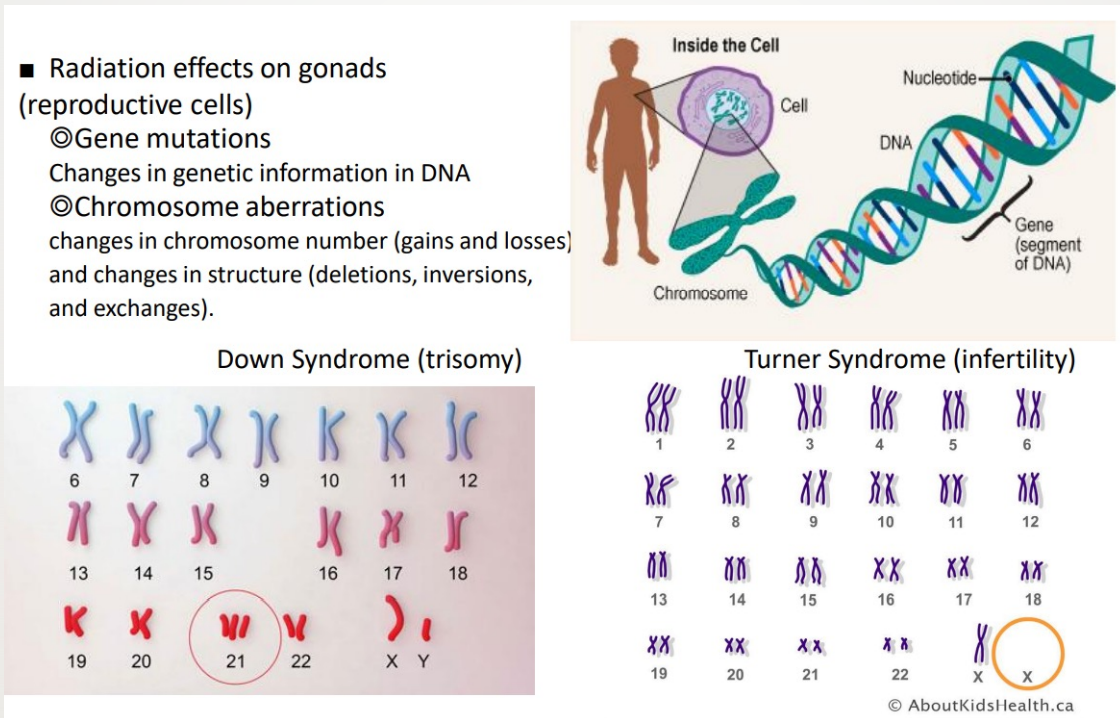
Disorders	Organs/Tissues	Incubation period	Threshold value (Gy)*
Temporary sterility	Testis	3 to 9 weeks	Approx. 0.1
Permanent sterility	Testis	3 weeks	Approx. 6
	Ovary	Within 1 week	Approx. 3
Deterioration of hemopoietic capacity	Bone marrow	3 to 7 days	Approx. 0.5
Skin rubor	Skin (large area)	1 to 4 weeks	3 to 6 or lower
Skin burn	Skin (large area)	2 to 3 weeks	5 to 10
Temporary hair loss	Skin	2 to 3 weeks	Approx. 4
Cataract (failing vision)	Eyes	20 years or longer	Approx. 0.5

* Threshold doses for symptoms with clear clinical abnormalities (**doses causing effects on 1% of people**)

6.3.B TYPE OF RADIATION DAMAGE
Somatic vs. genetic effects

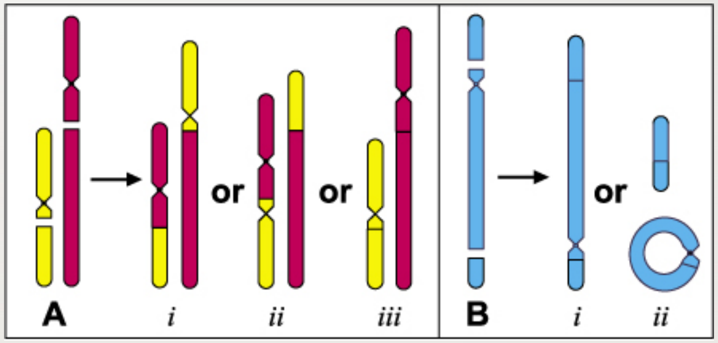
- Somatic effects are harm that exposed individuals suffer during their lifetime, such as radiation-induced cancers, sterility, and cataracts.
- Genetic or hereditary effects are radiation-induced mutations to an individual's genes (DNA) that can contribute to the birth of defective descendants

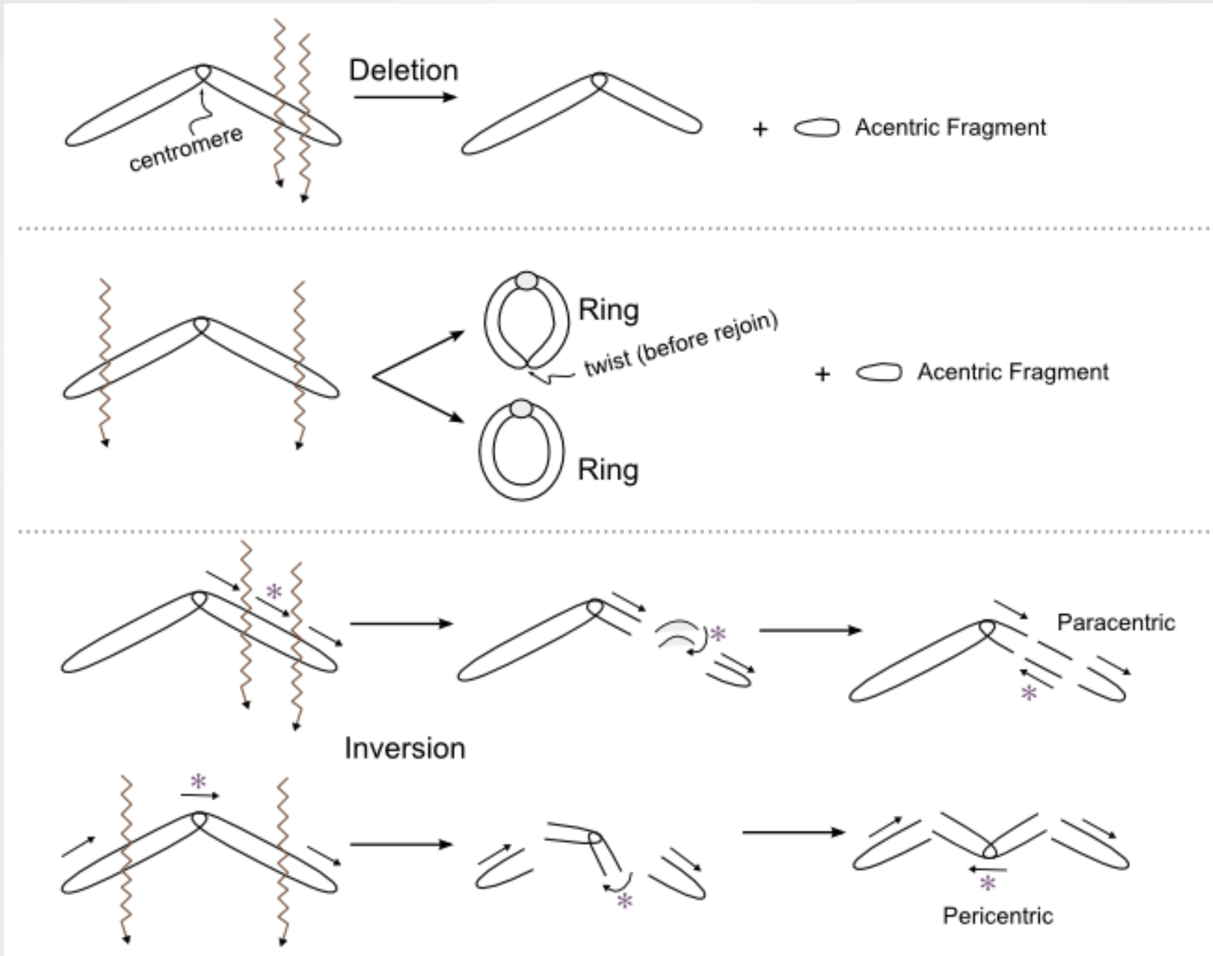
6.3.B Risks of Hereditary Effects for Human Beings



6.3.B Risks of Hereditary Effects for Human Beings

- Testicles or ovaries exposed to radiation
  - Gene mutations
  - Chromosome aberrations
    - Gains, losses
    - Deletions, inversions, translocations
- No evidence that this leads to inherited disease though ICRP estimated in 2007 that 0.2%/Gy (2 out of 1000 people) had possible heritable defects
- Epidemiologic studies on atomic bomb survivors





Deletion
centromere
+
Acentric Fragment
Ring
twist (before rejoin)
+
Acentric Fragment
Ring
Paracentric
Inversion
Pericentric

6.3.B Chromosomal Aberrations among Children of Atomic Bomb Survivors

Sources of aberrations	Number of children with chromosome aberrations (percentage)	
	Control group (7,976 children) Estimated exposure dose: <0.005 Gy	Exposed group (8,322 children) Average exposure dose: 0.6 Gy
Derived from either of the parents	15 (0.19%)	10 (0.12%)
Newly developed cases	1 (0.01%)	1 (0.01%)
Unknown (Examination of parents was not possible.)	9 (0.11%)	7 (0.08%)
Total	25 (0.31%)	18 (0.22%)

Source: "Chromosomal Aberrations among Children of Atomic Bomb Survivors (1967 - 1985 surveys)" on the website of the Radiation Effects Research Foundation (https://www.rerf.or.jp/programs/roadmap/health_effects/geneefx/chromeab/)

6.3.B Abnormalities at Birth among Children of Atomic Bomb Survivors (Malformations, Stillbirths, Deaths within Two Weeks)

- The surveys do not show any risks of congenital anomalies or stillbirths caused by fathers' radiation exposure.
- Mothers' exposure to radiation > 10 Gy in the ovary or womb increased premature births and stillbirths caused by deterioration of uterine function.

		Father's dose (Gy)			
		<0.01	0.01-0.49	0.5-0.99	>=1
Mother's dose (Gy)	<0.01	**2,257/45,234 (5.0%)**	**81/1,614 (5.0%)**	**12/238 (5.0%)**	**17/268 (6.3%)**
	0.01-0.49	**260/5,445 (4.8%)**	**54/1,171 (4.6%)**	**4/68 (5.9%)**	**2/65 (3.1%)**
	0.5-0.99	**44/651 (6.8%)**	**1/43 (2.3%)**	**4/47 (8.5%)**	**1/17 (5.9%)**
	>=1	**19/388 (4.9%)**	**2/30 (6.7%)**	**1/9 (11.1%)**	**1/15 (6.7%)**

6.3.B Classification of Radiation Effects

		Incubation period	e.g.	Mechanism of how radiation effects appear
Categories of effects	Somatic effects	Within several weeks = **Acute effects** (early effects)	**Acute radiation syndromes***1 Acute skin disease	Deterministic effects caused by cell deaths or cell degeneration*2 
		After the lapse of several months = **Late effects**	Abnormal fetal development (malformation)	
			Opacity of the lens	
			Cancer and leukemia	Stochastic effects due to mutation 
	Genetic/ Hereditary effects		Hereditary disorders	

*1: Major symptoms are vomiting within several hours after exposure, diarrhea continuing for several days to several weeks, decrease of the number of blood cells, bleeding, hair loss, transient male sterility, etc.
*2: Deterministic effects do not appear unless having been exposed to radiation exceeding a certain dose level.

6.3.C TYPE OF RADIATION DAMAGE
Acute (early) vs. late tissue or organ effects

- Acute effects manifest themselves soon after exposure to radiation and are characterized by:
  - Inflammation.
  - Edema (swelling caused by fluid in your body's tissues).
  - Skin changes: hair loss (alopecia), loss of superficial layers (desquamation)
  - Hemorrhage.
- Acute effects can be local or whole-body depending what was exposed to radiation.

6.3.C TYPE OF RADIATION DAMAGE
Acute (early) vs. late tissue or organ effects

- Radiation therapy
  - Acute: skin, mucous membranes
    - Rapidly dividing cells
    - Occur in most/all patients
    - Resolve in most/all patients
    - 2-4 weeks (dogs and cats and people)
  - Late: bone, nerve, lens
    - Slowly dividing tissues
    - Favors repair (6 hr)
    - Rare but permanent
    - Usually 6-12+ months after RT (dogs and cats)
      - (at least 3 months)
      - People longer

Early

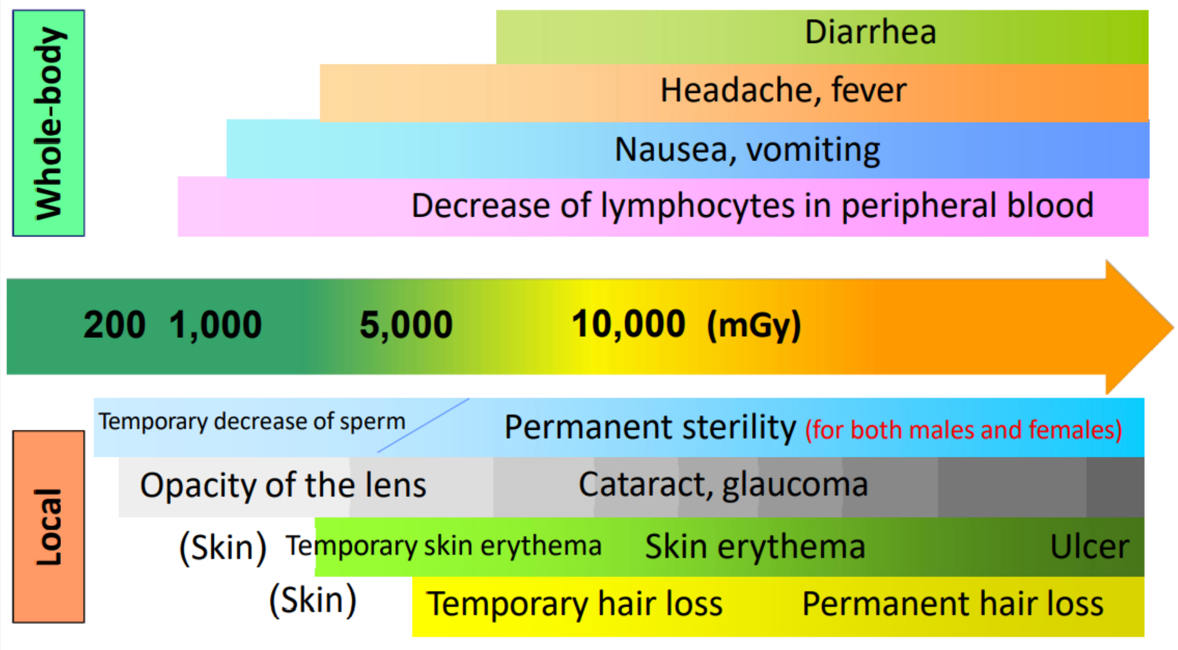
Desquamation

Late

Hair color change

- Leukotrichia
- Melanotrichia

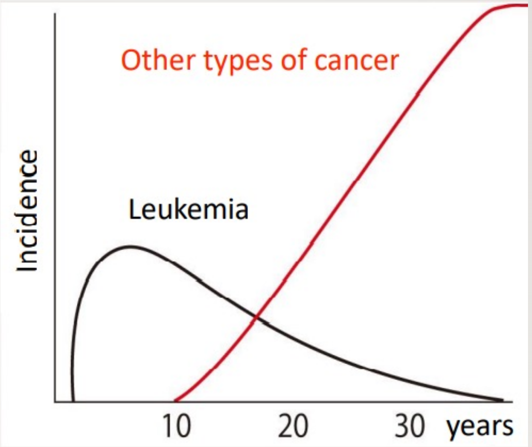
Whole-body Exposure and Local Exposure



Source: Rearranged based on the report of the Health Management Study Committee of the Nuclear Safety Commission (2000), etc

6.3.C TYPE OF RADIATION DAMAGE
Acute vs late tissue or organ effects

- Late effects have a LATENCY PERIOD: the time interval between exposure to radiation and the appearance of cancer
- Time course (humans)
  - Leukemia has a minimum latency of about 2 years after exposure; the pattern of risk over time peaks after ten years (most cases occur in the first 10-15 years) and decreases thereafter
  - Solid tumors show a longer latency than leukemia, by anything from 10 to 60 years or even more



CHAPTER 6. 3. Type of radiation damage TABLE OF CONTENTS (classes April 3rd, 8th, 10th, 15th)

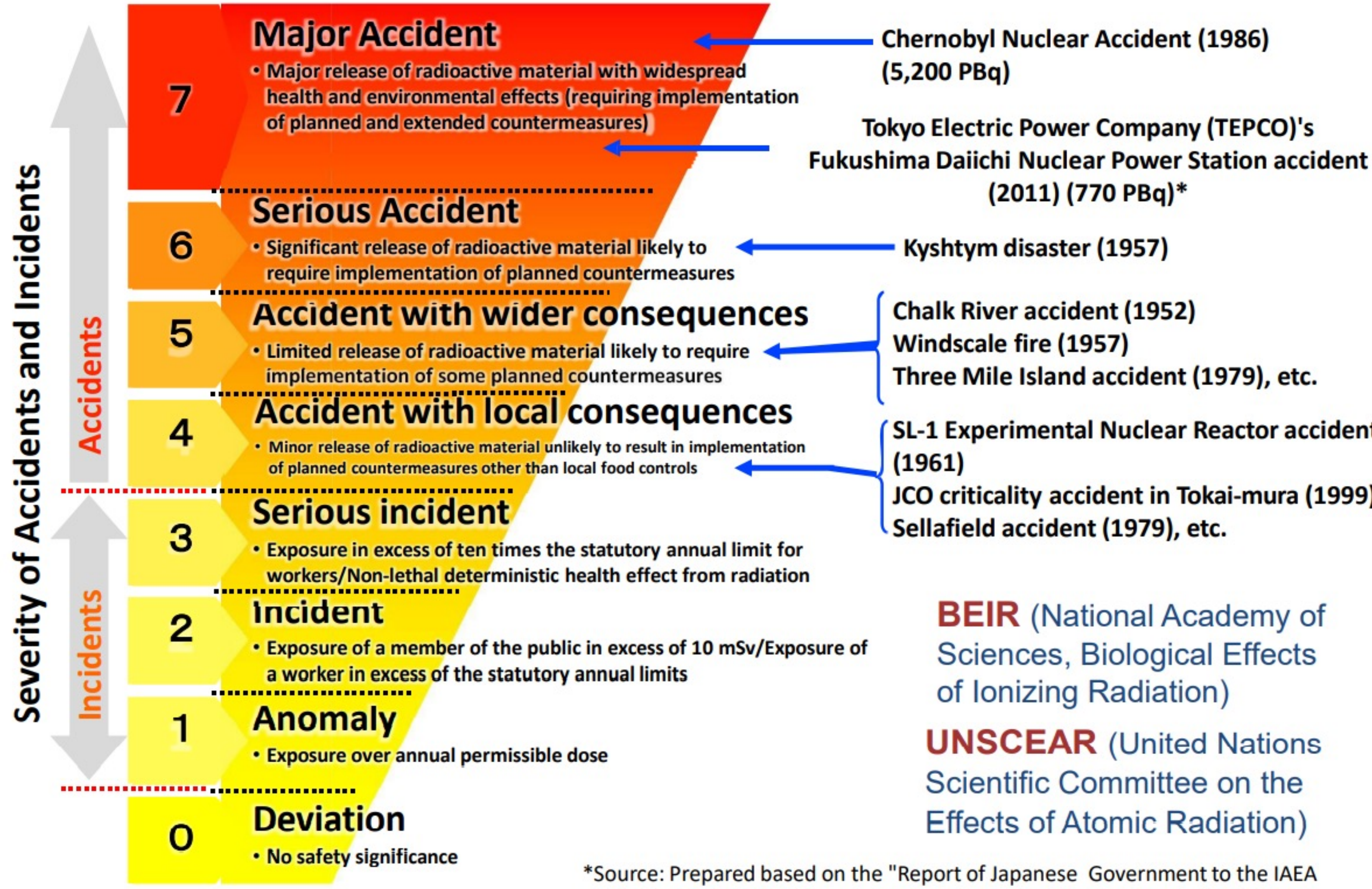
6.3.D TYPE OF RADIATION DAMAGE
Total body radiation exposure & ARS

- Acute radiation syndrome (ARS): occurs in humans after whole body exposure to large doses of ionizing radiation in short period of time.
- Response of an organism to acute total body irradiation exposure is influenced by the combined response to radiation of all organs constituting the organism.
- The effect on body systems depends on the total body dose above 1 Gy, and is described as THREE specific radiation syndromes:

• $1\ \text{Gy} < \text{Dose} < 10\ \text{Gy}$	(1) Hematopoietic syndrome
• $10\ \text{Gy} < \text{Dose} < 50\ \text{Gy}$	(2) Gastrointestinal syndrome
• $\text{Dose} > 50\ \text{Gy}$	(3) Central nervous system (CNS) syndrome

6.3.D TYPE OF RADIATION DAMAGE
Total body radiation exposure & ARS

- Sources of human data on specific radiation syndromes:
  - Accidents in industry and research laboratories (Chernobyl nuclear power plant accident)
  - Epidemiological studies of chronic exposures: Radium Dial Painters, Early Radiologists, Multiple Chest Fluoroscopy, Uranium Miners
  - Exposure to radioactive fallout from nuclear weapons testing (Marshall Islanders).
  - Atomic Bomb Survivors: Exposure of humans to high levels of radiation in Hiroshima and Nagasaki.
  - Medical exposure of humans to total body irradiations (TBIs, I131 therapy).

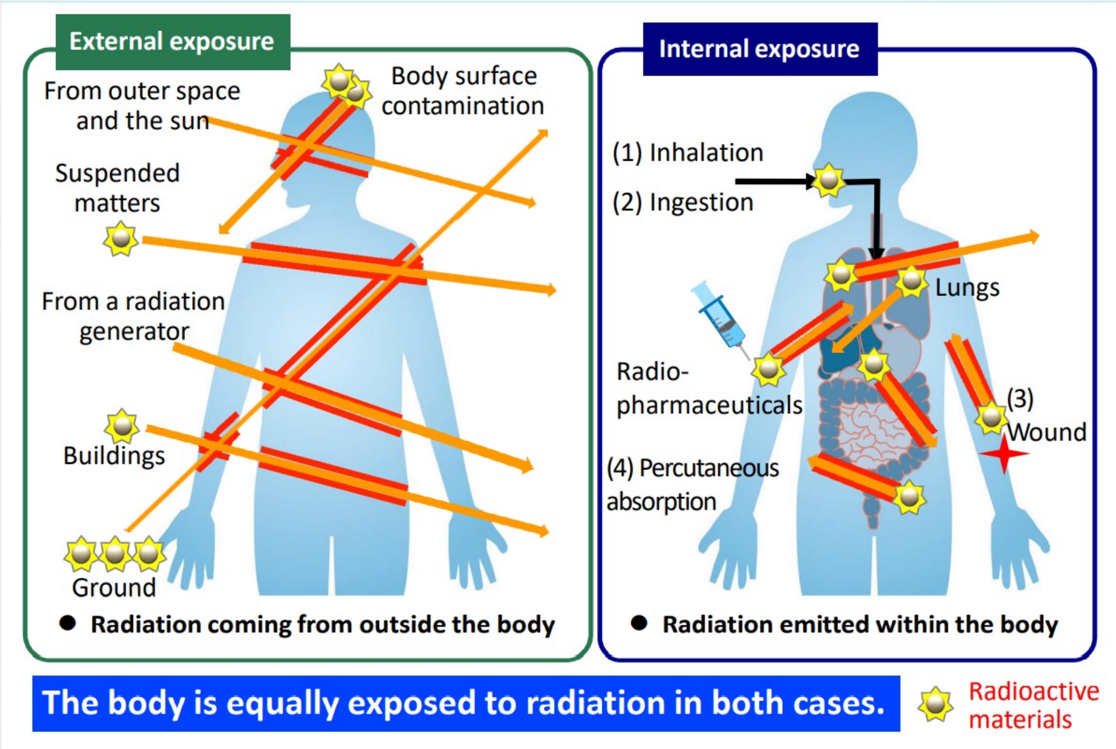


BEIR (National Academy of Sciences, Biological Effects of Ionizing Radiation)

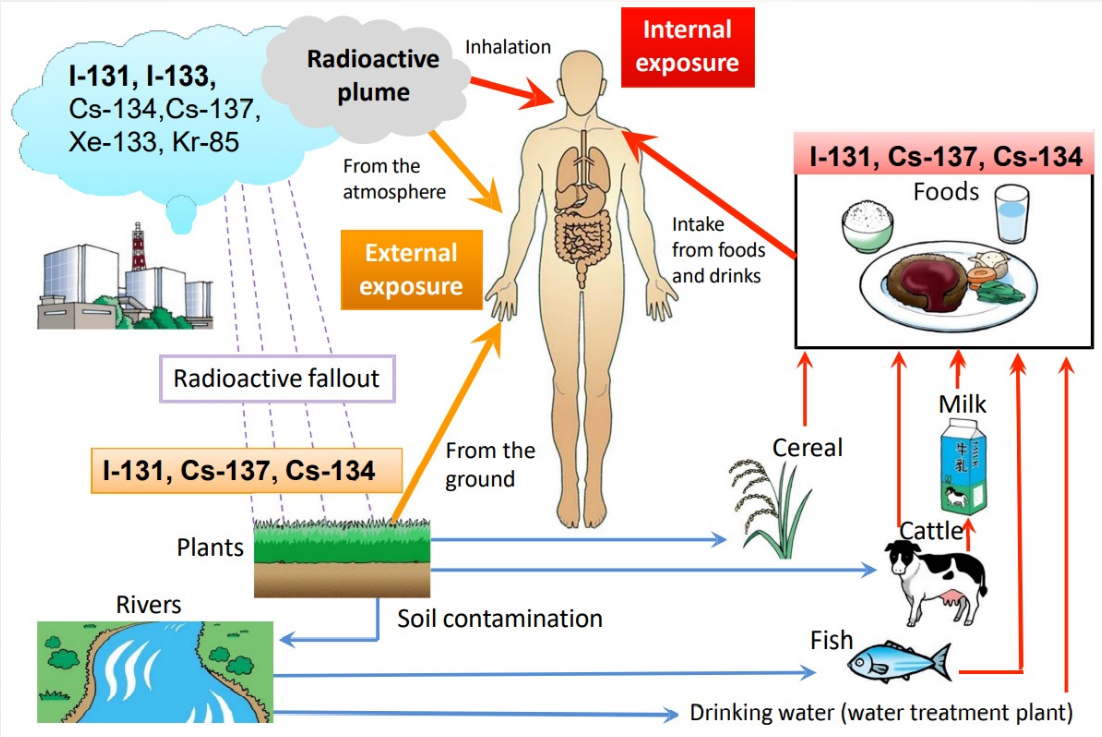
UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation)

*Source: Prepared based on the "Report of Japanese Government to the IAEA Ministerial Conference on Nuclear Safety" (June 2011)

Internal and External Exposure

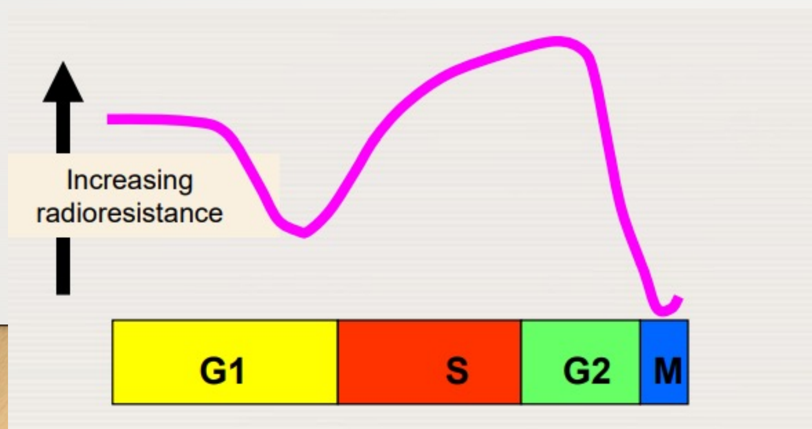


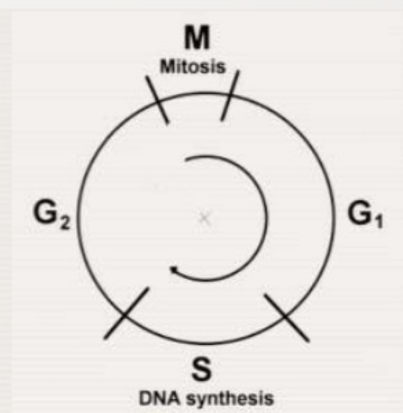
Effects of Reactor Accidents



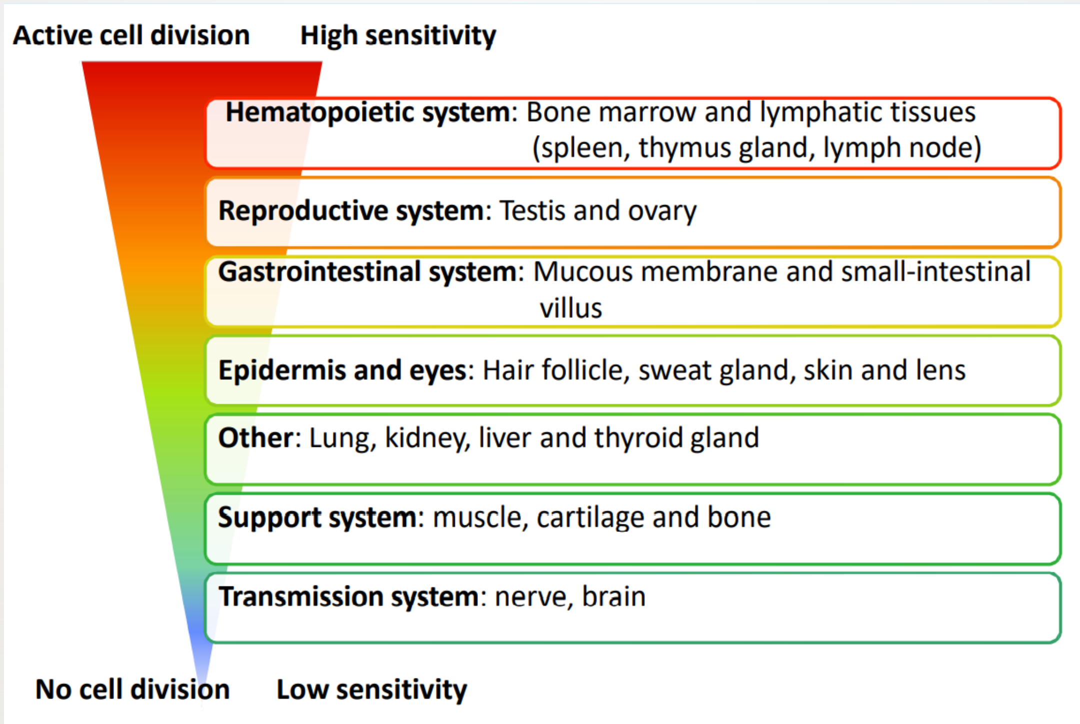
6.2 IRRADIATION OF CELLS

- Radiosensitivity differs throughout the cell cycle
- Law of Beronie’ and Tribondeau: the radiosensitivity of the cells is directly proportional to their reproductive activity and inversely proportional to their degree of differentiation (stem cells high reproductive activity, differentiated/mature cells do not have mitotic activity)

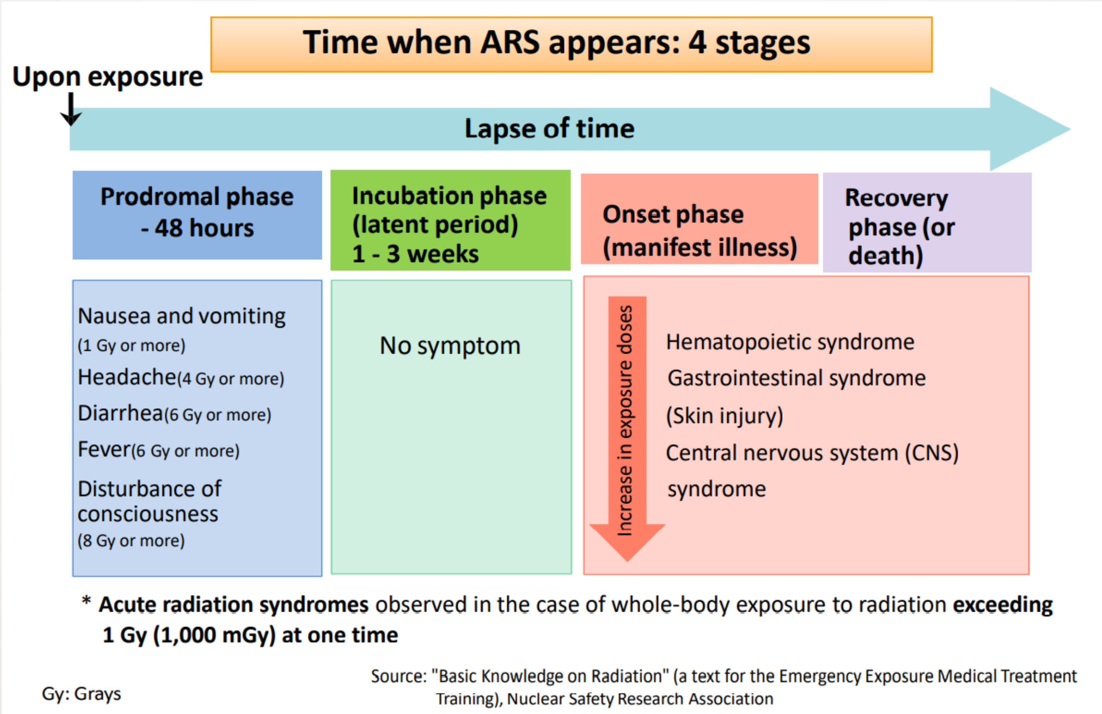




Radiosensitivity of Organs and Tissues



Acute Radiation Syndromes



6.3.D TYPE OF RADIATION DAMAGE
Total body radiation exposure & ARS

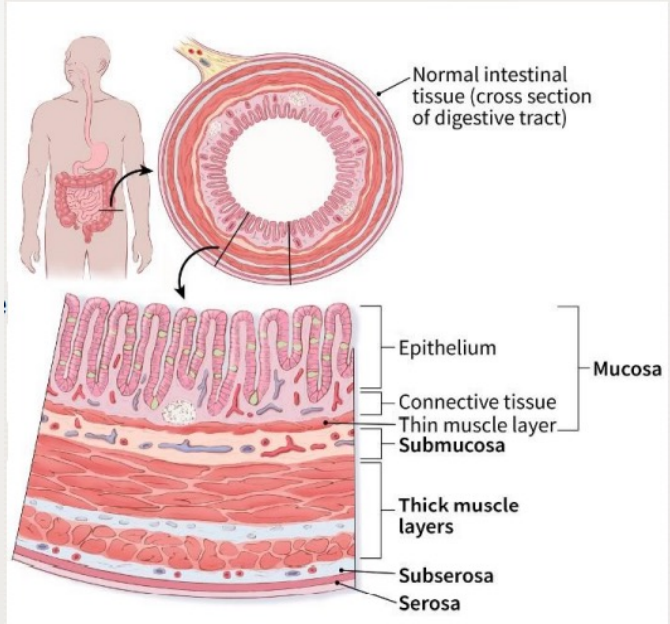
- Hematopoietic Syndrome (1-10 Gy)
  - Prodromal phase = mild (within a few hours and may persist for several days)
  - Latent period = no obvious signs of illness (lasts as long as 4 weeks)
    - Decreased red and white blood cell counts
  - Manifest illness
    - Possible vomiting, mild diarrhea, malaise, lethargy, and fever
    - If not lethal, recovery begins in 2 to 4 weeks, taking up to 6 months for full recovery
    - If the radiation injury is severe enough, low white blood cells leads to infection
    - Before death, hemorrhage and dehydration may be pronounced. Death occurs because of generalized infection, electrolyte imbalance, and dehydration.

6.3.D TYPE OF RADIATION DAMAGE
Total body radiation exposure & ARS

- Gastrointestinal Syndrome (10-50 Gy)
  - Prodromal phase = vomiting and diarrhea within hours of exposure and persists for hours to as long as a day.
  - Latent period = no symptoms are present (for 3 to 5 days)
  - Manifest illness
    - Second wave of nausea and vomiting, followed by diarrhea
    - Loss of appetite (anorexia) and may become lethargic
    - Diarrhea persists and becomes more severe.
    - Supportive therapy cannot prevent the rapid progression of symptoms that ultimately leads to death within 4 to 10 days of exposure.

6.3.D TYPE OF RADIATION DAMAGE
Total body radiation exposure & ARS

- Gastrointestinal Syndrome (10-50 Gy)
  - Intestinal cells are normally in a rapid state of proliferation and are continuously being replaced by new cells.
  - Turnover time for GI cells in a normal person = 3-5 days
  - Radiation exposure damages the proliferating cells
  - Without normal intestinal lining, fluids pass uncontrollably across the intestinal membrane, electrolyte balance is destroyed, and conditions promote infection.



6.3.D TYPE OF RADIATION DAMAGE
Total body radiation exposure & ARS

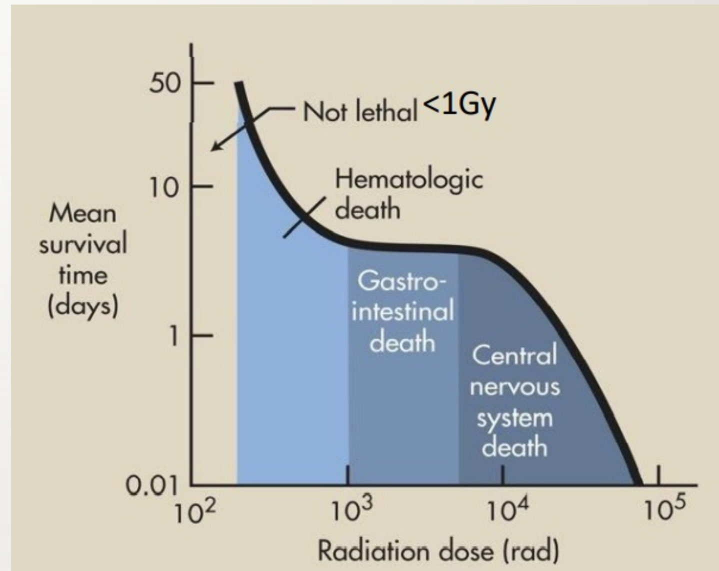
- <u>Central Nervous System (CNS) Syndrome (>50 Gy)</u>
  - Death within hours to days, even with medical care
  - Prodromal phase = severe nausea and vomiting, usually within a few minutes of exposure
    - The patient may become extremely nervous and confused, may describe a burning sensation in the skin, may lose vision, and can even lose consciousness within the first hour.
  - +/- Latent period (lasts up to 12 hours) - earlier symptoms subside or disappear
  - Manifest illness:
    - Symptoms of the prodromal stage return but are more severe.
    - Disorientation, loss of muscle coordination, difficulty breathing
    - Might have convulsive seizures, experience loss of equilibrium, ataxia, and lethargy
    - Lapses into a coma and dies.

6.3.D TYPE OF RADIATION DAMAGE
Total body radiation exposure & ARS

- Central Nervous System (CNS) Syndrome (>50 Gy)
  - Cause of death in CNS syndrome is increased fluid content of the brain (swelling)
  - Increased intracranial pressure, inflammatory changes in the blood vessels of the brain (vasculitis), and inflammation of the meninges (meningitis)
  - At doses sufficient to produce CNS damage, damage to all other organs of the body is equally severe.
  - Death occurs too quickly for the signs in other systems to appear (blood and GI)

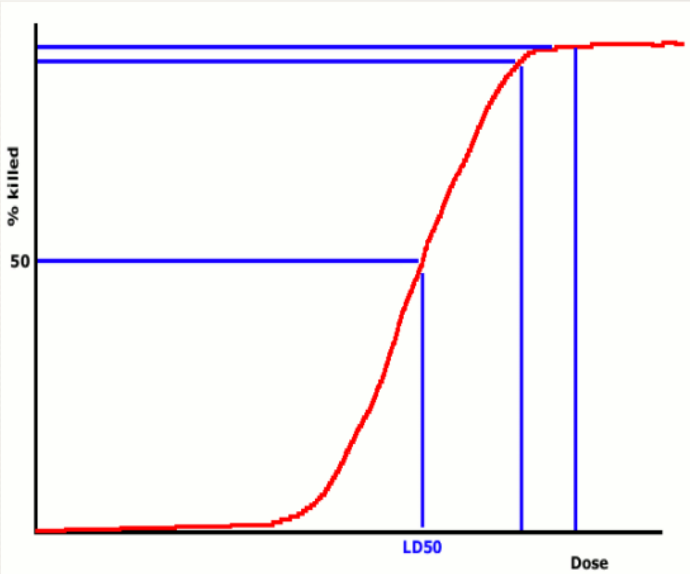
6.3.D TYPE OF RADIATION DAMAGE
Total body radiation exposure & ARS

- Acute radiation lethality follows a nonlinear, threshold dose-response relationship.
- > 6 Gy (600 rad), all those irradiated die unless vigorous medical support is available.
- > 10 Gy (1000 rad), even vigorous medical support does not prevent death.



6.3.D TYPE OF RADIATION DAMAGE
Total body radiation exposure & ARS

- Lethal dose LD50/30: The dose of radiation expected to cause death to 50 % of an exposed population within 30 days
- The LD 50/30 for adult human is estimated to be 3-4 Gy (3-4 Sv equivalent dose) without medical support, for x-ray and gamma ray
- Whole-body dose > 6 Gy may cause the death of the entire population in 30 days.



Source: ICRP Publications 118, 2012 and 103, 2007
https://www.nrc.gov/reading-rm/basicref/glossary/lethal-dose-ld.html

CHAPTER 6. 3. Type of radiation damage TABLE OF CONTENTS (classes April 3rd, 8th, 10th, 15th)

6.3.E Type of radiation damage
Dose in radiation safety

- Absorbed dose is a measure of the energy deposited in a medium by ionizing radiation.
  - Name of unit is **Gray** (Gy) where 1 Gy = 1 J/kg
- The sievert (symbol Sv) is the SI unit of dose equivalent.
  - The sievert represents the **stochastic** effects of different radiation types.
- W_R :weighting factor that accounts for type of ionizing radiation
- The rem (an acronym for roentgen-equivalent-man) was the cm-gram-second unit of effective dose and was officially replaced by the Sievert many years ago.
- 1 Sv = 100 rem

6.3.E Type of radiation damage Equivalent and effective dose

- Equivalent dose considers the type and energy of radiation
  - Equivalent Dose unit: Sievert (Sv)
  - ICRU defines Equivalent Dose as: $D_T \times W_R = H_T$
  - D_T = Absorbed dose to tissue type "T" – (Gy)
  - W_R = radiation weighting factor
  - H_T = Equivalent dose to tissue type "T" – (Sv)

- Effective dose considers the radiosensitivity of the tissue/organ

6.3.E Types of radiation damage

Equivalent Dose: Radiation Weighting Factors- W_R

Radiation Type		w_R
Photons, electrons, positrons, mu mesons		1
Protons		2
Neutrons	< 10 keV	5
	10 keV to 100 keV	10
	100 keV to 2 MeV	20
	2 MeV to 20 MeV	10
	> 20 MeV	5
Alpha particles, fissile fragments, nuclei		20

$$D_T \times W_R = H_T$$

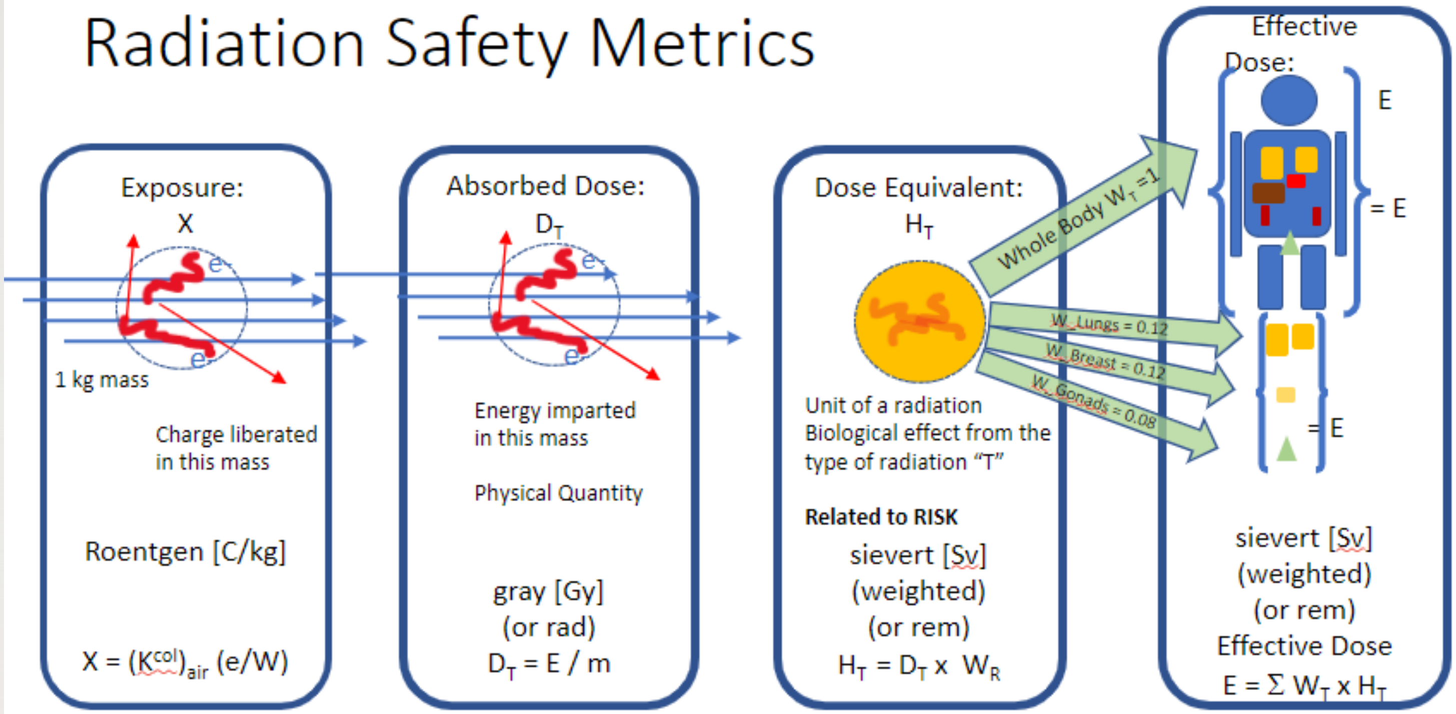
Effective Dose-Tissue Weighting Factors W_T

Body tissue	ICRP 60	ICRP 103
Lung	0.12	0.12
Colon	0.12	0.12
Stomach	0.12	0.12
Breast	0.05	0.12
Bladder	0.05	0.04
Liver	0.05	0.04
Esophagus	0.05	0.04
Thyroid	0.05	0.04
Skin	0.01	0.01
Bone surface	0.01	0.01
Brain		0.01
Salivary glands		0.01
Gonads	0.20	0.08
Red bone marrow	0.12	0.12
Remainder	0.05	0.12
Total	1.00	1.00

6.3.E Types of radiation damage
Effective dose

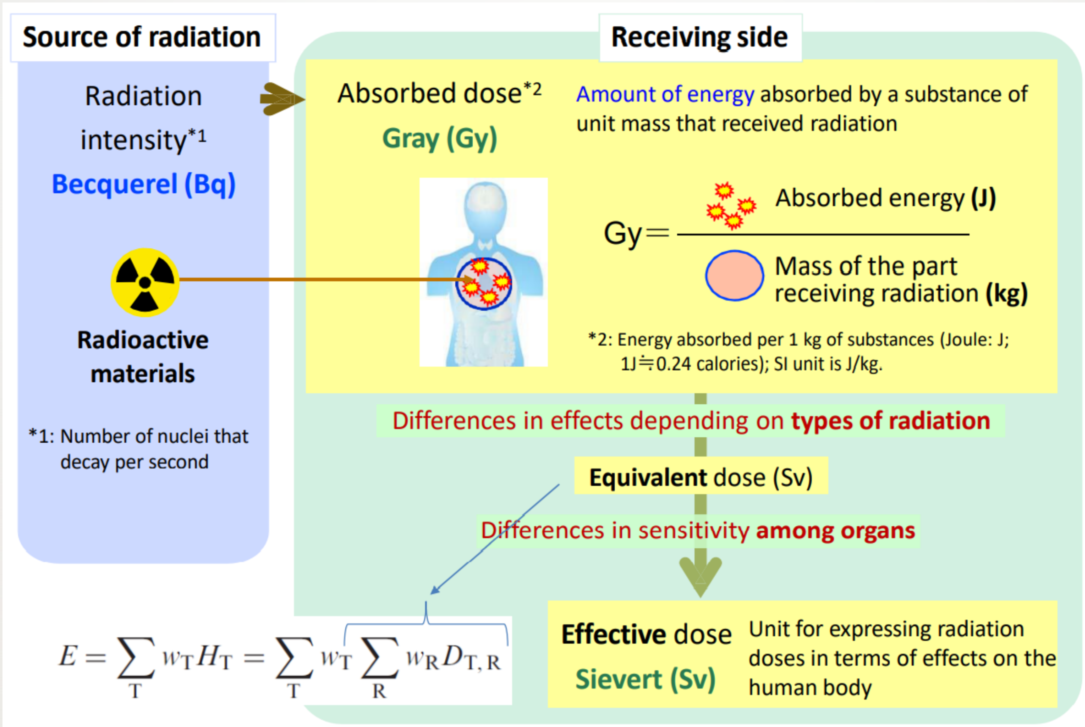
- Compares the stochastic risk of different types of tissues
  - Different tissues have different risks of developing fatal cancers from the same physical dose.
- Tissue-weighted sum of the *equivalent doses* in all specified tissues of the human body
  - Effective dose carries the same effective risk as the same equivalent dose applied uniformly to the whole body

Radiation Safety Metrics

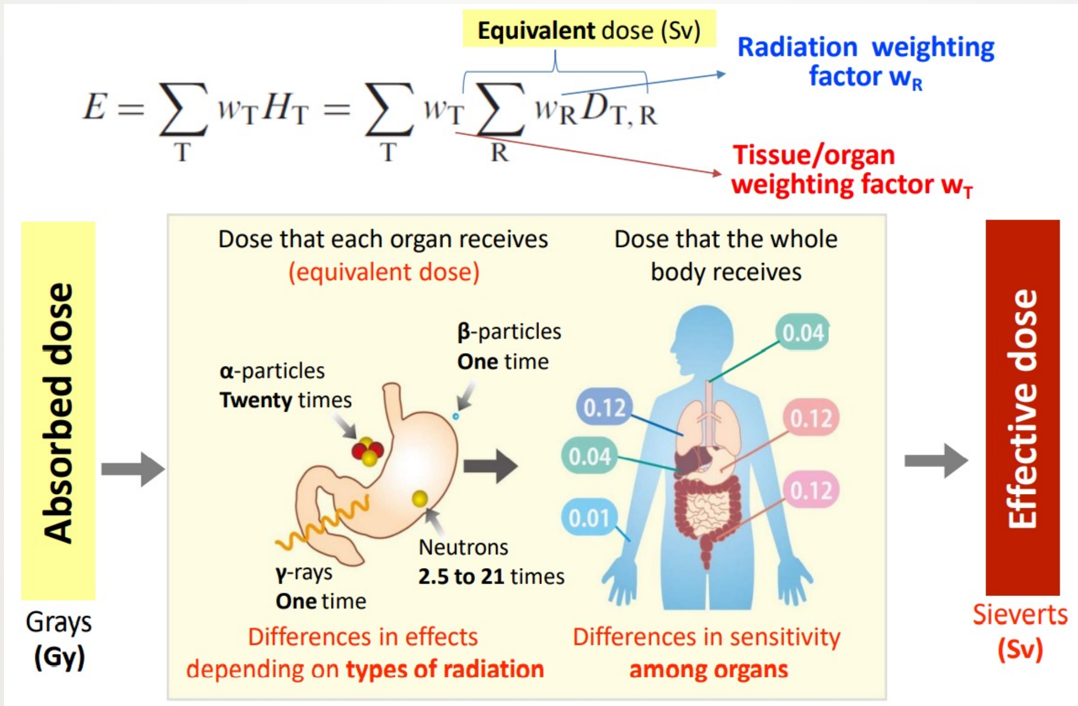


Slide from P. Basran

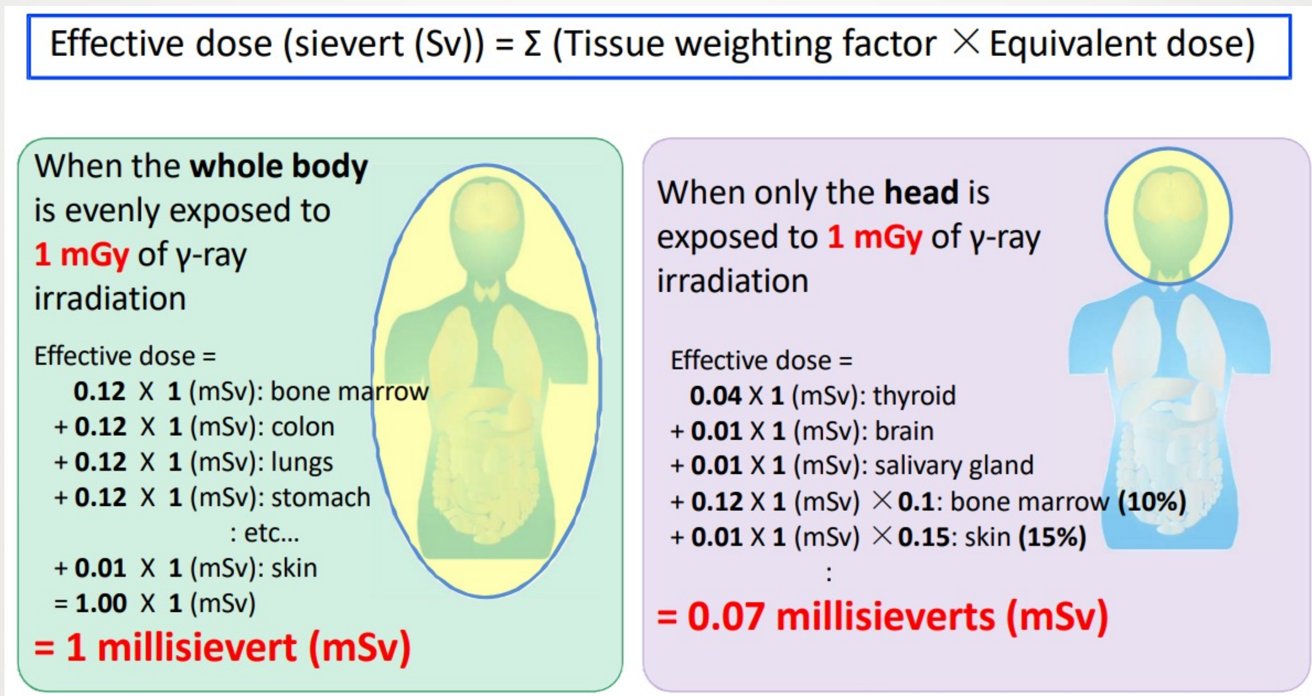
Units of radiation: relationship between units



Units of radiation: convert Gray to Sievert



Calculation of Equivalent Dose and Effective Dose



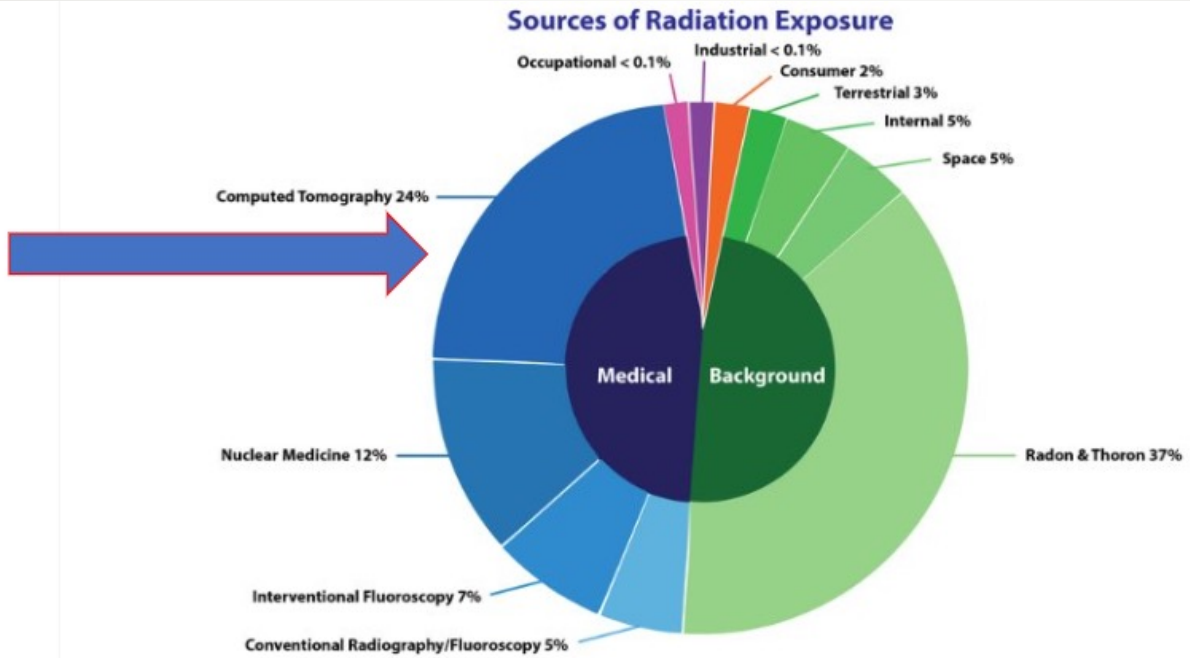
Radiation safety

- ALARA - As Low As Reasonably Achievable
- Time
- Distance
- Shielding

Natural background radiation

- Natural background radiation is everywhere
  - Terrestrial and cosmic sources
  - Variable by location
- Typical natural background are about:
  - 0.6 mSv in NE, E, W, and Central States;
  - 0.45 mSv in Atlantic and Gulf Coastal states
  - 1.2 mSv in Colorado Plateau
- Largest single source is radon, locally variable, national average = 2 mSv/yr
- Exposure from all sources are equivalent
- Medical ~ Occupational ~ Background Exposure

Sources of radiation exposure in the US



Average Annual Radiation Dose

Sources	Radon & Thoron	Computed Tomography	Nuclear Medicine	Interventional Fluoroscopy	Space	Conventional Radiography/ Fluoroscopy	Internal	Terrestrial	Consumer	Occupational	Industrial
Units mrem (United States) mSv (International)	228 mrem 2.28 mSv	147 mrem 1.47 mSv	77 mrem 0.77 mSv	43 mrem 0.43 mSv	33 mrem 0.33 mSv	33 mrem 0.33mSv	29 mrem 0.29 mSv	21 mrem 0.21 mSv	13 mrem 0.13 mSv	0.5 mrem 0.005 mSv	0.3 mrem 0.003 mSv

(Source: National Council on Radiation Protection & Measurements, Report No. 160)

“One in a million” (NRC regulatory guide, risks from occupational radiation exposure)

- Being a 60-year-old male for 20 minutes
- Living in New York City for 2 days
- Riding 6 miles on a bicycle
- Driving 300 miles in a car
- Flying 1,000 miles in an airplane
- Working 10 days in a factory
- Smoking 1.4 cigarettes

Maximum Permissible Dose

- What is the MPD for Radiation Workers?
  - 50 mSv/year
  - 1.0 mSv/week
- Pregnant Workers?
  - 5.0 mSv/entire pregnancy
  - 0.1 mSv/week

Basic Exposure Limits from NCRP Report No. 116 and ICRP Publication 60

	NCRP-116	ICRP-60
Occupational Exposure		
Effective Dose		
Annual	50 mSv	50 mSv
Cumulative	10 mSv × age (y)	100 mSv in 5 y
Equivalent Dose		
Annual	150 mSv lens of eye; 500 mSv skin, hands, feet	150 mSv lens of eye; 500 mSv skin, hands, feet
Exposure of Public		
Effective Dose		
Annual	1 mSv if continuous 5 mSv if infrequent	1 mSv; higher if needed, provided 5-y annual average ≤ 1 mSv
Equivalent Dose		
Annual	15 mSv lens of eye; 50 mSv skin, hands, feet	15 mSv lens of eye; 50 mSv skin, hands, feet

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