Authorized User Training for Research PIs

Module 5: Radiation Biology and Radiation Protection Standards

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Introduction

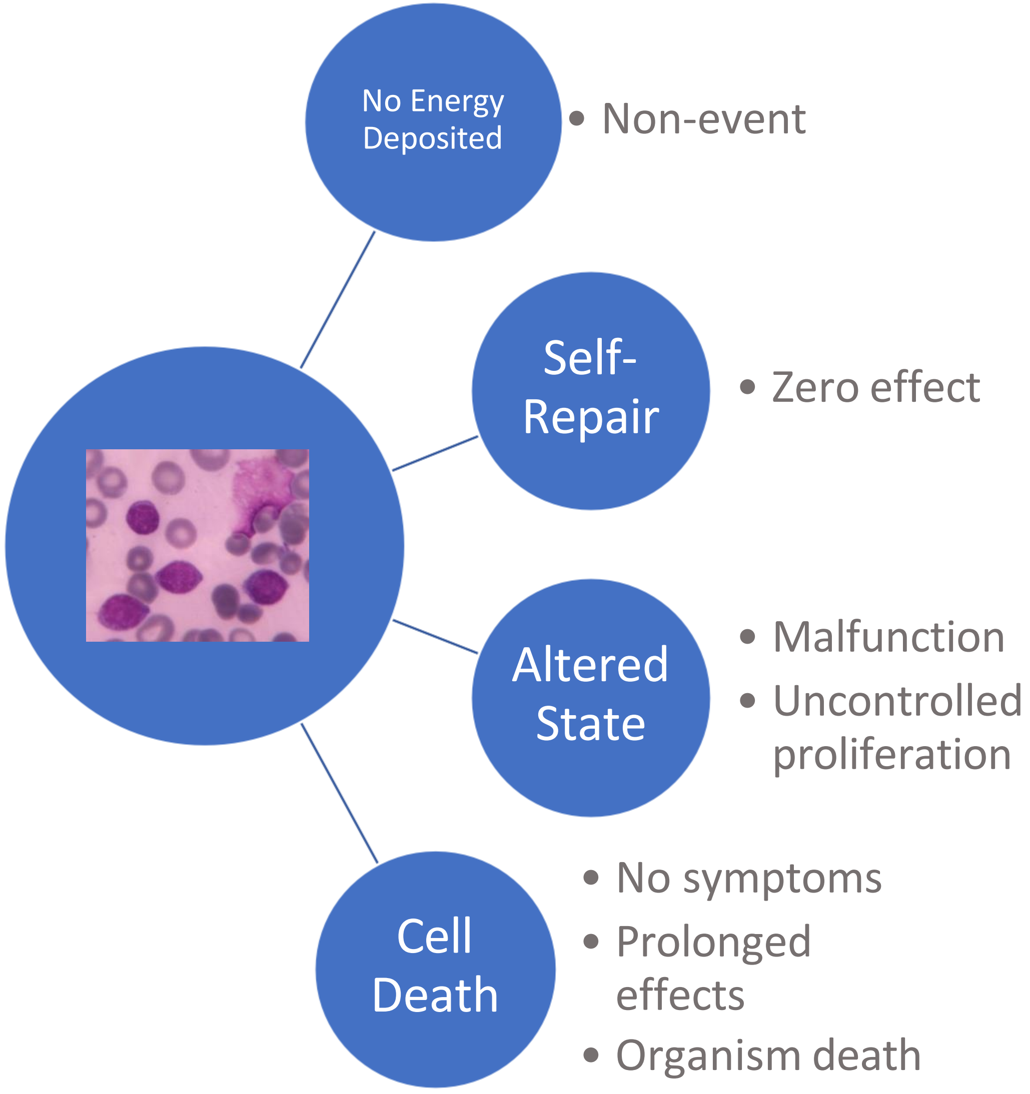
- This module introduces the basic concepts and terminology of radiation biology.
- Also included are the consequences and bioeffects of ionizing radiation interactions with tissue and cells.
- Radiation protection standards are linked to radiation biology, and therefore are introduced to the reader in this module.
- After completing this module, the reader will be knowledgeable about radiation-induced bioeffects and how safety could be impacted by occupational exposure.
- Assigned reading:

  5.1. NRC Reg Guide 8.29, Instruction Concerning Risks from Occupational Radiation Exposure, 1981
  5.2. NRC Reg Guide 8.13, Instruction Concerning Prenatal Radiation Exposure, 1999

Outline

- Basic Concepts of Radiation Biology
- Interactions with Tissue and Cells
- Dose Response Curves
- Stochastic and Non-stochastic Effects of Radiation
- Acute and Delayed Biological Effects
- Radiation protection standards
- Occupational Dose Limits – General Public and Radiation Workers
- Quiz

Biological Effect of Ionizing Radiation



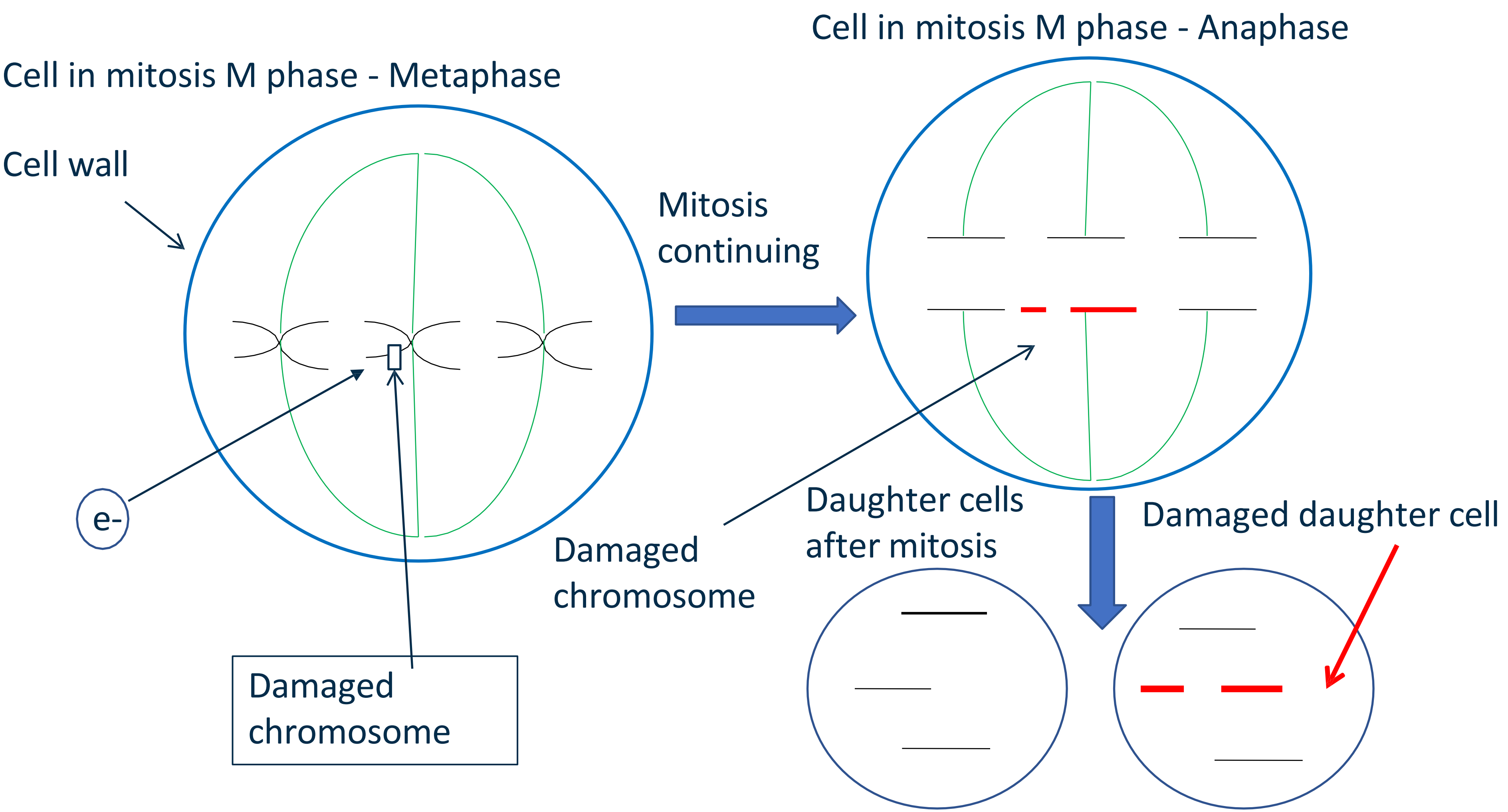
- The diagram shows the 4 possible outcomes when cells are exposed to ionizing radiation:
  1. Most of the time, no damage.
  2. Sometimes, damage that is repaired.
  3. Sometimes, damage where the repair fails and a malfunctioning cell results.
  4. Lastly, cell death, if there is enough radiation in a short period of time.
- Biological damage can occur through:
  - Single-strand DNA breaks
  - Double-strand DNA breaks

Basic Concept: Radiosensitivity

- In 1906, Bergonié and Tribondeau made the initial assumptions of radiation biology:
  - Cells that are young, undifferentiated, and actively dividing are more radiosensitive, e.g., bone marrow and reproductive cells.
  - Cells that are mature, differentiated, and not actively dividing are more radioresistant, e.g., nerve and connective cells.
- In general, the radiosensitivity of a cell is directly proportional to division rate and inversely proportional to the state of differentiation.
- DNA is the critical target of ionizing radiation. For actively dividing cells at M phase during mitosis, chromosomes are condensed, paired, and aligned along the cellular equator.
- With the double helix configuration, there are single-strand and double-strand DNA breaks.
- For non-actively dividing cells, the break of one bond will not cause cell damage, and this broken bond could be repaired within the cell.

Basic Concept: Radiosensitivity *(continued)*

Example of ionizing radiation (electron) interaction with chromosome of an actively dividing cell



Basic Concept: Radiosensitivity *(continued)*

Examples of relative radiosensitivity of organs and tissue	
Relative sensitivity	Organs and tissue
High	Lymphoid organs, bone marrow, intestines, reproductive organs
Fairly High	Skin, lens, stomach, organs with epidermoid linings such as oral cavity, bladder
Medium	Fine vasculature, growing bone
Fairly Low	Mature bone, salivary glands, kidney, liver, thyroid, pancreas
Low	Muscle, brain, spinal cord

These effects are for very large, acute doses of radiation; external beam radiation therapy would be an example.

Reference: Rubin P, Casarett GW. Clinical Radiation Pathology As Applied to Curative Radiotherapy. *Cancer*. 1968;22(4):767-78.

Basic Concept: Radiation Effects and Time

- DNA damage due to ionizing radiation is the primary biological effect that leads to acute and delayed syndromes and effects.
- Mammalian DNA can be damaged directly by radiation or indirectly by free radicals (discussed in the following section).
- The free radicals are created in water, a process that involves physical and chemical stages which happens in less than 10^{-6} s. Free radicals diffuse to the vicinity of DNA and cause chemical bond breaks in less than 10^{-3} s.
- The damage to DNA affects cell division in the next few hours after a complete cell cycle.
- The acute syndrome is often noticed in the following days or weeks, and long-term effects may be expressed over decades.

Basic Concept: Radiation Effects and Time *(continued)*

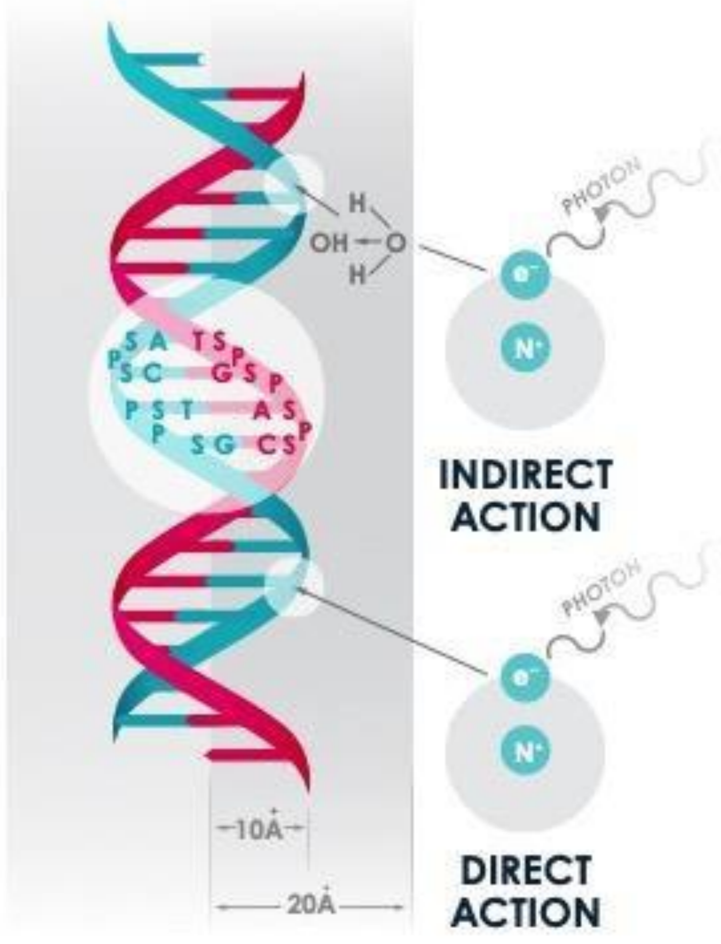
General ionizing radiation reaction time frame	
Physical and chemical stage: $\leq 10^{-6}$ s	Formation of free radicals
Biological stage I: $\leq 10^{-3}$ s	Free radicals react with biological molecules, chemical bonds break
Biological stage II: Second, minutes, hours	Cell division malfunction
Biological stage III: Days, weeks, years	Acute syndrome (tiredness, nausea, etc.) Delayed effect (cancer, cataracts, etc.)

Types of Radiative Interactions with Tissue and Cells

- Because about 70% to 80% of mammalian cells are composed of water, ionizing radiation's reaction with water is relevant to understanding biological effects.
- When interacting with a water molecule, ionizing radiation produces charged particles —electrons or protons. DNA can be damaged either directly or indirectly by these charged particles.
- In direct action, electrons or protons break the DNA chemical bond through electric forces.
- With indirect action, the secondary electrons or protons interact with other water molecules in the vicinity of DNA to create free radicals which in turn break the DNA chemical bond.
- A free radical is a neutrally charged atom or molecule with an unpaired electron, for example, hydroxyl radical "OH." The unpaired electron is highly reactive and breaks DNA bonds chemically.

Ionizing Radiation's Biological Impact

- Direct Action
  - Radiation directly ionizes a DNA atom, ultimately producing a biological effect
  - Accounts for ~1/3 of double strand breaks (DSBs)
- Indirect Action
  - Radiation ionizes a non-critical target, resulting in production of free radicals which then interact with DNA, producing a biological effect
  - Accounts for ~2/3 of DSBs



Dose Response Curves

- Biological effects are related to the amount of radiation received. They can be modeled as response functions of radiation dose.
- The four most popular dose response models used at present:
  - Linear no threshold
  - Linear threshold
  - Linear quadratic
  - Hormesis

Dose Response Curves *(continued)*

- The **linear no threshold model** states that the biological effect is a linear function of radiation dose: at zero dose, there is no biological effect, but no matter how low the radiation dose is, there is always a probability to induce cancer, and this probability increases linearly as the dose gets higher.
  - Using sun exposure as an analogy: every minute exposed to the sun is harmful.
- The **linear threshold model** states that there exists a dose threshold below which there is no biological effect, but beyond this level, the possibility to induce cancer increases linearly as dose gets higher.
  - The Health Physics Society suggests that if an individual's annual dose is below 5 rem or lifetime dose is less than 10 rem (in addition to background radiation), the risk of health effects is either too small to be observed or nonexistent.[1]
  - Continuing the sun analogy: one hour in the sun does not cause any harmful effects, but after one hour, harmful effects can be seen and get worse the longer you spend in the sun.

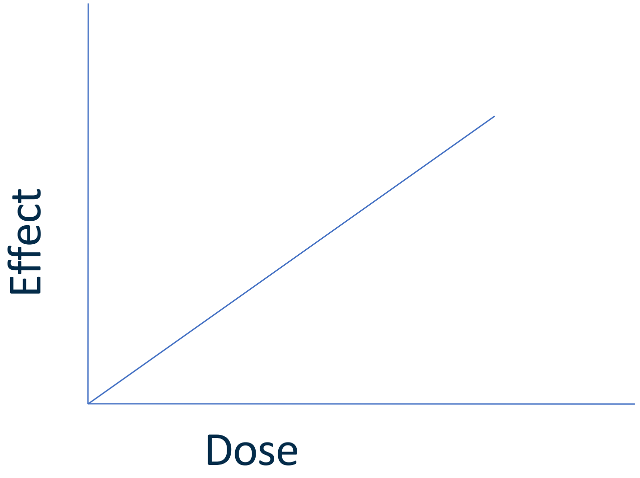
Reference: 1. Burk, RJ. Radiation Risk in Perspective. Position Statement of Health Physics Society. Revised Aug 2004.

Dose Response Curves *(continued)*

- The **linear quadratic model** states that the probability to induce cancer increases linearly at low doses, while the probability curve is quadratic at higher doses.
  - Minutes of sun exposure are a little bad, but hours of prolonged exposure get really bad.
- The **hormesis model** states that at low doses above background radiation, the ionizing radiation is beneficial. The idea is that the body becomes more adaptive at single-strand and double-strand DNA repair. The hormesis model is a J-shaped dose response curve.
  - Small amounts of sun exposure are actually good for you and reduce other harmful effects, but prolonged exposure overcomes your body's ability to respond to stimuli and the sun becomes harmful again.

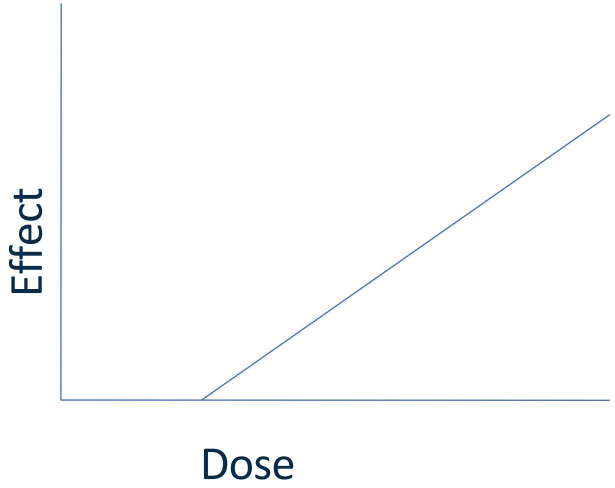
Dose Response Curves *(continued)*

Linear no threshold dose response



Linear no threshold (LNT) model – any amount of radiation results in a health effect. This is the model used by regulatory agencies to set occupational dose limits, general public dose limits, and patient release criteria. The model has been criticized and challenged as being too conservative, leading to excessively stringent standards and unnecessarily adding to the costs of regulatory compliance.

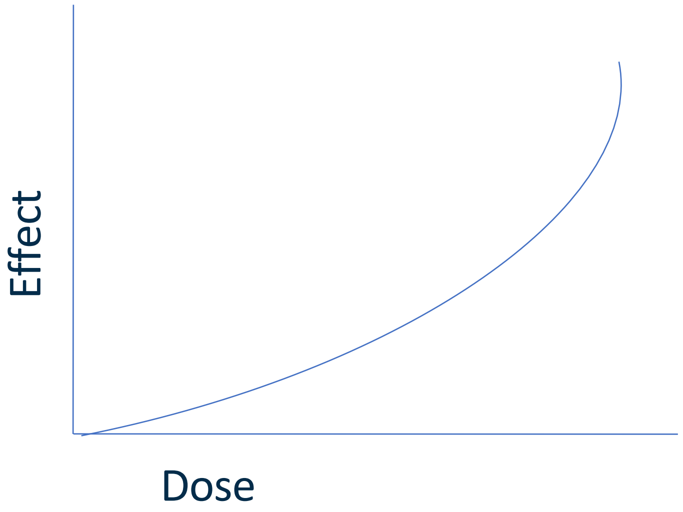
Linear threshold dose response



Linear threshold model – below a certain amount of radiation, no health effect is noticed

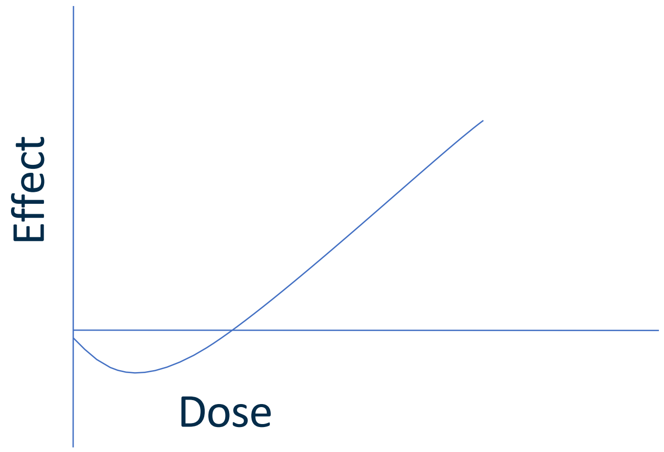
Dose Response Curves *(continued)*

Linear quadratic dose response



Linear quadratic model – at low levels of radiation, the health effect is linear. At high radiation levels, the health effect is quadratic.

Hormesis dose response



Hormesis model – the negative part of the dose response curve suggests that low-level radiation is beneficial to health

Stochastic and Non-stochastic Effects of Radiation

- The biological effect of radiation depends on the dose, type of radiation, and target organ or tissue. In general, it can be divided into two categories, stochastic and non-stochastic.
  - **Stochastic**, or probabilistic, means a health effect that occurs randomly and for which the *probability* of the effect's occurring, rather than its *severity*, is a linear function of dose without threshold. Major stochastic effects are (a) heritable abnormalities caused by genetic mutations and (b) cancer. Heritable effects have only been demonstrated in fruit flies and mice, and never in humans, thereby leaving cancer as the only stochastic outcome of concern.
  - **Non-stochastic**, or **deterministic**, means health effects whose *severity* is dependent upon the dose and for which a threshold exists. Typical non-stochastic effects are radiation-induced cataracts (an occupational risk for radiation workers), skin erythema, epilation and ulceration (a risk for high dose fluoroscopy patients).
- From the above definitions, the differences between stochastic and deterministic effects are:
  - Stochastic effects have no dose threshold; deterministic effects have a dose threshold.
  - Stochastic effects are random, and the probability of occurrence increases with dose; deterministic effects are certain and predictable.
  - The severity of stochastic effects is not related to radiation dose; the severity of deterministic effects is dose-related.

The stochastic effect of exposure to sun is skin cancer. The higher the exposure, the higher is the probability of developing melanoma. The deterministic effects of sun exposure are freckles and sunburn. The higher the exposure, the more severe sunburns can get.

Acute Biological Effects

- Acute exposure to ionizing radiation has no quantifiable health effect at background or occupational levels, but it can be harmful in large quantities.
- A single, large, short-term, whole-body dose of acute ionizing radiation causes "acute syndrome," where vital tissues and organs are damaged simultaneously. The severity and effects depend on the dose, and specific responses differ from person to person.
  - Think of exposure to sunlight. A little bit over a short period of time is fine. However, if you were to spend 100 times the amount of time 100 times closer to the sun, the effect would be devastating.
- The lethal dose that would be fatal to about 50% of a species in 30 days is indicated as LD50/30. The LD50/30 for humans is about 4 Gy (Gray) of an acute dose of whole body gamma radiation without medical intervention.
  - Note that this is a tremendous amount of radiation which would be impossible to generate in a typical veterinary nuclear medicine practice.

Acute Biological Effects *(continued)*

Effective Dose Received from Common Clinical Diagnostic Exams[2]	
Exam	Effective Dose (mrem)
Lumbar Spine AP X-Ray	70
Mammogram Four View	70
Dental Panoramic	9
CT Head	200
CT Chest	700
CT Abdomen	1000
Angioplasty Heat Study	750–5700
Various PET Studies with ^{18}F FDG	1400

Reference: 2. Radiation Exposure From Medical Diagnostic Imaging Procedures. Health Physics Society Fact Sheet.

Acute Biological Effects *(continued)*

- Acute syndrome can be characterized by four stages:

1. **Prodromal period:**
   - Lasts 48 hours after exposure
   - Signs and symptoms include tiredness, nausea, loss of appetite, and sweating
2. **Latent stage:**
   - Lasts from 48 hours to about 3 weeks after exposure
   - No signs or symptoms during this stage
3. **Manifest stage:**
   - Lasts until 6 to 8 weeks after exposure
   - Hematologic system damaged, GI symptoms occur. Other symptoms include fever, loss of hair, etc. Signs and symptoms return to prodromal level or worse.
4. **Recovery stage:**
   - Reached if the individual survives the third stage
   - Lasts an additional several weeks or months

- Acute syndrome should not be seen in a veterinary or human nuclear medicine practice.

Acute Biological Effects *(continued)*

Acute Clinical Effects of Ionizing Radiation[3]		
Dose (rem) to whole body	Characteristic Symptom(s)	Incidence of Death
0–100	None	None
100–200	Mild leukopenia	None
200–600	Severe leukopenia, hemorrhage, hair loss	0–80%
600–1000	Severe leukopenia, infection, erythema	80–100%
1000–5000	Diarrhea, fever, electrolyte imbalance	90–100%
>5000	Convulsion, tremor, ataxia, lethargy	90–100%

Reference: 3. National Council on Radiation Protection and Measurements. Report 107: Implementation of the Principle of as Low as Reasonably Achievable (ALARA) for Medical and Dental Personnel. Bethesda, MD; 1990.

Delayed Biological Effects

- Delayed effects may be caused by exposure to external or internal ionizing radiation. Primary delayed effects are stochastic, but some are non-stochastic.
- Cancer is the major concern among stochastic delayed effects. It is impossible to accurately estimate the occurrence of cancer at low radiation levels, but cancer risk has been extrapolated from human data at high doses, primarily from Hiroshima and Nagasaki atom bomb survivors.
  - The prevalent model for radiation-induced solid cancer and leukemia comes from the BEIR-VII report (National Academy of Science's committee on Biological Effects of Ionizing Radiaiton), 2006: The baseline rate of cancer induction is 42%*, *i.e.*, 42 out of 100 people will be diagnosed with cancer unrelated to radiation exposure. If these 100 people were exposed to 10 rem (100 mSv) of ionizing radiation, there would be **one** additional cancer in the group; *i.e*, the risk would increase from 42% to 43%, thereby providing a *Lifetime Attributable Risk* of 1% per 100 mSv. The model is based on the LNT hypothesis, and is controversial. A more recent model, ICRP-103 (International Commission on Radiological Protection), 2008, derives an *Overall Detriment* of 0.5% per 100 mSv, or half the risk predicted by the BEIR-VII model.
  - The cancer risk coefficient of 1% per 100 mSv *must not* be used to derive cancer risk for medically-necessary use of radiation, because there is no evidence of such an effect. Sensational media articles are often published based on this estimate, leading to numerous patients cancelling much-needed and lifesaving diagnostic medical procedures that use radiation.

*The 42% figure comes from the weighted average of probability of developing cancer in the US, of 43.9% in males and 37.4% in females, during the time period 2003-2005. Current statistics, for 2015-2017, are 40.5% for males and 38.9% for females, Cancer Facts and Figures 2021, American Cancer Society.

Delayed Biological Effects (continued)

Cataracts are a typical non-stochastic effect of radiation, significant for radiation workers. The occupational dose limit for Lens of the Eye is 15 rem/y, more stringent the limit for any other organ of the body (50 rem/y).

- The NCRP (National Council on Radiation Protection and Measurement), in 2016, recommended making the Lens of the Eye standard more restrictive, down to 5 rad/y (= 5 rem/y for a beta emitter such as ^{90}Y), based on a recent uptick in radiation induced cataracts in many parts of the world. However, this still remains a recommendation, and has not been adopted as a regulation by the NRC or Agreement States.

Radiation Protection Standards

- **Natural Background Radiation** pervades our planet. We are all exposed to it from cosmic rays, from soils and rocks, and from food and water. Background radiation is higher at greater altitudes, and in regions where heavy elements predominate the ground. Across much of the United States, we are exposed to about **300 mrem** of natural background per year, which adds up to 24,000 mrem (24 rem) over an 80 year lifetime. People living on the Colorado Plateau receive about 450 mrem per year, due to its elevation and minerals in the rocky mountains. The world average is about 240 mrem per year. There also are Very High Background Radiation Areas (VHBRAs) where people are exposed to several thousand mrem over their lifetime, with no statistically significant adverse health effects.

- **Medical Radiation** from diagnostic imaging exams (x-rays, CT scans, nuclear medicine exams) and radiation therapy procedures (including radiation dose to families of pets that have undergone ^{131}I, ^{90}Y or ^{117m}Sn procedures) constitute another significant source of radiation to the public. Medical radiation dose *per capita* in the US increased from 53 mrem in 1989 to 300 mrem in 2009, and has since decreased slightly to 220 mrem in 2019.

- **Radiation Protection Standards** are designed to protect people from the harmful effects of radiation. They are quoted as Occupational Dose Limits (ODLs), and exclude Natural Background Radiation, Medical Radiation, as well as other anthropogenic sources such as nuclear fallout.

Radiation Protection Standards *(continued)*

- There are two classes of ODLs:
  1. For members of the general public, and
  2. For radiation workers, declared pregnant workers, and minors

- Individuals who are exposed to ionizing radiation as part of their employment are classified as radiation workers. At your facility, this will include the RSO, Authorized users, and Supervised Individuals. Everyone else, including visitors to the facility, and owners of animals treated with radioactivity are classified as members of the general public.

- There are two ODLs for members of the general public:
  a. An individual's dose must not exceed **100 mrem** (0.1 rem or 1 mSv) in 1 year from a licensed operation
  b. Cumulative dose in an unrestricted area must not exceed **2 mrem in any 1 hour**

- The above limits also mean that an employee exposed to >100 mrem in a year can be classified as a radiation worker, and that any areas where the dose is greater the 2 mrem in 1 hour must have restricted access. Anyone at the facility expected to receive >100 mrem annual must have radiation safety training commensurate to their doses.

Radiation Protection Standards *(continued)*

- There are three ODLs for radiation workers:

  a. Dose to any individual organ of the body, including the skin, and extremities (arms below the elbow and legs below the knees) must not exceed **50,000 mrem** (50 rem, or 500 mSv) / year. Technically, this is called the **Shallow Dose Equivalent (SDE).**

  b. Dose to the lens of the eye (as an exception from standard a) must not exceed **15,000 mrem** (15 rem, or 150 mSv) / year. Technically, this is called the **Lens Dose Equivalent (LDE).**

  c. Dose to the whole body (the head, neck, trunk, arms above the elbows and legs above the knees) must not exceed **5000 mrem** (5 rem, or 50 mSv) / year. Technically, this is called the **Deep Dose Equivalent (DDE).**

- All three standards are measured using a single dosimetry badge. Additionally, extremity doses are measured using a ring badge. Dosimetry reports are considered legal documents, admissible in a court of law.

- Standards a and b are designed to protect the workers from deterministic effects of radiation. Standard b is specific to the induction of cataracts from radiation exposure. A 2016 recommendation to make this more stringent, to 5 rem/year has been made, but has not become a regulation yet. Standard c is to protect workers from the stochastic (*i.e.*, cancer causing) effects of radiation.

- All licensed facilities are required to follow **ALARA** goals, by which doses are maintained well below ODLs by applying principles that keep doses **As Low As Reasonably Achievable**. For most medical facilities, ALARA is set at 10% of ODLs, meaning that the licensee strives to meet the following standards:

  Individual organs and extremities: 5000 mrem/y (50 mSv/y)
  Lens of the eye: 1500 mrem/y (15 mSv/y)
  Whole Body: 500 mrem/y (5 mSv/y)

Radiation Protection Standards *(continued)*

- There is one ODL for minors:

If an individual below 18 yrs is occupationally exposed, they are not to receive more than **10% of the ODL for adults**. In other words, ALARA limits become ODLs for minors.

- There is one ODL for the unborn fetus:

- A radiation worker who is pregnant can voluntarily declare her pregnancy. This has to be done in writing to the RSO, and must provide the estimate the month and year of conception. After a review of the workers dosimetry, if it is determined that the worker is likely to receive more than 100 mrem in a year, a fetal radiation monitoring badge, and **NRG Reg guide 8.13** (Instruction concerning prenatal radiation exposure) are issued.

  The fetal dose limit is **500 mrem over the entire gestation period**, until the woman is no longer pregnant or until the declaration is withdrawn.

  An additional NCRP recommendation is for the fetal dose not to exceed **50 mrem in any single month**.

- The employer has to take measures (which may include measures in addition to routine measures) to ensure that fetal dose limits are met for a declared pregnant worker; this may include a change in job description.

- Declaration of pregnancy is not mandatory; it is entirely the choice of the worker. She has every right to continue her pregnancy without declaring pregnancy, in which case fetal dose limits do not apply. The worker also has the right to withdraw her pregnancy declaration (in writing to the RSO) at any point, for any reason. In this case, fetal dose limits only apply for the duration for which the declaration was in effect. However, a non-declared or un-declared worker does not have the legal rights to sue the employer for radiation-induced damage to the fetus.

Radiation Protection Standards *(continued)*

- **Animal release criteria** following treatment are tied to the ODL for the general public: 100 mrem/y. This means that you are required to retain the treated pet in-house until the external dose rate meets certain criteria, thereby ensuring that no member of the family receives more than 100 mrem from the pet in 1 year. There are no additional 10% ALARA considerations for this standard.

- The equivalent standard for exposure to families of **human patients** released after diagnostic nuclear medicine exams, and after therapeutic treatment with radioisotopes, is more liberal: in this case, the 'infrequent exposure' standard of 500 mrem/y applies. This means that a human patient, or research subject who emits radiation can be released from the licensed facility as long as he / she does not expose any bystanders to more than 500 mrem in a year.

- This apparent double standard exists because pets may receive multiple treatments during a year, or multiple pets in a family can be treated in a year, increasing the potential cumulative dose to the owners; whereas in human families, treatment with radiation is not expected to be a frequent event.

- Therefore, the NRC and State Regulatory Agencies have adopted a very stringent approach to protecting the general public from the harmful effects of radiation.

Summary of Module 5: Radiation Biology

- Knowledge of how radiation interacts with tissue and cells is essential to understanding its bioeffects.
- DNA damage from direct or indirect action can cause cell malfunction or death. A cell at M phase of mitosis is the most sensitive to radiation, and the DNA damaged during this period can be passed to daughter cells.
- There are different theories of dose response to explain radiation effects. Each model suggests a different possibility of biological response; however, results are inconclusive. The theory with the most scientific data to support (or not refute) it is the linear threshold model.
- Radiation-induced bioeffects depend on received dose. Acute symptoms are expressed within days of radiation exposure, and delayed effects could have a latent period of years or tens of years.
- Radiation biology is a field that covers cell biology, radiation physics, chemistry, radiation safety, etc. Information on this topic will continue to evolve as knowledge is obtained about radiation interactions at the cellular level.
- Occupational Dose Limits apply to Members of the General Public as well as for Radiation Workers.

Supplemental Reading Material

Assigned reading material for Module 5:

5.1. NRC Reg Guide 8.29, Instruction Concerning Risks from Occupational Radiation Exposure, 1981
5.2. NRC Reg Guide 8.13, Instruction Concerning Prenatal Radiation Exposure, 1999

Upon successful completion of the Module 5 quiz, you may continue to Module 6.