EXUBRION THERAPEUTICS

Authorized User/Radiation Safety Officer Training for Synovetin OA®

Module 5: Radiation Biology

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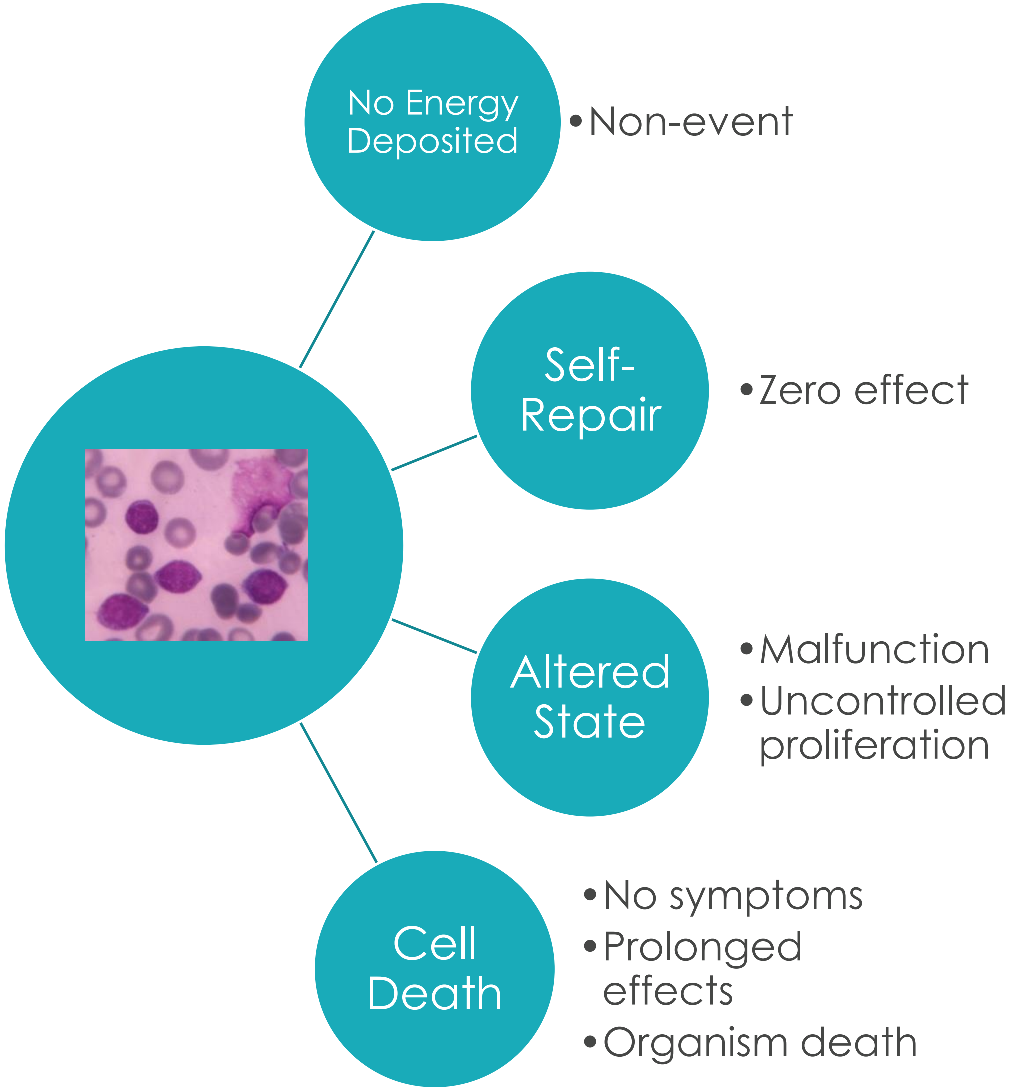
Introduction

- 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.
- After completing this module, the reader will be knowledgeable about radiation-induced bioeffects and how safety could be impacted by occupational exposure.
- Assigned reading:
  1. NRC Reg Guide 8.10
  2. NRC Reg Guide 8.29
  3. NRC Reg Guide 8.13

Outline

- Basic Concepts of Radiation Biology
- Radiative Interactions with Tissue and Cells
- Dose Response Curves
- Stochastic and Non-stochastic Effects of Radiation
- Acute and Delayed Biological Effects
- 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

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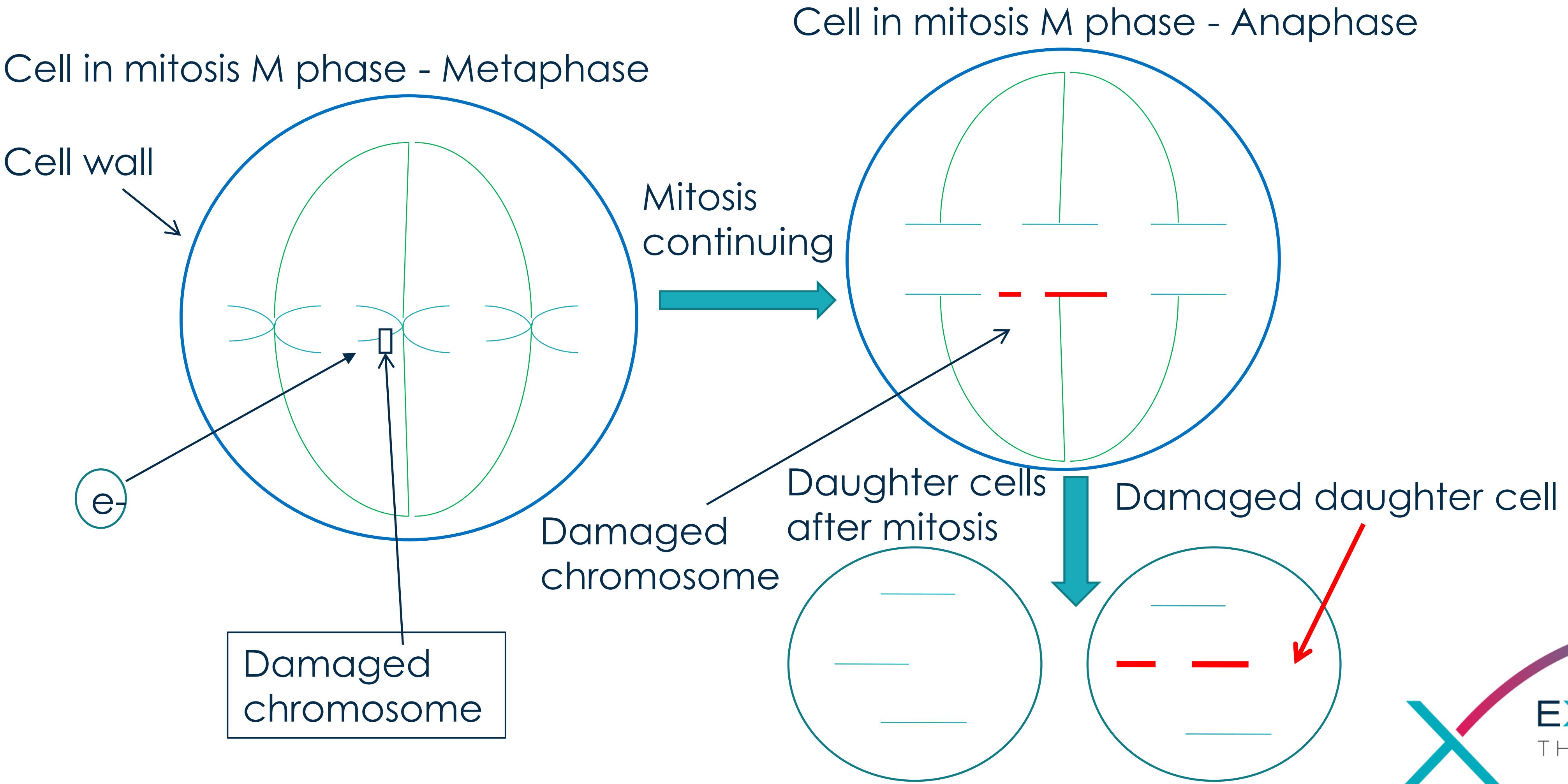
Basic Concept: Radiosensitivity

- 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 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 (which will be 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.

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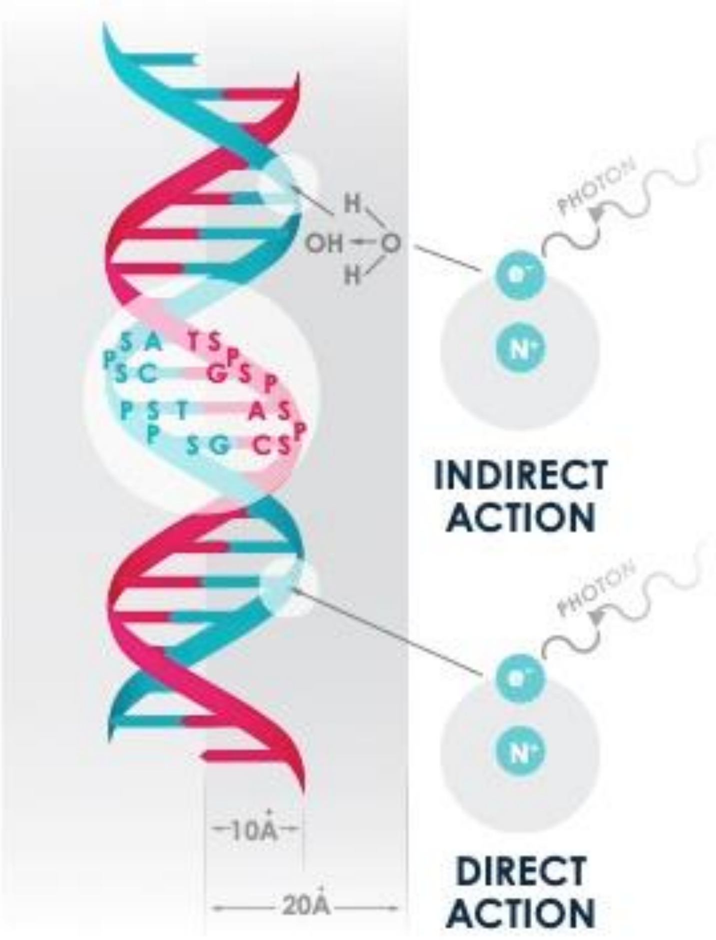
Ionizing Radiation's Biological Impact

- 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



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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.

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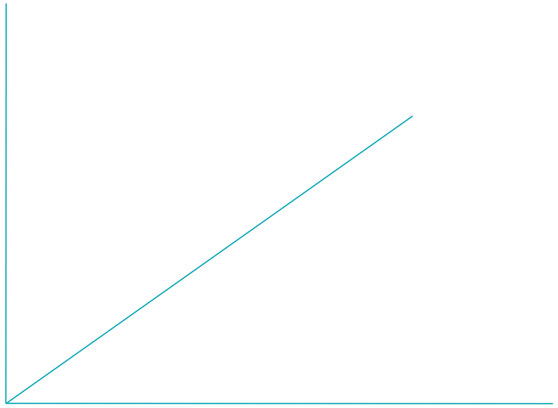
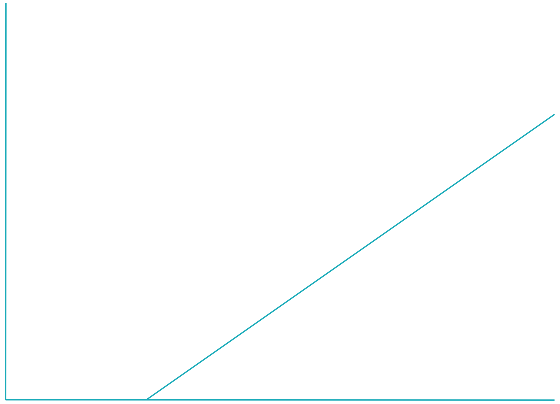
Dose Response Curves *(continued)*

Linear no threshold dose response



Linear no threshold model – any amount of radiation results in a health effect

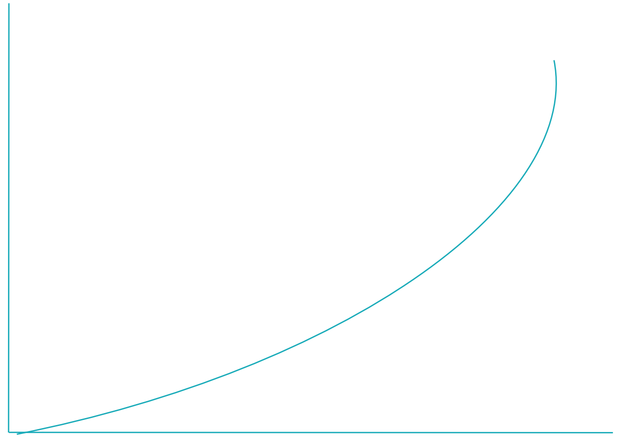
Linear threshold dose response



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

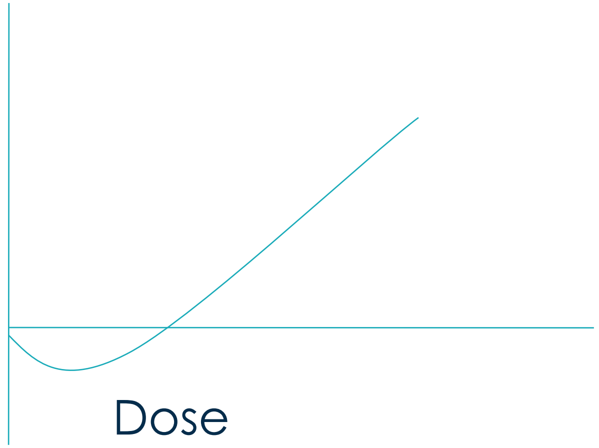
Dose Response Curves *(continued)*

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

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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 whole body gamma ray without treatment.
  - Note that this is a tremendous amount of radiation which would be impossible to generate in a typical veterinary nuclear medicine practice.

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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	800
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)	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.
  - In a National Research Council report, cancer risk is estimated following a linear no threshold model: the average lifetime risk of death from cancer following an acute dose equivalent to all body organs of 10 rem is estimated to be 0.8%, which is 8×10^{-3} $person^{-1}$ 10 rem^{-1}.[4] This means that if an acute dose of 10 rem were received, 800 of 100,000 people of all ages would be expected to die from cancer.
- Cataracts are a typical non-stochastic effect of radiation. The ICRP (revised 2011) suggests a threshold dose of 0.5 Gy regardless of dose rate. The latent period for radiogenic cataract could be years.
  - Occupational doses from veterinary ^{117m}Sn are estimated to be maximally 50 *milli*rem per year.

Reference: 4. National Research Council. *Health Effects of Exposure to Low Levels of Ionizing Radiation: BEIR V*. Washington, DC: The National Academies Press, 1990, p162. https://doi.org/10.17226/1224.

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.

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Supplemental Reading Material

Assigned reading material for Module 5:

1. NRC Reg Guide 8.10
2. NRC Reg Guide 8.29
3. NRC Reg Guide 8.13

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