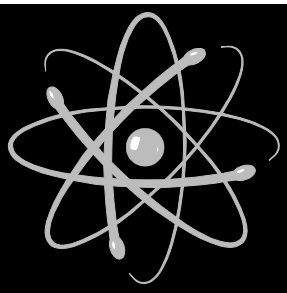

A Study Guide For

RADIATION BIOPHYSICS

NUC-412-GS

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Thomas Edison State College
Distance & Independent Adult Learning (DIAL)

This course was produced for Distance & Independent Adult Learning at Thomas Edison State College by Ohio University Independent Study.

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Graphic Design and Layout: Libby Dudding

First printing November 1994
Revised October 1996
Revised September 1999, May 2000, July 2001, January 2005

The Study Guide Author

I, Thomas N. Massey, am pleased to be writing a guided study course on Radiation Biophysics. My earliest scientific research was on the radiation chemistry of an organic heterocycle. I have since been involved in research in radiochemistry and nuclear physics. The majority of my grounding in radiation safety was at San Jose State University's Nuclear Science Facility. This facility was the only teaching facility at an undergraduate level in the entire United States during my three years there. After graduating, I worked at Lawrence Livermore National Laboratory and shared office space with the Health Physics Group for several years. I have been fortunate to be able to observe the radiation safety practices at a large number of accelerator facilities both in the United States and abroad.

I wish to dedicate this work to my wife, Kathy. Her help in organizing the material and preparing this Study Guide was invaluable. The timely revision of the Study Guide was made possible by the support and encouragement of my wife.

Table of Contents

NUC-412-GS
Introduction To This Study Guide

This *Study Guide* contains the general instructions and lessons for Radiation Biophysics. General instructions for Guided Study (GS) are contained in your *Course Manual* from Thomas Edison State College. Further information on this course is given below and in the Course Syllabus within the *Course Manual*.

COURSE OBJECTIVES

This course has been designed to provide current information on the interaction of radiation with biological systems. Although this course is directed primarily toward radiation safety professionals, it is general enough to be of interest to the user of radiation sources and the informed general public.

COURSE OVERVIEW

The prerequisites for the NUC-412-GS are introductory level courses in Radiation Science: Biology and Chemistry, and Radiation Science: Physics, or their equivalents. Corequisites are one year each of physics, calculus, biology, chemistry, and the course Radiation Interactions NUC-413-GS. The requirement for a physics, chemistry and biology background is a minimum for comprehending all pertinent portions of this course. Physics describes the radiation and its interaction with matter. Chemistry formulates the primary and secondary chemical reactions induced. Biology organizes the topics of the larger-scale effects of the radiation. This course will cover these topics in much greater detail.

REQUIRED TEXTBOOKS

ISBN 0-323-02555-2 Stewart C. Bushong, *Radiologic Science for Technologists: Physics, Biology, and Protection*, 8th ed., Elsevier Mosby, 2004.

ISBN 0-7817-2649-2 Eric J. Hall, *Radiobiology for the Radiologist*, 5th ed., Lippincott Williams & Wilkins, 2000.

The Bushong text has been chosen for its clear explanation of the topics in radiation biology, radiation, and interaction of radiation with matter, although only one-quarter of the book is devoted to health physics issues. Bushong has a very straightforward and understandable approach to the topics. The Hall text was chosen because of the broad range of material on radiobiology that it covers.

Supplemental Text

ISBN 0-471-97590-7 A.H.W. Nias, *An Introduction to Radiobiology*, 2nd ed., Wiley, 1998.

This text is **not** required for the course, but it does have clear, undergraduate-level explanations of the topics in radiation biology. Reading assignments from this text are provided in the course lessons for your information.

Information on the Internet

Much new and important information on topics in radiobiology is available from various places on the World Wide Web. A good place to start is a set of links at **http://www.phy.ohiou.edu/~massey/radiation.html**. Your instructor may have other suggestions, or you may want to use one of the search engines to look for a topic in your reading. A Web search may be a good source of material for your course paper (see Lessons 3 and 12).

THE WRITING ASSIGNMENTS

The writing assignments will consist of vocabulary, short-essay, and problems requiring deductive reasoning. The vocabulary work will be weighted as a quarter of the entire assignment. This weight on vocabulary is to encourage your interdisciplinary communication skills. During the course of future work you will need to communicate effectively with people who are relatively unfamiliar with your discipline. Improving your vocabulary will enhance your ability to communicate with these individuals. Further, any reading on the subject requires that you understand the exact meaning of the words used to properly interpret the information in journals and professional meetings.

Problems based on deductive reasoning and short-essay questions will make up the balance of the writing assignments. The percentage of each lesson devoted to deductive reasoning will vary from lesson to lesson depending on the topic.

THE EXAMINATIONS

The course has two examinations, a midterm and a final. The midterm consists of a series of questions that require short answers. The final contains a similar series of questions and also has a series of multiple choice questions. Both exams are designed to cover the important points in each lesson they cover. Questions based on interrelationships of various lessons will be as straightforward as possible. **The examinations are designed to test your understanding of the material rather than your ability to take tests.**

Each exam will be two (2) hours long. The midterm examination covers Lessons 1–6. The final examination covers all of the material in the course.

THE COURSE PAPER

The paper is intended to acquaint you with the literature in the field of Radiation Biophysics. The paper is to be on a current topic in the field. A basic background on current topics in Radiation Biophysics is given in Lesson 3; however, you will choose the subject of the paper.

The topic should be chosen and sent to the instructor for approval and suggestions as part of Written Assignment 2, which is described in the Course Syllabus in the *Course Manual.*You will submit the paper as the assignment for Lesson 12, just prior to taking the final examination.The paper should be 5–10 pages in length, plus a bibliography of at least 5 sources.The paper will be counted as 10% of the total grade.

YOUR GRADE FOR THIS COURSE

The course work will consist of each individual lesson's writing assignment, the paper, a midterm exam, and a final exam. The percentage for each element is given below:

ITEM	NUMBER OF ITEMS	PERCENT OF FINAL GRADE
Lessons	11	20%
Paper	1	10%
Midterm Exam	1	35%
Final Exam	1	35%
		100%

LESSON 1

An Introduction to Radiation

❖ Preview ❖

READING ASSIGNMENT

Hall: Chapters 1 and 15

Bushong: Chapters 1 (all), 4 (pp. 39-47), and 5 (all)

Nias: Chapters 1 (all), 4 (pp. 47-59), and 9 (pp. 141-151)

LESSON OBJECTIVES

Upon completion of this unit you will review:

- ❖ the definition of ionizing versus non-ionizing radiation
- ❖ the basic definition of units used in radiation biophysics
- ❖ the properties of electromagnetic radiation
- ❖ the basics of radioactive decay and radiation
- ❖ the decay of the positron

(continued)

DISCUSSION

Introduction

The initial part of radiation biophysics is understanding the interaction of radiation with matter. In this lesson we will review the basic units, general definitions, and concepts of radiation. Each of the concepts discussed here is important for understanding the interaction of radiation with biological systems.

A Brief History of Radiation Biology

X-rays were discovered by Wilhelm Roentgen in 1895. The history of radiobiology began in 1896 with the observation of hair loss following irradiation. The crude dosimetry of "skin erythema" was used until 1928 when the roentgen (R) unit was adopted. In 1896 and 1898, Antoine Henry Becquerel and Marie Curie discovered the radioactive properties of uranium and radium. In 1927, Müller demonstrated dose-response relationships with the mutation rate in the Drosophila fruit fly. In 1956, Puck and Marcus demonstrated the exponential radiation dose-response curve. In 1906, the "law" of Bergonié and Tribondeau demonstrated that actively-dividing cell populations are more radiosensitive than non-dividing tissue. Lastly, in 1959, Elkind and Sutton showed that cellular repair of radiation damage is possible.

- ❖ the conversion of mass into energy
- ❖ the concept of half-life
- ❖ the concept of the Bohr's model of the hydrogen atom
- ❖ the deBroglie wavelength for particles
- ❖ the Compton wavelength for particles

Basic Units

There are two basic sets of units used in the scientific literature, the MKS and the CGS system. The *CGS system* is composed of the units of **centimeter** for length, **grams** for mass and **seconds** for time. The *MKS system* has **meters** for length, **kilograms** for mass and **seconds** for time. The MKS units use **coulombs** for charge while the CGS units use **electrostatic units** (esu).

The three most important units in radiation biology and health physics are activity, absorbed dose, and dose equivalent. The earliest units applied in radiobiology were the "skin erythema" dose and the pastille unit. A later unit to the measurement of exposure was the **roentgen** (R) defined as 1 esu/cm^3 of dry air, with units of charge per unit mass (CGS units). The roentgen unit is a unit of exposure; therefore, it does not indicate the amount of the dose actually absorbed by the material.

Activity is the measure of the number of decays per second and is expressed in curies. The **curie** is 3.7 x 10^{10} disintegrations per second. A curie is roughly the rate of decay of one radioactive material relative to the rate of decay in radium (1 curie per gram). The SI unit for measuring the amount of a radioactive isotope, which decays in radioactivity with a half-life, is a **becquerel** (Bq), replacing the older unit of curie.

Absorbed *dose* is the energy absorbed per unit mass of tissue in the body. The concept of *dose* was developed where a **rad** is defined as 100 erg/g in the CGS system or a **gray**, defined as 1 J/kg in the MKS system. From the definition it is easy to see that 1 gray = 100 rad. One centigray (cG) is exactly equal to one rad. The rad (radiation absorbed unit) is the absorption of 10^{-2} joules of radiation per kilogram of material. [A tissue exposed to a dose of 1 roentgen of x-rays will receive an absorbed dose of 0.95 rad; therefore, the R and rad are considered equivalent in most cases when gamma or x-rays are used.]

The *dose equivalent* is the absorbed dose multiplied by a biological effectiveness factor. The dose equivalent is defined by the formula:

$$H = D(Q)N$$

where H is the dose equivalent, Q is the quality factor for the radiation, and N is the dose distribution factor. The units of H are in **rem** if the dose is in rad, and in **sieverts** (*Sv*) if dose is in gray. The quality factor Q is often taken to be the equivalent of the relative biological effectiveness (RBE) which is defined by:

$$RBE = \frac{D_R}{D_X}$$

where D_R is the standard radiation (usually gamma-rays or x-rays) and D_X is dose needed from the radiation X to achieve the same biological result.

Two types of dose may be calculated—whole body dose and organ dose. *Whole body dose* is calculated by the following equation:

Whole Body Dose = Energy Absorbed/ Mass of Body

Organ dose is calculated by the following equation:

Organ Dose = Energy Absorbed/ Mass of Organ

This organ dose is important when describing exposure to ingested radionuclides and when exposure is in a non-uniform radiation field.

Several related terms are used to describe the behavior of radiation. The *particle fluence* is defined as the number of particles passing through a given area, in units of particles per unit area. The *particle fluence density* is number of particles passing through an area in a given time period or, equivalently, the rate of change of the particle fluence. Since each particle can carry energy, the *energy fluence* can be defined as the amount of energy passing through a given area. The energy fluence is also equal to the average particle energy times the

particle fluence. The *energy flux density* can be defined as the amount of energy passing through a defined area per unit time or, equivalently, the rate of change of the energy fluence.

The concept of *kerma* is extremely important in determining the damage done to materials from tissues to semiconductors. Kerma is defined as the sum of all of the kinetic energy of all primary and secondary charged particles in a defined volume element of a given material. The charged particle equilibrium is the condition where the number of charges entering a volume is equal to and the same sign as those leaving the volume. When this condition is met, kerma is equal to the dose.

Kerma is the preferred method of quantifying energy deposition in the medical physics community. The large kerma factor in the reaction $^{10}B(n,\alpha)^{7}Li$ is why this reaction is being explored as a treatment for inoperable cancer. A large program is underway at Lawrence Livermore National Laboratory to use all available nuclear data to model interactions of radiation with models of an individual patient and calculate the kerma factors for planning radiation therapy.

Linear energy transfer (LET) is a measure of the energy loss along the length of a particle's trajectory. The LET depends on both the type of particle and its energy. A high value for LET means more energy deposited in a given particle. Particles with high LET often also have high RBE and quality factors. This is discussed in greater detail in Lesson 7.

General Definitions

In review, *radiation* is defined as the energy emitted that can be transmitted through a vacuum as well as matter. The following are the two main types of radiation:

1. *Ionizing radiation*, for example, X-rays, gamma-rays, α particles

2. *Non-ionizing radiation*, for example, visible light, microwaves and radio waves.

Ionizing radiation is capable of removing an electron from the atom with which it interacts (ionization). Non-ionizing radiation frees particles through interaction with the medium. For instance, microwaves interact with a medium to heat up the material.

Electromagnetic Radiation

Electromagnetic radiation is a special form of radiation. This radiation type is typified by the behavior of light. It has properties like both a wave and a particle. The wave-like behavior is best shown in diffraction where light interferes with itself. The particle-like properties of light are clearly shown when the photoelectric effect is studied. In the *photoelectric effect*, photons of a given frequency impinge on a metal, emitting monoenergetic electrons regardless of the intensity of the light. Thus, the photon acts a particle with one photon knocking out one electron. Two commonly used formulas with electromagnetic radiation should be recalled:

$$E = h\nu;\ C = \lambda\nu$$

where E is the energy of the photon, h is Planck's constant, v is the frequency of the photon, lambda, λ, is the wavelength, and C = speed of light. For example, sunlight has its greatest intensity at a wavelength of 4.83×10^{-7} m. The frequency of this light can be calculated:

$$C = \lambda\nu;\ \nu = \frac{C}{\lambda} = \frac{3.0 \times 10^{8} \frac{m}{s}}{4.83 \times 10^{-7} m} = 6.21 \times 10^{14} s^{-1}$$

Because of their very high frequency and very short wavelength, X-rays and gamma rays ionize any molecule in their path and can penetrate the whole body. All electromagnetic radiation travels in a straight line and the intensity of the radiation falls off with distance travelled, as described by the inverse square law.

Radioactive Decay

There are three common modes of radioactive decay that can result in ionizing radiation. These basic decay modes are:

1. alpha decay—the emission of a helium nucleus.

2. beta decay (both β^- and β^+)—the emission of an electron and an antineutrino or the emission of an anti-electron (positron) and a neutrino, respectively. (The fate of the positron is discussed below.)

3. electron capture—the capture of an orbital electron by the nucleus with the emission of a neutrino.

The origin of the names for these decays are discussed on pages 44-55 of the Bushong text, if you are interested.

Gamma and X-ray Emission

Electromagnetic radiation is often emitted following radioactive decay. You will recall that electromagnetic radiation is named according to its origin, in the transitions of the orbital electrons of the atom for X-rays, and in transition within the nucleus for gamma-rays. Gamma-rays are commonly emitted during the deexcitation of the daughter nucleus following any of the nuclear decay modes. The nuclear decays can often interact with the atomic electrons. When this occurs, X-rays will result. The interaction of photons with matter is discussed in the next lesson.

Energy from Mass

All radioactive decay occurs due to the final products having less mass (and thus energy) than the initial nucleus. This difference of mass can be converted to energy using Einstein's formula:

$$E = mC^2$$

where E is the energy, m is the mass and C is the speed of light. The energy available for a decay is always the maximum possible energy that can be deposited per decay. For the alpha decay of ^{255}U to ^{231}Th, the mass difference is 0.00499 amu.

$$0.00499\,amu \cdot 1.660565 \times 10^{-27}\,\frac{kilograms}{amu} \cdot (3.0 \times 10^{8})^{2}\,\frac{meters^{2}}{second^{2}} =$$

$$7.46 \cdot 10^{-13}\,\frac{kg\ m^{2}}{s^{2}} = 7.46 \cdot 10^{-13}\,Joules \cdot \frac{1MeV}{1.6022 \cdot 10^{13}\,Joules} = 4.656\,MeV$$

Each individual decay gives off very little energy as compared to macroscopic sources of energy such as a stove flame, an electric heater, or your own body heat. We will review in the next lesson how radiation interacts with matter to deposit energy.

Positron Decay

A special point with β^{+} or positron decay is that it happens when an electron and its anti-particle, a positron, are created in the region of the nucleus. The electron is absorbed by the nucleus and the positron is emitted. Thus, for a nucleus to decay by this mode, the nucleus must have twice the rest mass of an electron available (i.e., 1.022 *MeV*). The positron is the anti-particle to the electron and will eventually annihilate with an electron in the material, yielding two photons of 0.511 *MeV* energy emitted back-to-back. This is known as *annihilation radiation*. (Positron emitters are becoming increasingly important to medical imaging, as the two photons emitted by annihilation of the positron can be used to precisely determine the position of the positron at the time of annihilation in positron emission tomography or PET. PET scans are currently used for imaging the heart and brain in real time.)

The Concept of Half-life

Half-life is defined as the time it takes a given activity of a specific nuclide to decay to half its initial value. The half-life was found to be independent of the temperature, pressure, and phase of matter by scientists such as Rutherford and the Curies in the first three decades of this century. In review, an exact expression for determining the activities at times between half-lives is:

$$N = N_0 \exp\left(-\frac{ln2}{T_{\frac{1}{2}}} t \right)$$

$$A = \frac{dN}{dt} = -\frac{ln(2)}{T_{\frac{1}{2}}} N = -\lambda N$$

where N is the number of a nuclide at time, t, N_0 is the number of the nuclide present at a given initial time, and $T_{½}$ is the half-life of the given nuclide. The activity A from a nuclide is directly proportional to the amount present where λ is the mean life (also known as the decay constant). The half-life is important in environmental concerns discussed in Lessons 10 and 11.

Let's review using this relationship in a problem using ^{131}I, which has a half-life of 8.040 days. Since this isotope is often used to treat hyperthyroidism, the maximum amount left in the body after a typical two-week treatment is of great interest to the patient and the health physicist. This can be directly calculated, assuming no excretion of the iodine, by the formula:

$$\frac{N}{N_0} = \exp\left(-\frac{ln2}{8.040\ days}\ 14.\ days \right) = 0.299$$

where N is the number of nuclei present at time t and N_0 is the number of nuclei initially present.

Bohr Atom

A quick review of Bohr's atom is useful in preparing for Lesson 2. You may recall that the Bohr's atom was a simplified model of the atom with the electrons in quantized orbits around the nucleus. The orbital electrons could change orbits by absorbing or emitting a quanta of light. This is a rough understanding of the physics behind the photoelectric effect discussed in Lesson 2.

De Broglie Wavelength

A quick review of the wave-like properties of particles will be useful in understanding the interaction of radiation with matter. In 1924, de Broglie postulated that a particle must have a wavelength of:

$$\lambda = \frac{h}{mV}; \; \nu = \frac{E}{h}$$

where V is the velocity of the particle, m is the mass of the particle, h is Plank's constant, ν is the frequency of the particle's wave packet, and E is the kinetic energy of the particle. The wave-like properties were confirmed by Davisson and Germer in electron diffraction from a nickel crystal.

Compton Wavelength

A useful concept for a particle's wavelengths is the Compton wavelength:

$$\lambda = \frac{h}{mC}$$

The Compton wavelength represents the smallest size that a particle can have (the size it would have when traveling near the speed of light). For example, a 10 eV electron would have a de Broglie wavelength of 3.878×10^{-8} cm, while the minimum wavelength an electron can have is 2.42621×10^{-10} cm.

While the minimum wavelength of the electron is small, the size of the nucleus ranges from 1.2 – $8x10^{-13}$ cm. The wave function of an electron is much larger than the nucleus at any energy. The positrons needed for β^+ are created at the time of decay by the creation of a positron and an electron from a photon near the nucleus. The electron is absorbed by the nucleus. The electrons for electron capture are from the small amount of an electron's wave function found at the nucleus from the innermost electrons with wave functions at the origin (e.g., 1s, 2s, 3s 4s, . . .). Note: the interaction is largest when the two wave functions involved in the interaction have roughly the same wavelength.

WRITING ASSIGNMENT - LESSON 1

Complete the following assignment and submit it according to the directions in your Thomas Edison course information booklet.

Vocabulary

Please write the term and its definition on your paper. Your definition should be in your own words and limited to one or two sentences.

newton
joule
watt
units of length (centimeters and meters)
frequency
hertz
coulomb
potential difference
volt
dose equivalent (sievert and rem)
relative biological effectiveness (RBE)
linear energy transfer (LET)
particle flux density
energy flux density
ionizing radiation
ground state
becquerel
half-life
atomic number
neutron number
radionuclide
isotone
de Broglie wavelength
Bohr atom
gamma-ray
units of mass (grams and kilograms)
erg
second
electric current (ampere)
exposure (roentgen)
dose (rad and gray)
capacity
particle fluence
energy fluence
rest mass
curie
decay constant
mean-life
atomic mass number
nuclide
isobar
auger electrons
Compton wavelength
X-ray
alpha particle
visible light
radio waves
daughter nucleus
parent nucleus
microwave
excretion
skin erythema dose
specific activity
whole body dose
organ dose

Problems And questions

These problems and questions require numerical or short-essay answers. Please show your work and circle your final numerical answers. Limit your short-essay answers to one page or less.

1. Sunlight has its maximum intensity at a wavelength of 4.83×10^{-7}m; what energy does this correspond to in *eV*?

2. In Figure 5-6 in the Bushong text, the electromagnetic spectrum is given in terms of frequency and energy. Choose any three of the electromagnetic radiations shown and calculate the wavelength of a photon for that radiation (e.g., X-rays, gamma-rays, ultraviolet, visible, microwaves, etc.).

3. What is the wavelength and frequency of a photon emitted by a transition of an electron from a n=2 orbit to a n=1 orbit?

4. What is the wavelength and frequency of a photon emitted by transition of an electron from a n=∞ orbit to a n=1 orbit?

5. Using standard symbols (i.e., ${}^{A}Z$, e^{-}, e^{+}, etc.) define alpha decay, β^{+} decay, β^{-} decay, and electron capture showing all particles emitted.

6. How much energy in *MeV* is given off in the following decays:

   (a) $${}^{3}H \rightarrow {}^{3}He + e^{-} + \bar{\nu}$$

   where the mass of ^{3}H is 3.016049265 amu, e^{-} is 5.4865 x 10^{-4} amu, and ^{3}He is 3.016029308.

   (b) $${}^{148}Gd \rightarrow {}^{144}Sm + \alpha$$

   where the mass of ^{148}Gd is 147.918112 amu, ^{144}Sm is 143.911997 amu, and the mass of an alpha particle is 4.002603 amu.

   (c) $${}^{26}Al \rightarrow {}^{26}Mg + e^{+} + \nu$$

   where the mass of ^{26}Al is 25.986892 amu, ^{26}Mg is 25.982593, and the electron mass is 5.4865 x 10^{-4} amu.

7. You received a shipment 20 days ago of ^{131}I for treatment of hyperthyroidism. What fraction of the original shipment would you still have with a half-life of 8.040 days for ^{131}I?

8. You are using a ^{60}Co source labeled as having the activity of 3.7×10^{10} counts/second in 1945. What is this source's current activity? (The half-life of ^{60}Co is 5.271 years.)

9. What are the three most important types of units in radiobiology? Explain the meaning of each.

LESSON 2
Interaction of Radiation with Matter

DISCUSSION

❖ Preview ❖

READING ASSIGNMENT

Hall: Chapters 1 (all) and 7 (pp. 112-114)

Bushong: Chapter 12

Nias: Chapters 4 (all) and 9 (pp. 140-151)

LESSON OBJECTIVES

- ❖ This lesson will cover the interactions of photons with matter by the processes of:
  1. Raleigh scattering
  2. Compton scattering
  3. Photoelectric effect
  4. Pair production
- ❖ The energy loss of the energetic electrons produced by the last-mentioned three processes occurs in three main ways:
  1. multiple-collision energy transfer
  2. photoelectric process

(continued)

Introduction

This lesson will focus on the transfer of energy to matter, specifically, the interaction of high-energy photons with tissue. X-ray production will also be discussed.

To complete the review of the interaction of radiation with matter, the interaction of electrons, alpha particles, and neutrons will be briefly surveyed.

Absorbed Energy

When radiation passes through tissue or other matter, energy is lost from the system. Some of the energy imparted is lost, whereas some is absorbed. This is shown in the following formula:

$$\Delta\epsilon_{AB} = \Delta\epsilon_{TR} - \Delta\epsilon_{L}$$

where $\Delta\epsilon_{AB}$ is the energy absorbed, $\Delta\epsilon_{TR}$ is the energy transferred and $\Delta\epsilon_{L}$ is the energy lost. An example of energy lost to a system is during *Compton scattering* (discussed below), where the incoming photon interacts with an electron and the scattered photon often escapes the material.

3. bremsstrahlung
4. direct collisions

❖ The idea of dose is reviewed and the basic definitions related to this are included in the written assignment.

Interactions of Photons with Matter

X-rays and gamma rays have similar properties when interacting with matter. There are four main processes of energy transfer involving gamma rays for photons: *the photoelectric process*, *Compton scattering*, *Raleigh scattering (coherent scattering)*, and *pair production*. Only Compton scattering and the photoelectric effect are appreciable in biological systems. Whereas Compton scattering has a negative effect on the clarity of X-ray films, the photoelectric effect is the basis of all X-ray photography.

Raleigh Scattering

Coherent scattering involves the interaction of low-energy gamma rays (< 10 MeV) with loosely bound electrons. The energy of the photon is converted into kinetic energy of the medium—no energy is transferred to individual electrons. This results in a excitation of the medium which subsequently decays by the emission of electromagnetic energy. This *Raleigh scattering* phenomenon increases the angular dispersion of the incoming wave without depositing energy into the medium.

Compton Scattering

Compton scattering, also known as incoherent scattering, involves gamma-rays of moderate energy (see figure). At higher energies, between 0.5 MeV and 5.0 MeV, Compton scattering is predominant. Again, as in coherent scattering, the photon interacts with the loosely bound electrons, ionizing the atom as well as reducing the energy of the photon. Due to the low binding energy, energy is conserved as shown in the following formulas:

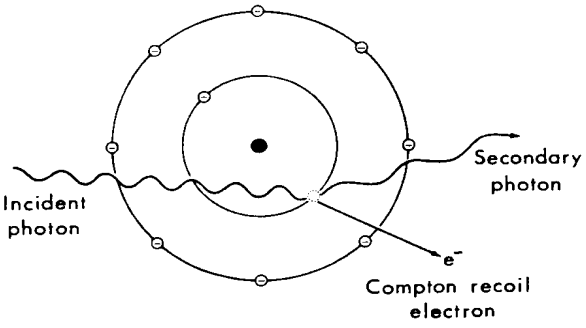


Fig. 2-1. The Compton process

$$\epsilon_e = h\nu - h\nu'$$

where $h\nu$ is the initial photon energy, $h\nu'$ is the recoil photon energy, and ϵ_e is the electron energy. The electron energy is also given by the formula:

$$\epsilon_i = \epsilon_s + (\epsilon_b + \epsilon_{ke})$$

where ϵ_i is the energy of the incident photon, ϵ_s is the energy of the scattered photon, ϵ_b is the binding energy of the electron, and ϵ_{ke} is the kinetic energy of the electron. Using the derivation of the formulas in the text, it can be shown that maximum energy transfer will have a 180° backscatter when 2/3 of the energy is transferred to the electron. Likewise, no energy is transferred at an angle of zero degrees. This process is most important for photons in the energy range of 100 keV to 10 MeV in biological systems.

Photoelectric Effect

In contrast to the above two processes, the *photoelectric effect* affects only bound electrons. With X-rays energies less than 0.5 MeV, the photoelectic effect is the predominant method of interaction. This process is very dependent on atomic number, as the binding energy affects the electrons of the interacting atom, resulting in the ejection of a photoelectron and orbital shift of at least one other electron, as shown by the formula:

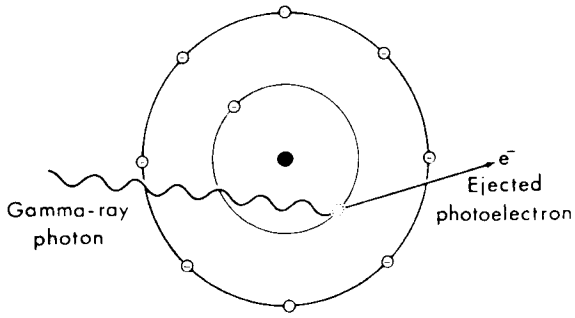


Fig. 2-2. The photoelectric effect

$$\textit{photoelectron kinetic energy} = h\nu - BE$$

where $h\nu$ is the photon energy and *BE* is the binding energy of the electron. This process is likely to occur if the energy of the incident photon is just greater than the binding energy of the electron it interacts with. In fact, the probability of interaction is inversely proportional to the third power of the photon energy. It is also proportional to the third power of the atomic number of the absorbing material. The photoelectric cross-section relation to energy and atomic number of the absorbing material is:

$$\sigma_{PE} \propto \frac{Z^3}{E_\gamma^3}$$

where E_γ is the photon energy and Z is the atomic number of the absorber.

Pair Production

In the final energy-transfer process, *pair production*, an energetic photon approaches the nucleus of an atom and creates a new positron (a positively charged anti-particle of an electron) and an electron. At still higher energies, in excess of 1.02 MeV, x-ray photons are involved in the process of pair production. Since two energy equivalents of the mass of the electron are required (2 x 0.511 MeV), this process only involves photons with at least 1.022 MeV of energy. The kinetic energy distribution can be calculated with the aid of the following formula:

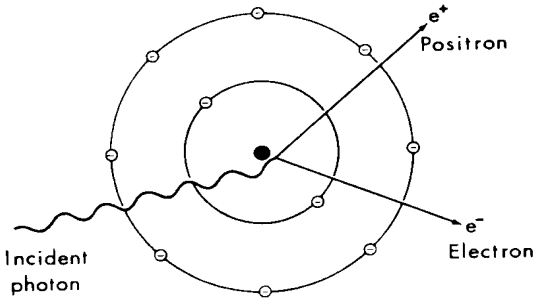


Fig. 2-3. Pair production

$$h\nu - 1.022 \text{ MeV} = \epsilon_{positron} + \epsilon_{electron}$$

where $\epsilon_{positron}$ is the kinetic energy of the positron, and $\epsilon_{electron}$ in the kinetic energy of the electron.

Positron Annihilation

After a pair production occurs, an annihilation reaction will also occur. In this process, the positron loses energy and forms an uncharged "positronium" atom by capturing an electron. The electron and the positron in this atom quickly annihilate one another, resulting in two photons of 0.511 MeV being emitted back-to-back. (The positronium decay was discussed in Lesson 1.) Therefore, in the pair production process, energy is usually lost to the system.

Differential Absorption

An interesting application of these energy-transfer processes is found in the medical use of X-rays for imaging. Basically, an X-ray image results from the difference between those X-rays absorbed photoelectrically and those not absorbed at all. This process is called *differential absorption*. Interestingly, the radiographic image results from less than 1% of the photons emitted from the X-ray machine.

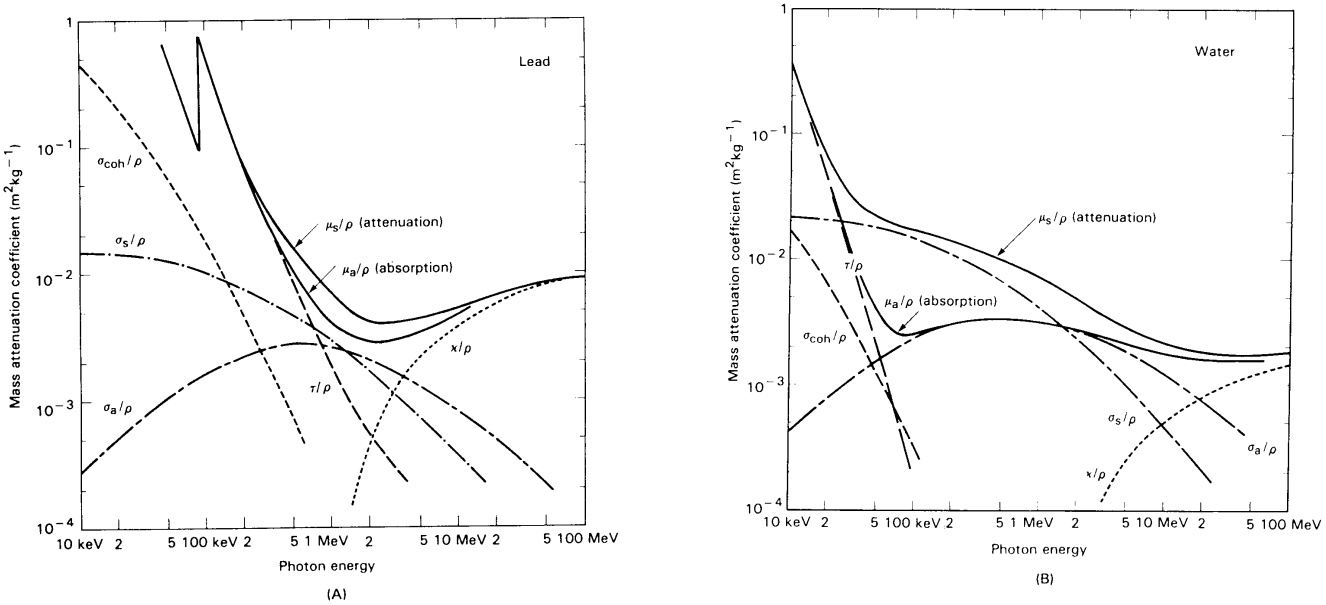


Fig. 2-4. (A) Mass attenuation coefficients for lead. The relative contributions of the three scattering processes as a function of energy are shown. Also shown are the energy absorbed cross sections. (B) Mass attenuation coefficients for water. Same notation as for part A.
(Source: Alpen, Edward, *Radiation Biophysics*, Prentice-Hall, 1990, Fig. 5-2, pp. 78-79)

Using the "rule of thumb" for the photoelectric process, the probability of interaction being proportional to the third power of the atomic number, we can see why an X-ray machine has a much greater interaction with bone (average atomic number 13.8) than with soft tissue (average atomic number 7.4). Because of their high atomic numbers and the greater interaction relative to soft tissue, barium and iodinated compounds are used to image internal organs. There must also be a balance between the energy of the X-ray used. At low energies, the majority of the X-ray interactions are photoelectric, whereas at high energies Compton scattering predominates. The Compton effect, due to the backscattering, results in film fog, and obliterates the image sought in X-rays.

Energy Absorption by Tissue

To move beyond the theory in the four processes addressed in this lesson, let's look at the Compton scattering and the photoelectric effect as they occur in an organism. The principal contribution to dose in all organisms is from Compton scattering, the prime process in occupational radiation exposure. When dealing with elements having high atomic numbers, such as calcium, copper and lead, there is a significant contribution from the photoelectric process.

Interaction of Energetic Electrons

In the last three processes of photon interaction (photoelectric effect, Compton scattering and pair production), an energetic electron is produced. The energy is transferred through the interaction of this energetic electron with the bound electrons and the nuclei of the material (cells) through which it passes. The rate of energy transfer is greatest as the particle approaches the end of its path because the transfer of energy is inversely proportional to both the kinetic energy and the velocity of the particle.

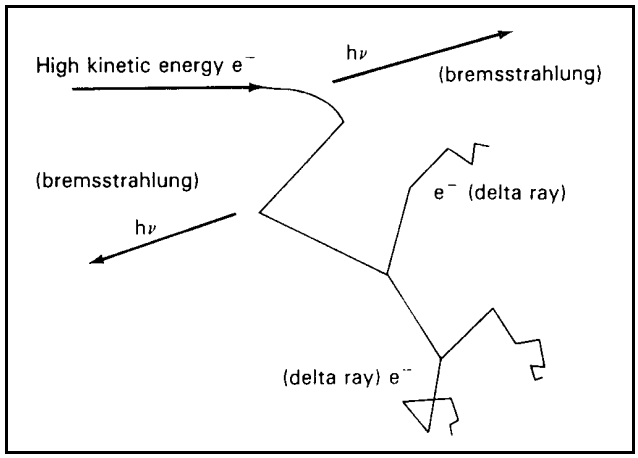


Fig. 2-5. Life history of a fast electron.

(Source: Alpen, Edward, *Radiation Biophysics*, Prentice-Hall, 1990, Fig. 5-4, p. 83)

Energy Transfer to Tissue

There are four main ways through which energy is transferred to the tissue.

(1) **Multiple-collision energy transfer**—In this process, the electron undergoes multiple small ionization losses by columbic interaction with the bound electrons of the cells. This electron will travel a random path to its end. Another electron may be given enough energy to have collisions and a track of its own. This electron is called a *delta ray*.

(2) **Photoelectric process**—In tissue with a high average atomic number (such as bone), the primary electron will be absorbed, resulting in the ejection of a K or L orbital electron and an electron shift of an outer orbital electron.

(3) **Bremsstrahlung**—In this process, the electron has a high amount of kinetic energy. It undergoes numerous columbic interactions as it decelerates. At each change of direction during the slowing of the electron, photons are emitted. These photons are called *bremsstrahlung*, or literally, "braking radiation."

(4) **Direct collision**—In this rare occurrence, the electron gives up all of its energy in a single hit.

Therefore, the energy imparted to the tissue in two processes—ionization and excitation. In ionization, the result will be a positively-charged atom and a negative electron. In excitation, the orbital electron of an atom will be raised from its usual ground state to an excited state. In summary, it is only this energy which is absorbed which is important to the final damage of the tissue.

The Concept of Dose

Dose is a measure of the energy absorbed by the medium (cells, tissue), as defined in Lesson 1. The dose reaches its maximum where the rate of forming new fast electrons is just equal to the rate of stopping electrons in the tissue. This point is referred to as *charge particle equilibrium*. These final concepts will assume central importance as we study the next lesson, discussing the interaction of radiation with the cell.

Interaction of α and β Particles with Matter

The interaction of β particles (electrons from the nucleus) and alpha particles with matter results primarily in fast electrons which will interact as described above. These interactions are primarily important for internal exposure for alpha decay and unshielded radiation sources for β decay.

One additional feature for β decay is the possibility of producing Cherenkov radiation. When a charged particle travels faster than the speed of light in the medium, light is produced in a forward cone. This is responsible for the blue light which is observed in pool-type reactors or very radioactive beta sources stored in water. This effect is also responsible for the flashes of light due to cosmic rays seen by astronants.

The interaction of alpha particles with matter is based primarily on the coulomb interaction. The main components of this interaction are:

(a) elastic scattering from electrons

(b) inelastic scattering from electrons

(c) elastic scattering from nuclei

(d) inelastic scattering from nuclei

The energy loss is dominated by interactions with electrons. This results in a fairly straight path and a fairly defined range, due to the statistical interaction with the electrons and the large mass of the alpha particles relative to the mass of the electrons. The most important thing about the alpha-particle energy loss versus range is that the greatest energy loss, and thus the most biological damage, is at the end of the range.

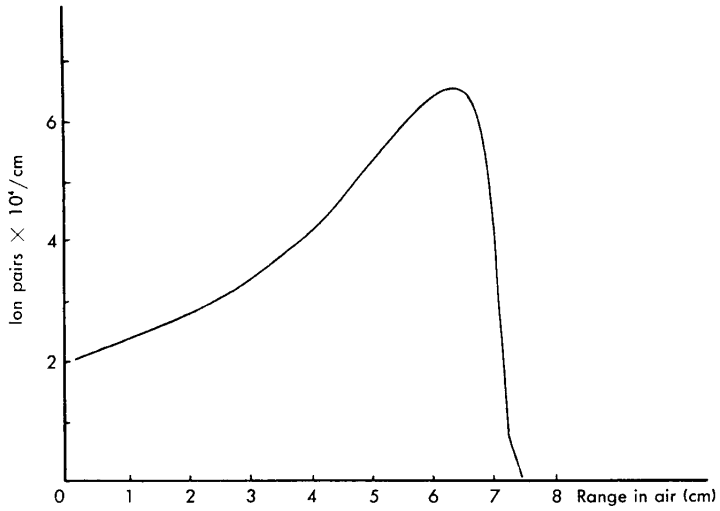


Fig. 2-6. Bragg curve for ^{214}Po alpha particles (E = 7.69 MeV) showing specific ionization as function of distance traveled from the source in air.

Fig. 2-7. An alpha track.

(Source: Arona, Victor, *Ionizing radiation and life*, C.V. Mosby, 1971, Fig. 6-1 & 6-2, p. 91)

Interaction of Neutrons with Matter

The main interaction of neutrons with matter is elastic scattering from hydrogen in the tissues. This elastic scattering comprises over 90% of all energy deposited in tissue. When the neutron scatters elastically off a proton, the recoil proton can have up to the same energy as the incoming neutron. This recoil proton from elastic scattering of the neutron causes damage to the tissue in a similar manner to the alpha particle discussed above. It is very important to note that even small-angle collisions can give the proton enough energy to have a very large LET. In the body a neutron can have multiple collisions, thus the effects of neutron energy deposition

can be multiplied under some extreme situations.

Of secondary importance to the dose from neutrons are neutron-induced charged-particle reactions. Below 1.0 MeV, the neutron capture reaction of the type $^{12}C(n,\gamma)^{13}C$ can be a strong contributor to the absorbed dose. Neutron-induced reactions of the type $^{12}C(n,\alpha)^{9}Be$ also contribute to the absorbed dose. Because of the high LET of low-energy alphas, the reaction $^{10}B(n,\alpha)^{7}Li$ is currently being used with monoclonal antibodies attached to boron compounds to deliver a dose directly to the site of inoperable cancer.

Linear Energy Transfer

The importance of linear energy transfer is that as the density of ionization increases, there is an increasing probability that radiation energy will be deposited directly in a biological molecule so that damage will occur; the higher the linear energy transfer, the more the biological damage. As linear energy transfer increases, the relative biological effectiveness increases. Alpha particles are more effective than neutrons, which are more effective than x-rays. With densely-ionizing radiation, the oxygen effect is much less, as is the capacity of the cells to shed sublethal and potentially lethal radiation damage. There is also less variation in the radiosensitivity of cells in different phases of the cell cycle. The "overkill effect" occurs with linear energy transfer above keV/μm, due to the fall in relative biological effectiveness. This will be discussed in Lesson 7 in relation to the biological implications.

Summary of the Interaction of Different Types of Radiation with Matter

1. *Alpha particles*

   The alpha particles are positively-charged since they consist of two protons and two neutrons. As they are massive, they move slowly through tissue and penetrate only a short distance. Alpha particles are very densely-ionizing, with the greatest density of ionization occurring at the end of the short and straight alpha particle track. They come to rest as helium atoms in the tissue.

2. *Neutrons*

   The neutrons have no electric charge, so no ionization is produced directly. Interaction can only result from direct collisions with atomic nuclei. Slow neutrons enter atomic nuclei and are "captured," a process which makes hydrogen and nitrogen radioactive. Fast neutrons interact mainly by elastic collisions with nuclei. Elastic scattering occurs with nuclei of oxygen, carbon, and nitrogen. Inelastic scattering occurs with heavier atomic nuclei in tissue. The absorption of neutrons is proportional to the concentration of hydrogen in tissues.

3. *Pions* (Negative Pi- mesons)

   These are subatomic particles with a mass 276 times that of an electron but with the same negative charge. The deposition of energy mainly occurs when they slow and are captured by nuclei present in tissues.

4. *Accelerated charge particles*

   Atomic nuclei of carbon, helium, neon, argon, and other elements have physical and biological properties similar to negative pions. The dose delivered at "the depth" is more effective because they are more densely ionizing than orthodox radiation.

5. *Beta particles*

   Beta particles, which are electrons, are also used in cancer treatments. Because they are negatively charged and have a small mass, electrons are deflected easily from their track, producing an erratic path. The greatest density of ionization occurs at the end of this track.

6. *Gamma rays*

   Interact with the electrons within a material via the coulomb interaction. The elastic and inelastic scattering of the photon by the electrons in a material result in high-energy electrons. These energetic electrons then transfer energy to the surrounding material. At high enough energies, a photon can produce a positron-electron pair.

WRITING ASSIGNMENT - Lesson 2

Complete and submit this assignment.

Vocabulary

Please write the term and its definition on your paper. Your definition should be in your own words and limited to one or two sentences.

coherent scattering
Compton scattering
incoherent scattering
photoelectric effect
pair production
differential absorption
annihilation reaction
direct collisions
dose
charge particle equilibrium
bremsstrahlung
positron
positronium
multiple-collision energy transfer
pions
accelerated charge particles
RBE
LET

Questions

Answer each of the following short-essay questions in one page or less.

1. How are Raleigh scattering and Compton scattering different?

2. At what energies will the photoelectric effect, Compton scattering, and pair production be the most important process for energy loss of photons in tissue?

3. Why is there a threshold for pair production?

4. For photons of 50 keV, 500 keV, and 5 MeV, what will be the most likely initial interaction with tissue?

5. For a photon of 5 MeV, describe the initial interaction of the photon and any secondary particles (such as photons, electrons, positrons . . .).

6. Considering the relative size of the nucleus and the atom, why are direct collisions rare events?

7. Describe the energy-loss interactions of a 1 MeV electron until it is at rest.

8. What is the most damaging part of the alpha particle range?

9. Why are neutrons so damaging to tissue?

10. What is the maximum energy of a proton recoiling from a 1 MeV neutron?

11. Explain the relationship between LET and RBE.

12. Compare and contrast both densely-ionizing and sparsely-ionizing radiation.

LESSON 3

Current Issues in Radiation Biophysics

❖ Preview ❖

READING ASSIGNMENT

Recent issues of *Health Physics; Acta radiologica: Oncology, radiation therapy, physics and biology; International Journal of Radiation Biology and related studies in physics, chemistry, and medicine*

Hall: "Milestones in the Radiation Sciences," pp. 1-4

LESSON OBJECTIVES

- ❖ This lesson is to help you pick a subject of current interest in radiation biophysics on which to write a research paper of 5 to 10 pages. This will likely require some outside reading to find a topic you are interested in researching.

DISCUSSION

Radiation biophysics as presented in this course covers the effects of radiation from its origin to the damage that occurs in cells, tissues, organs and organisms. This research paper is intended to give you an understanding of the information available in the current literature on a topic somewhere in this range of subjects. You need to choose a topic for your paper before the first examination to allow yourself sufficient time to complete the research paper before the end of the term. The writing assignment for this lesson will also give your instructor an opportunity for input and approval.

Due to the scope of the field, one of your hardest tasks is to narrow the topic down far enough to have a reasonable problem to discuss. For this reason, preliminary research to find enough material for a paper of this length would be an excellent idea. Some general topics that are covered in the course are:

- ❖ The effect of the interaction of various types of radiation on biological systems.

- ❖ The effect of various agents at modifying the response of biological systems.

- ❖ The response of cells, tissues, organs and organisms to radiation.
- ❖ Genetic damage caused by radiation.
- ❖ Background radiation from man-made and natural sources.

Of general interest are several human disasters, accidents, and intentional exposure:

- ❖ Exposure of early radiologists
- ❖ Exposure of overseas flight crews
- ❖ Exposures from radiation therapy and medical procedures
- ❖ The atomic bombs at Hiroshima and Nagasaki
- ❖ Three Mile Island maximum exposures
- ❖ Chernobyl accident and cleanup
- ❖ The natural reactor found in Africa

Some topics of great interest to people in radiation safety are:

- ❖ The human biological response at low doses of radiation is very important for setting the safety standards:

  (a) Is the shape linear or quadratic?
  (b) Is there a threshold dose (or is there a natural incidence for this)?

- ❖ The response of biological systems to radioactive labeled compounds.
- ❖ How can the scope of the radon problem be determined on a human scale?
- ❖ What is the result of occupational exposures to radiation of flight crews, astronauts, radium dial painters, tritium dial painters, etc.?

- What are the results of radiation experiments conducted in secret after World War II?
- What is really known about the Silkwood incident?
- What is the industrial safety in the nuclear industry?
- What are the ethics of public exposure to radiation?

To begin your search, you may wish to visit the Web site:

http://www.phy.ohiou.edu/~massey/radiation.html

This Web site has links to some of the good starting points to information on biophysics available on the World Wide Web.

You will find a full list of references to amplify and expand on the discussion in the text at the end of each chapter in the primary text and the supplemental references by Nias. These references can serve as starting points of your literature search in two ways. The common way is to look up the reference. However, with the *Science Citation Index* you can find all recent works that cite a particular paper. In addition, more recent works by the same author may also be found by a search on that particular author. Using the *Science Citation Index* is one way in which all papers on a given subject may be found quickly.

WRITING ASSIGNMENT - Lesson 3

Please write a one- or two-sentence description of the topic and a tentative outline of the paper. Include a list of references found to date. The final paper should be written to correspond to the style of a journal of your choice or whatever style your mentor requires. The bibliography should include at least five different sources, three of which should be from one or more journals.

LESSON 4
Radiation Chemistry

❖ Preview ❖

READING ASSIGNMENT

Hall: Chapters 1 (all), 2 (all), and 9 (pp. 136-137)

Bushong: Chapter 35

Nias: Chapters 4 (pp. 55-62), 5 (all), and 6 (all)

LESSON OBJECTIVES

After this lesson, you should be able to:

- ❖ Define *spur*, *blob*, and *track* in the process of energy transfer.
- ❖ List the products of water radiolysis.
- ❖ Describe the three stages of water radiolysis.
- ❖ Explain the difference between direct and indirect energy transfer.

(continued)

DISCUSSION

Radiolysis of Water: Energy Transfer

This lesson deals with the effects of radiation on the cell, via the process of water radiolysis. Energy transfer will be studied, as well as direct and indirect transfer of this energy. While briefly mentioning the effects of radiation on other cell organelles and cellular macromolecules, the effect of radiation on the cell's DNA will be the main focus. The role of radiation on cell aging will be explored. The cellular basis of cancer, in regards to growth kinetics, will be addressed. Lastly, cellular death and mitotic death will be differentiated, and the formation of giant cells will be discussed.

From the previous lesson, one might assume that the process of energy transfer from an electron slowing-down is a continuous process. This does not occur, however; the energy is deposited in discrete events classified as:

1. *spur*: 6–100 eV
2. *blob*: 100–500 ev
3. *short track*: 500–50,000 ev

- Explain the relationship between molecular weight and target size.
- Describe the effects of radiation on various cellular organelles.
- Describe the effects of radiation on the cellular macromolecules.
- Describe the five types of DNA damage.
- Explain the difference between cellular and mitotic death.
- Describe the formation of a giant cell.
- Describe how DNA damage can result in cancer.
- Explain the role of radiation in the three models of cellular aging.

During these energy transfers, three events can occur—ionization, excitation, or superexcitation. In superexcitation, the energy available is greater than that needed for ionization. All three of these events result in unstable molecules.

As we learned in the last lesson, delta rays (secondary electrons) are also formed, which then form their own spurs, blobs, and short tracks. A 1 Mev electron deposits 65% of its energy in spurs, 15% in blobs, and 20% in short tracks. However, each of these interaction sites are separated to the degree that very little interaction occurs between them.

Radiolysis Products

Cells are predominantly water. Seventy-five percent of cell volume is accounted for by water. Water makes up the cytoplasm of the cell. These excitations and ionizations occur in the water of the cell, forming the following products: H_2O^+, H^+, OH^-, and H_3O^+. Some of these reactions are shown here:

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

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

The primary products of radiolysis in the first 10^{-11} seconds are $H^\bullet$, $OH^\bullet$ and e_{aq}. The hydrated electron, e_{aq}, is much more stable than a free electron. These products, while still close together, may recombine and convert their energy to thermal energy. However, after 10^{-11}s, diffusion separates the products, making recombination impossible.

After primary radiolysis and recombination, the third stage of the radiolysis of water occurs—chemical stage. These reactions, which are very complex, result in the production of various chemical ions and molecules, such as OH^-, H_3O^+, H_2, H_2O_2, etc. The important result of "ionizing" radiation is the production of free radicals, which disrupt the normal molecular structures and damage the biological target.

For ordinary radiation, the highest yields are the free radicals e_{aq} and $OH^\bullet$; however, the yield of e_{aq} may be reduced by scavenger molecules. Densely-ionizing radiation has an increased yield of H_2O_2, which accounts for the lower oxygen effect with densely-ionizing radiation, a concept which will be further explored in Lesson 7.

Time Scale

The above-mentioned reactions occur within a very brief time frame, which makes them difficult to study. Therefore, various techniques are used to study the processes involved in irradiation of a cell. The physical processes of ionization and excitation occur in 10^{-18} seconds. The *pulse radiolysis* technique is used to detect reactions with free radical ions, a process lasting 10^{-12} seconds. The *rapid mix* technique is used to study the decay of radicals in target molecules, reactions occurring in 10^{-6} seconds. Low dose rate and mutant cells are used to observe the enzymatic processes that remove toxic radiation products and repair damaged molecules. The *Puck and Marcus process*, which can be used for a period of several weeks, studies the altered cell molecules, which may lead to cell death and the loss of proliferative capacity.

Direct & Indirect Action

From a biological point of view, it makes little difference whether a molecule is damaged directly or indirectly. At the point reached by the previous reaction equations, only the water present in the cytoplasm of the cell has been affected, resulting in the production of various hydrated species. In order to permanently damage the cell, the biological molecules, such as DNA or proteins, of the cell must be affected. This can occur in two ways—direct action and indirect action. The direct effect of ionizing radiation is represented by the following two equations:

$$RH \longrightarrow RH^*$$

$$RH^* \longrightarrow R^\bullet + H^+ + e^-$$

The indirect effect also operates, producing the free radicals OH and H, which combine with organic molecules in the following fashion:

$$HR + OH^\bullet \longrightarrow R^\bullet + H_2O$$

$$RH + H^\bullet \longrightarrow R^\bullet + H_2$$

In **indirect action**, a *scavenger molecule*, such as Fe^{2+}, will interact with the radicals in order to bring the hydrolysis to an end. The scavenger will then diffuse and interact with a biological molecule, such as DNA. The hydroxyl radical, $OH^\bullet$, is the predominant molecular species in the diffusion-limited reactions. An example of the use of these scavengers is the quantification of the amount of radiation dose using the Fricke dosimeter. The oxidation of the ferrous ion (Fe^{2+}) to the ferric ion (Fe^{3+}) in a radiation field is detected by simple photometric methods. This dosimetric method is a standard method for measurement of doses in 1000-of-rad range.

It is very important to note that the indirect effects occur more frequently with sparsely-ionizing radiation; whereas, the direct effect operates more with densely-ionizing radiation.

To repeat an important point, in **direct action**, the high-energy electron's energy will be deposited directly on the biological molecule (DNA). Due to the absence of intervention of radiolytic species, a dose-response relationship can be derived:

$$\varepsilon = \varepsilon_0 e^{-kD}$$

where

ε_o = undamaged molecules
ε = molecules remaining after dose
k = inactivation constant
D = dose

There is, in addition, a relationship between the molecular weight of the molecule and the target size. This is illustrated by the following formula:

$$target\ molecular\ weight = \frac{7.28x10^{11}}{D_{37}}$$

where D_{37} is the dose required to reduce the biological activity to 37% of its original value. A wide range of bioactive molecules lose their biological activity as a result of a single ionization. On average, 75 eV is used in each interaction for an ionization event.

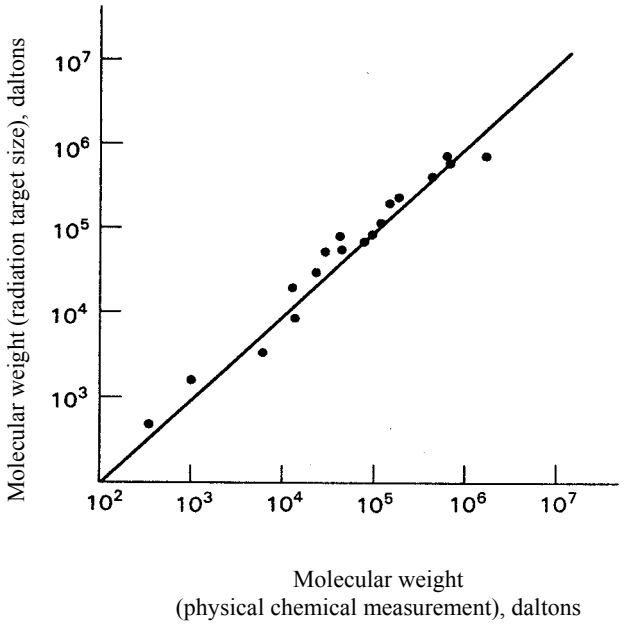


Fig. 4-1. Molecular weights for a wide range of biologically active molecules were determined independently by physicochemical methods and by radiation target size determination. The data are plotted from the results of Hutchinson and Pollard (1961). (F. Hutchinson and E. Pollard, *Mechanisms in Radiobiology*, Vol. 1, M. Errera and A. Forssberg eds., Academic Press, Inc., New York. p. 85.)

Radiation and DNA: DNA Structure

As a review, cells group in patterns that are recognizable as tissues. The tissues form organs. The entire organism consists of an orderly arrangement of such organs. This paragraph offers a brief review of tissue types which will make the information on the sensitivity to radiation and causation of cancer easier to understand.

Mammalian cells are classified into five types of tissue:

1. *Epithelial* tissues consist of cells that grow into sheets that cover organs and line cavities. Such cells may be squamous, cuboidal, or columnar.

2. *Connective* tissue cells form the structural units of the body, such as bone, cartilage, and tendon.

3. *Muscular* tissues have the property of contracting to produce movement or tension.

4. *Blood cells* consist of red cells, which are specialized for the transport of oxygen, white cells, which combat infection, megakaryocytes, which produce platelets, and lymphocytes, which aid in the immune response.

5. *Nervous tissue*, which includes the brain, the spinal cord and all of the nerves in the body.

This section will focus on the effects of radiation to the cell, by looking at the effects of radiation on cell physiology. The cell contains many organelles or "little organs" which may be affected by radiation. For example, the ribosomes are small, spherical bodies that are the site of protein synthesis. They consist of ribosomal RNA and protein. Another organelle, the Golgi apparatus, stores and transports secretory products and aids in formation of the cell wall. Lysosomes are sacs containing enzymes responsible for the digestion of material in food vacuoles. They also aid in the breakdown of damaged cell structures. Lastly, the centrioles play a role in cell division. Interaction between the organelles is essential for the cell to remain viable.

Looking at the cell, the nucleus is the most obvious target of radiation damage in the cell. However, the other organelles in the cytoplasm are also affected. Figure 4-2 shows the nucleus and the main organelles that are affected by radiation. Radiation damage to the cell membrane can interfere with its role of regulation in exchange of material inside and outside the cell, for example, problems with nerve impulse transmission in the nervous system due to the essential precise movement of sodium and potassium ions across the membrane of the nerve cell (neuron). Since protein synthesis is controlled by the nucleus, radiation damage of the endoplasmic reticulum has little effect on the cell. Radiation can cause the lysosomes, which are essentially sacs of proteolytic and other enzymes, to release their contents. The increase of free enzymes can cause damage to the cell. The mitochondria, site of Kreb's cycle and the electron transport chain, can be fragmented by the effects of radiation. Since the mitochondria are responsible for energy production, they are most numerous in cells with a high level of metabolic activity. This could lead to the death of the cell, as is shown by the effects of radiation on the thymus.

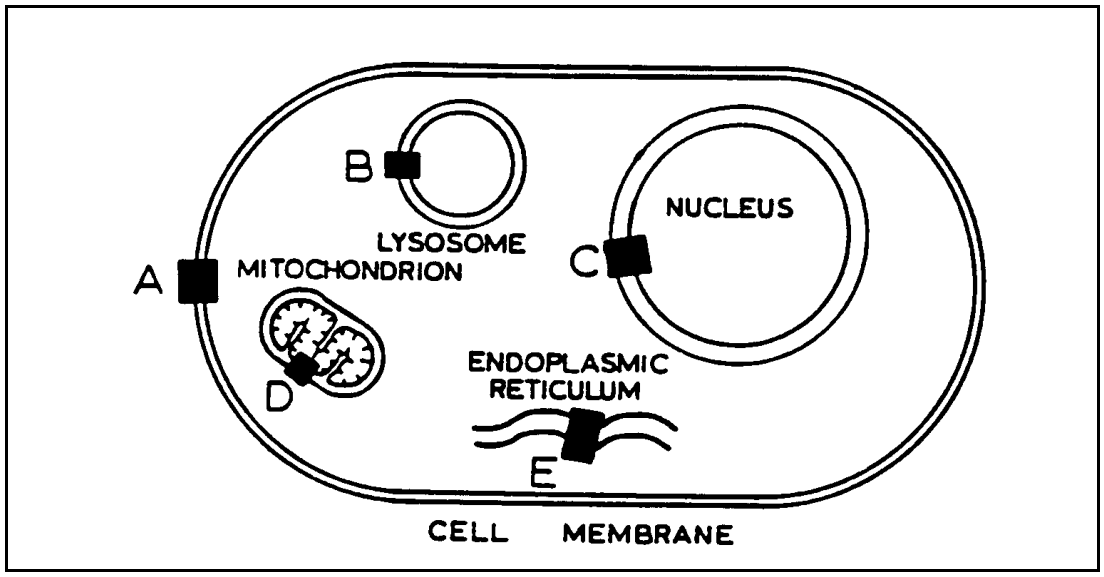


Fig. 4-2. Possible sites of membrane damage known to occur, cell membrane (A), lysosome (B), nuclear (C), mitochondrion (D), and endoplasmic reticulum (E). The damage to any of these membranes will cause failure to maintain normal ion balance and disturbance of metabolism. Damage to the lysosome membrane can cause release of active enzymes (i.e., the cell can digest itself!).

Irradiation not only affects the organelles but the macromolecules which compose the cellular structures. Irradiation has the following specific effects on macromolecules in the cell:

1. Carbohydrates undergo degradation.
2. Lipids experience oxidation in a chain reaction.
3. Proteins suffer breakage of hydrogen bonds responsible for the secondary and tertiary structure. Changes in the secondary and tertiary structure can cause loss of function in a protein or an enzyme.
4. Nucleic acids have change/loss of base, single strand breaks, and double strand breaks.

It is important to note that the macromolecules may have different radiosensitivities in different areas or organelles of the cell. Radiation damage to the cell is followed by the expression of molecular damage in the following sequence : DNA→RNA→proteins→lipids and other macromolecules.

As has been introduced previously in this section, DNA is the primary biological target in the cell. Figure 4-3 shows the primary and secondary structure of DNA. DNA, which resides in the nucleus of the cell, carries the information required for self-replication, biochemical renewal in the cell, and cell division. The DNA, in the human species, is arranged into 46 chromosomes. The term *genome* refers to the complete set of chromosomes of a species. The molecule itself is a double-stranded helix, each molecule consisting of a nitrogenous base, a phosphate, and a sugar ring.

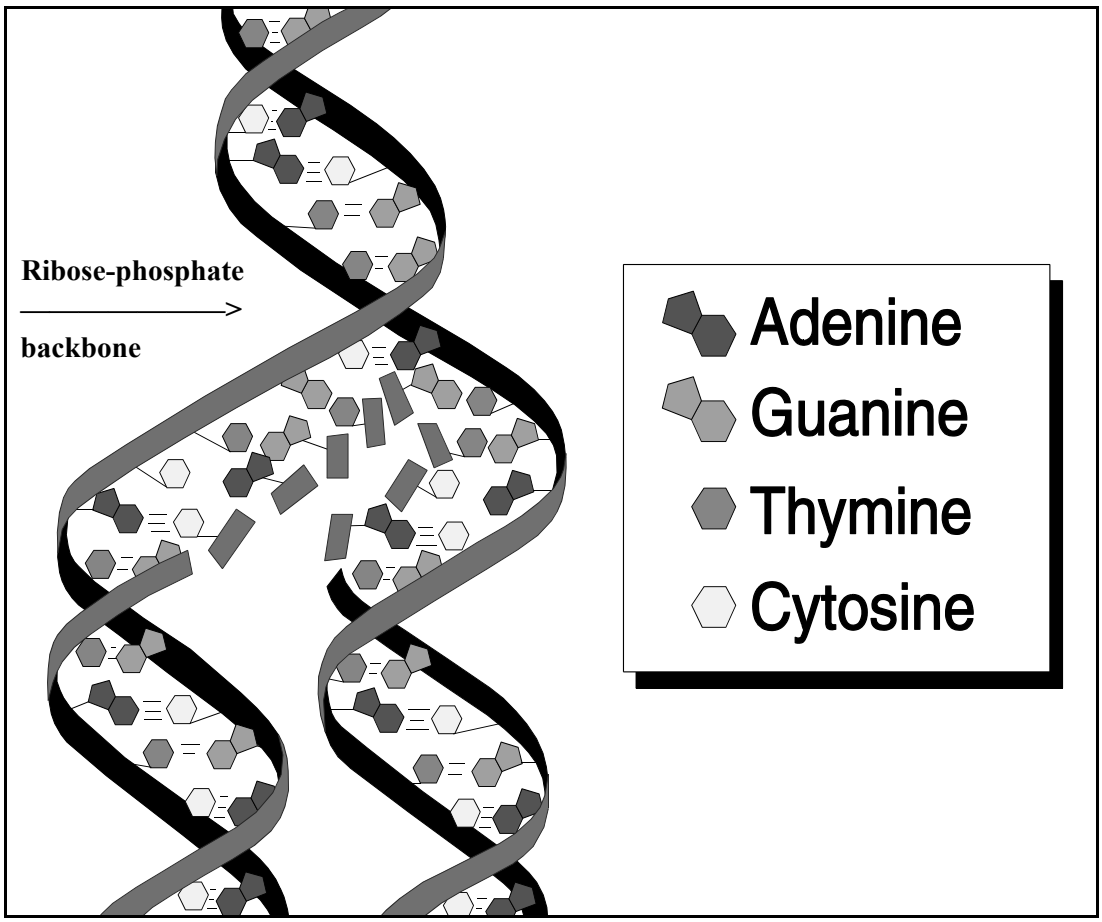


Fig. 4-3. DNA Replication

The DNA carries its message in the sequence of its nitrogenous bases (adenine, thymine, cytosine, and guanine). The nucleotide sequence leads to the formation of a gene. When genes are expressed, they result in the formation of a specific protein product, such as an enzyme or a structural protein. The loss of an enzyme for a metabolic pathway such as respiration could lead to the death of the cell. Therefore, the loss of a base or problem with base pairing can lead to the death of the cell due to the loss of an essential enzyme.

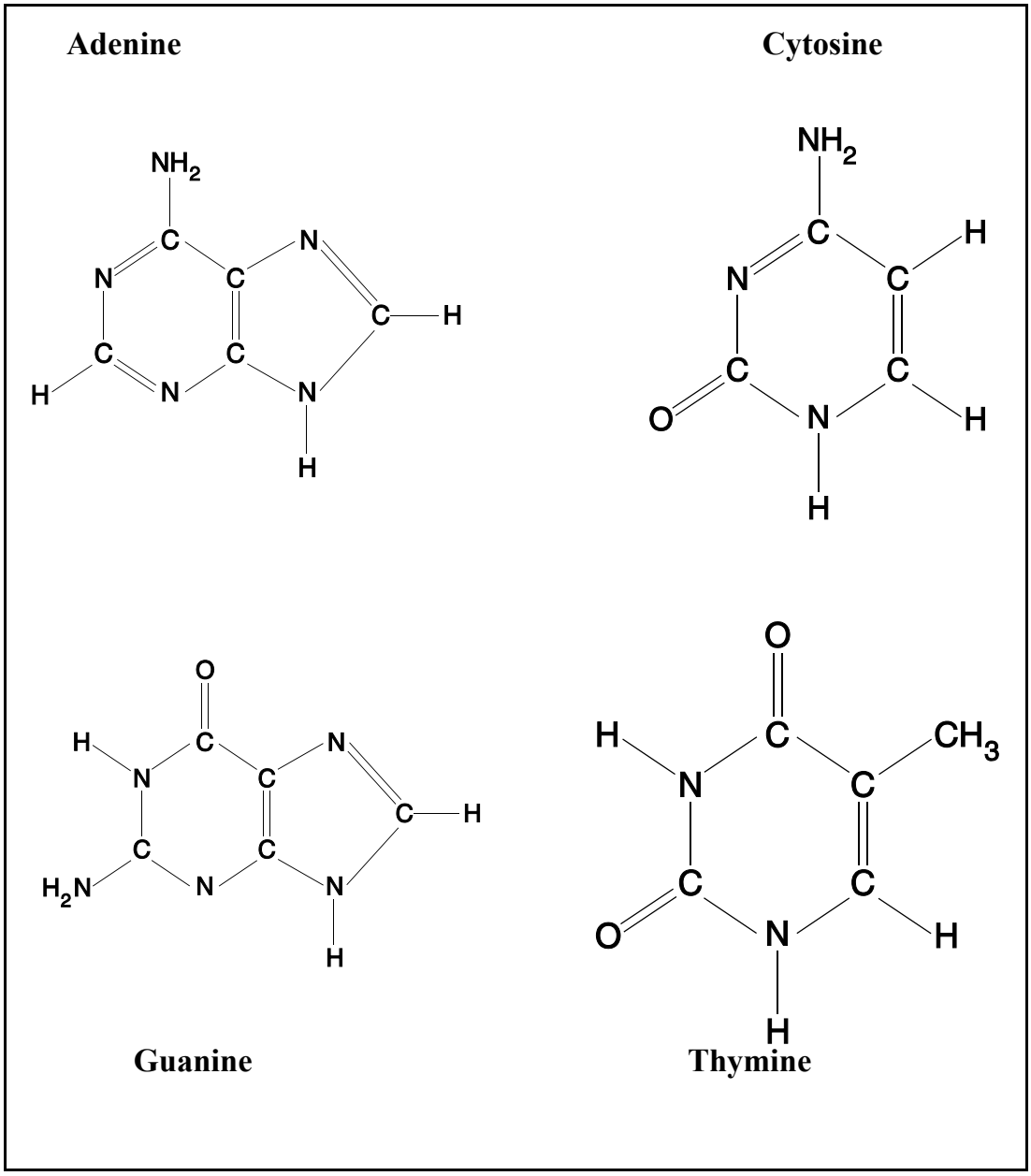


Fig. 4-4. DNA Bases

DNA Damage

There are five main ways in which damage can occur to DNA:

1. Altered functional group of purine/pyrimidine
2. Loss of purine/pyrimidine
3. Free-radical transfer, causing loss of base and chain breakage
4. Single-strand break
5. Double-strand break

Of the mechanisms listed above, attacks on the bases (purines and pyrimidines) are not as serious. There are many enzymatic repair systems in place for this sort of damage. Attacks on the sugar-phosphate backbone, that is single-strand and double-strand breaks, are of the greatest importance.

Most forms of DNA damage, base damage and single-strand breaks, only rarely cause loss of function in the cell. Many repair mechanisms, which are discussed in Lesson 6, exist to repair such damages.

Double-strand breaks, on the other hand, are much more serious. With the break, there is no template for damage repair. Repair may be faulty, resulting in genetic mutation or loss of reproductive capacity. As discussed earlier in the lesson, double-strand breaks can occur by direct action through interaction with high energy electrons, or by indirect action, through interaction with the products of water radiolysis.

Cancer

DNA is damaged by irradiation. Such damage can result in a lack of control of division of the cell. Such a condition is cancer. Cancer is a disorder of cell growth. The more common cancers are made up of epithelial cell types and are called *carcinomas*. Connective tissue cells may also become

malignant and are called *sarcomas*. There is no difference in intrinsic radiosensitivity between normal and malignant cells of the same tissue type. Tumor cell populations may show decreased radiosensitivity, however, when a fraction of cells are lacking in oxygen.

Tumors are of two types: benign and malignant. Benign tumors have a more organized structure, remain localized, and retain the characteristics of original tissue cells. Malignant tumors grow rapidly and invasively, destroying neighboring tissues.

Total cell number increases in only two instances: during childhood and in tumors. Tumors increase in size due to an increasing number of cells; however, tumors may also increase in size due to proliferation of connective tissue or vascular elements, increased blood supply, hemorrhage, or cyst formation.

Cell Death

Cancer cells may appear immortal due to their ability to divide indefinitely. This observation leads to the concept of *cell death* and *mitotic death*. Absolute sensitivities of living cells to the lethal effects of radiation vary widely, but, in general, mammalian cells are particularly sensitive. Except for cells in the lymphocyte series and the oocyte, which may show death during interphase, mammalian cells respond to moderate radiation doses by mitotic death. During mitotic death, the cells do not die immediately after irradiation but begin to die when they come into mitosis. Even though they have not lost functional integrity, they are doomed to perish due to the lack of reproductive capacity. These cells are "sterilized."

Interphase death, which is an immediate death, is uncommon with ionizing radiation. In interphase death, the cells die before they reach the next mitosis. Mitotic death, which is death at the time of mitosis, occurs at about 1.5 Gy. Some cells sterilized by radiation will enlarge and become polyploid, forming "giant cells." This occurs because the process of mitotic division has been inhibited, but all other metabolic functions of the cell have continued normally. This cell can not grow in number, only in size due to synthesis of macromolecules. In terms of reproduction, this cell is dead, even though all

its other functions are intact. Giant cells only form in cell populations that undergo mitosis normally. Other cells damaged by radiation will proliferate into colonies of ten before mitosis ceases.

Regardless of the manner of death, *pyknosis* occurs in the dying cell. In this process, the DNA condenses to form a compact mass, which is followed by karyolysis. All that remains of the cell is a non-nucleated mass of cytoplasm.

Radiation and Cell Aging

Radiation is known to cause life-shortening in both humans and animals. The concept of radiation life-shortening can be understood by looking at the level of the cell. There are three hypotheses of aging of the cell: wear-and-tear hypothesis, accumulation of toxins, and somatic mutations. The wear-and-tear hypothesis suggests that a cell will accumulate injuries until it eventually reaches a point where cell death results. Free radicals, such as those formed by radiation-induced water hydrolysis, can greatly increase the injuries to the cell. The accumulation-of-waste hypothesis, which is due in part to cross-linking of collagen, is not believed to be affected by radiation. According to the somatic-mutation hypothesis, mutations to the DNA causes its information to become garbled and faulty. This causes problems in protein synthesis, leading to flaws in cell structure and function. In summary, radiation is known to damage DNA—it possibly leads to life-shortening by information loss in somatic mutations, wear-and-tear caused cell injuries, and from accumulation of toxins (that the cell can no longer metabolize).

Therefore, this lesson has started to explore the damage radiation can do to the cell, leading to problems on the organism level. Table 4-1 is an excellent summary of the effects of radiation on each biological level.

Table 4-1. Some of the types of mammalian radiobiological damage	
Level of biological organization	**Important radiation effects**
Molecular	Damage to enzymes, DNA, RNA, and biologically important molecules
Subcellular	Damage to cell membranes, nucleus, chromosomes, mitochondria, and lysosomes
Cellular	Inhibition of cell division; cell death
Tissue; organ	Disruption of central nervous system, hemopoietic system, epidermis, induction of cancer
Whole animal	Death; "radiation life shortening"
Populations of animals	Changes in genetic characteristics due to gene mutations in individuals
Based on Table 1.4 in J. E. Coggle's, Biological Effects of Radiation, (Wykeham Publications, London 1977).	

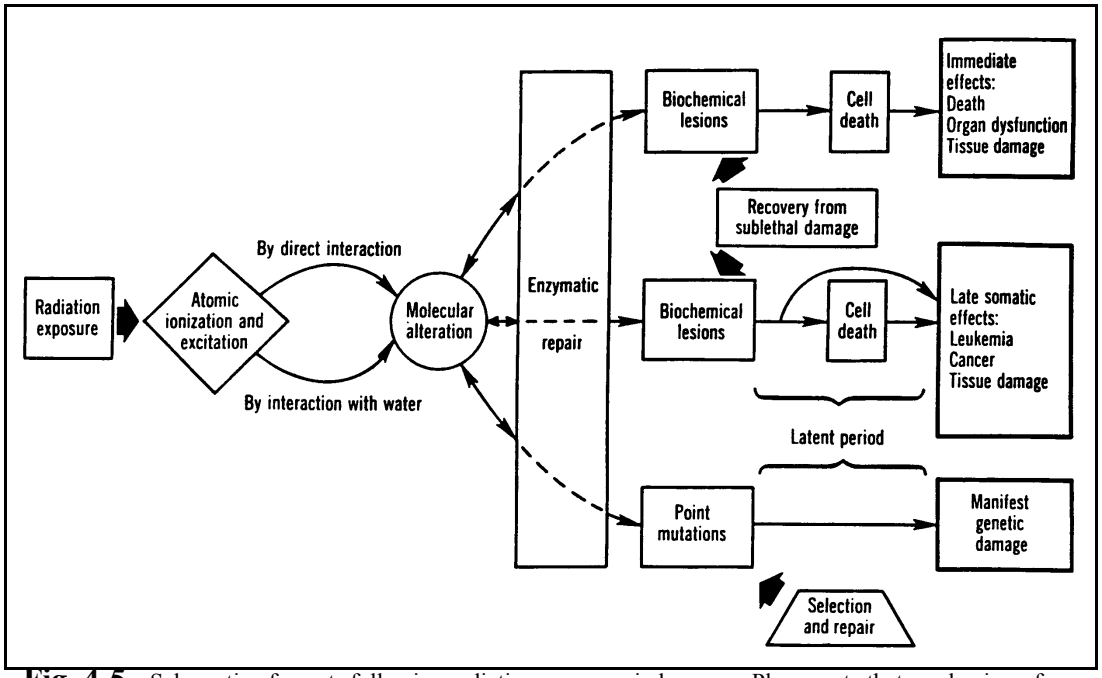


Fig. 4-5. Schematic of events following radiation exposure in humans. Please note that mechanisms for repair are available at most of the steps shown.

This lesson has also shown how radiation, through the atomic ionizations and excitations in the water radiolytic process, can affect the cell. These chemical species (OH^-, H_2^+, and others) can lead to cell death through biochemical lesions of the DNA or direct genetic mutation. Figure 4-5 is a summary overview of our study of the effects of radiation on the cells (Lessons 5–7), tissues (Lesson 8), organs (Lesson 9), and organisms (Lesson 9). Cellular death and mitotic death were introduced, as well as the formation of giant cells. A brief overview of cancer was also given in this lesson.

WRITING ASSIGNMENT - Lesson 4

Complete and submit this following assignments.

Vocabulary

Please write the term and its definition on your paper. Your definition should be in your own words and limited to one or two sentences.

spur
blob
short track
delta ray
scavenger molecule
radiation life-shortening
single strand break
double strand break
recombination
restitution
pulse radiolysis
Puck and Marcus process
giant cell
interphase death
mitotic death
superexcitation
hydrated electron
Fricke dosimeter
continuous slowing-down approximation

Questions

Answer each of the short-essay questions below in one page or less.

1. Explain the three hypotheses of cell life-shortening. Which hypotheses are affected by radiation?

2. What are the three stages of water radiolysis? What happens in each stage?

3. What is the difference between direct and indirect energy transfer?

4. What is radiation's effect on the following:

   (a) nucleus
   (b) endoplasmic reticulum
   (c) cell membrane
   (d) mitochondria

5. How could the loss of a single nitrogenous base lead to the death of a cell?

6. What are the chemical reactions for restitution and damage fixation?

7. Explain the role of the dissociation reaction, addition reaction, and hydrogen atom extraction in water radiolysis.

8. What is cancer? Explain the significance of the lack of growth kinetics.

9. What is the effect of irradiation on the four macromolecules?

10. How is a “giant cell” formed?

LESSON 5

Target Theory Model

❖ Preview ❖

READING ASSIGNMENT

Hall: Chapters 2, 3, and 4

Bushong: Chapter 35

Nias: Chapter 8

LESSON OBJECTIVES

This lesson should help you to:

- ❖ Explain the importance of clonogenic survival.
- ❖ Discuss the assumptions in the target theory model.
- ❖ Explain the difference between exponential and sigmoidal survival curves.

(continued)

DISCUSSION

Cell Survival Curve

This lesson will study the effects of radiation on the cell. Later lessons will look at the effect of radiation on the tissues, organs, and organisms. Two types of survival curves will be discussed—exponential and sigmoidal survival curves. Two aspects of target theory will be studied—single-hit and multiple-hit targets. Lastly, the effects of radiation on DNA will be explored, specifically the action of radiation on the cyclins. Various types of DNA damage will be detailed.

To begin to understand single- and multiple-hit target theory, we need to understand some of the basics of the cell survival curve. The cell survival curve describes the relationship between the fractional survival of a population of irradiated cells and the dose of radiation to which the cells have been exposed. This survival is specifically clonogenic survival. *A survivor that has retained its reproductive integrity and is able to proliferate indefinitely to reproduce a large clone or colony is said to be clonogenic. Or in other words, clonogenic survival* is the ability of a progenitor (clone) to produce at least 50 clones. This is closely related to the mitotic death discussed in Lesson 4, as each cell must pass through mitosis six times to produce at least 50 clones.

- ❖ Discuss the difference in cells used in single and multi-hit target models.
- ❖ Define D_{37} as used in the single-hit model.
- ❖ Explain the importance of threshold phenomenon.
- ❖ Explain why dicentrics are used for radiation dosimetry.
- ❖ Discuss briefly the linear quadratic model of cell damage.
- ❖ Name two types of chromosomal breaks and where they occur in the cell cycle.
- ❖ Discuss response of the chromosomes to different types of breaks.
- ❖ Discuss the importance of the p53 protein.
- ❖ Describe how radiation is able to affect the cell cycle.
- ❖ Define balanced translocation and dicentric fragment.
- ❖ Briefly discuss alternative cell survival theories.

Clones are offspring that are identical to the parent. This survival does not refer to true survival—it is very difficult to affect respiration and metabolism with incoming radiation. Rather, it refers to reproductive or mitotic death. In general, a dose of 10,000 rads (100 grays) is necessary to destroy cell function in nonproliferating systems, in contrast to 200 rads for proliferating populations. Non-dividing populations, therefore, are much more difficult to destroy.

Cell Survival Curves

A cell survival curve describes the relationship between the radiation dose and the proportion of cells that survive. Survival curves consist of a dose plotted on the linear scale and the surviving fraction on the logarithmic scale. At low doses for sparsely-ionizing radiations, the survival curve starts out straight on the log linear plot with a finite initial slope. At higher doses, the curve bends. At very high doses, the survival curve tends to straighten again, returning to an exponential function of dose. On the other hand, for densely-ionizing radiation, the cell survival curve is a straight line from the origin, indicating an exponential function of dose.

Target Theory

Lea produced one of the earliest models for cell killing: *target theory*. He made the following assumptions.

1. The killing of the cell is a multistep process.

2. The first step in the process is the absorption of a critical amount of energy.

3. Molecular lesions will result from the ionization and excitation caused by the energy.

4. The expression of the lesions causes the loss of the ability of the cell to reproduce.

Most interestingly, when he formulated these assumptions, Lea was not aware of the effects of radiation on DNA; however, his model fits well with today's understanding of the direct and indirect effects of radiation on DNA, covered in the previous lesson.

In the target model, the survival curve is described in terms of the initial slope, D_1, due to single event killing, a final slope, D_0, due to multiple event killing, and n or D_q to represent the width of the shoulder (termed the quasithreshold).

There are two main types of survival curves—the *exponential* survival curve and the *sigmoidal* (shouldered) survival curve. The exponential survival curve, whose graph is commonly shown as a straight line in the plot of the logarithm of the surviving fraction versus the applied dose, shows that the loss of clonogenic potential is related to dose in a strictly exponential fashion. This curve is applied to yeast, bacteria, and mammalian sperm, for example.

Whereas the exponential survival implies that simple, single events result in clonogenic death, the sigmoidal curve adheres to Lea's belief that there must be an accumulation of DNA damage before the cell experiences a clonogenetic death. The logarithmic graph shows a shoulder and a straight portion, the shoulder demonstrating the need for a minimum dose before clonogenetic death (see Figure 3-3 on page 36 of Hall).

It is interesting to note that when the radiation dose is delivered in a series of equal fractions, separated by time for repair, the effective survival curve is a straight line from the origin through a point, that is, it is an exponential function. This concept will be further discussed in Lesson 7 in the Dose Rate section.

According to target theory, for a cell to die following radiation exposure, its target molecule must be inactivated. The *target* is the area occupied by the target molecule or by a sensitive site on the target molecule. The target is probably DNA. A *hit* occurs when there is interaction between radiation and the target. As shown in previous lessons, the hits occur through both direct and indirect effects.

Target Theory: Single- and Multi-hit

There are two models in target theory: single hit and multi-hit. The single-hit theory applies to bacteria and viruses. Bacteria are prokaryotic. Prokaryotic cells lack a true nucleus. The DNA exists as a single, circular, double-stranded molecule. The multi-target, single-hit theory is applicable to human cells, or any complex cells such as plant or animal. These complex cells are eukaryotic. Eukaryotic cells have a true nucleus, one that is membrane-bound. The genome is divided into discrete units called chromosomes.

In the single-hit model, a single sensitive site is destroyed by an inactivating ionization, resulting in the death of the cell. Since the DNA exists as a single strand, it is easier to destroy its expression. When the radiation reaches a level sufficient to kill 63% of cells (37% survival), it is called D_{37}. The D_{37} is a measure of the radiosensitivity of the cell. A low D_{37} represents a highly radiosensitive cell. A high D_{37} represents a radioresistant cell. The equation for a single-hit is given below:

$$S = \frac{N}{N_0} = \exp\left(-\frac{D}{D_{37}}\right)$$

where S is the surviving fraction, N is the number of cells following dose D, and N_0 is the initial number of cells.

In the multi-target, single-hit model, a threshold phenomenon occurs— multiple targets must be destroyed to kill the cell. At lower doses, more cells will survive because not all the sensitive sites (possibly genes on the chromosomes) are destroyed. As in the single-hit model, fewer cells survive when subjected to an increasing radiation dose. At very high dose levels, the dose-response

becomes the same as single-hit because all additional sites have been destroyed. The equation for the survival fraction, *S*, of a cell colony in this model is:

$$S = \frac{N}{N_0} = 1 - \left[1 - \exp\left(-\frac{D}{D_0}\right)\right]^n$$

where D_0 is the dose required to reduce the survival to 37% from a single target, and n is the number of targets in the cell.

Chromosomal Damage

Whereas the target theory is the most widely-known theory of cell survival, there are several other theories mentioned in the text. For example, the molecular theory of radiation action, or *linear-quadratic model* (L-Q), assumes that the action of radiation is the rupturing of the bonds of DNA, producing lesions. These lesions will be completely or partially expressed as a result of repair processes. This linear quadratic model, which is commonly used in clinical radiotherapy, also deals with dual radiation action, meaning it assumes there are two components of cell killing by radiation, one that is proportional to dose and one that is proportional to the square of dose. Therefore, this model has a continuously bending survival curve, which has the expected initial slope but which never becomes exponential, even at high doses. Unfortunately, the actual cell survival curve does not really support this model since most actual survival curves do not fit the linear quadratic equation.

The sublesions produce by radiation may interact to form a lesion. The *repair-misrepair model* (RMR) theorizes that the irradiation stage is followed by a period of cell repair or damage enhancement. The cell passes through various phases, which may be followed by permanent alteration of the genetic material. The lethal-potentially lethal (LPL) model proposes that B lesions may converted to an undamaged A state or lethal C state by various processes.

Radiation and the Cell Cycle

Before further discussing damage to chromosomes, a short review of mitosis and meiosis might be useful. *Mitosis* produces two identical daughter cells. *Meiosis* leads to the production of one ovum (in oogenesis) or four sperm (in spermatogenesis). The products of meiosis are different due to crossing-over in prophase I. Meiosis is basically two divisions, resulting in the production of haploid cells. Study the Figure 5-1 to review mitosis.

Studies of chromosomal damage are primarily done using metaphase chromosomes of lymphocytes of mammals. New methods are allowing the study of chromosomes during interphase. These studies separate the damage to the chromosome according to which phase the chromosome was in the cell cycle. Study of the cell cycle is also due to autoradiography. Study of the effects of radiation on cell cycles is improved through the use of synchronously dividing cell cultures. Cells may be synchronized by physical methods, such as mitotic selection, volume selection, or by chemical methods, through the use of phase-specific drugs such as vincristine and cytosine arabinoside. Whereas the chemical methods can be used "in vivo," the physical methods cannot be.

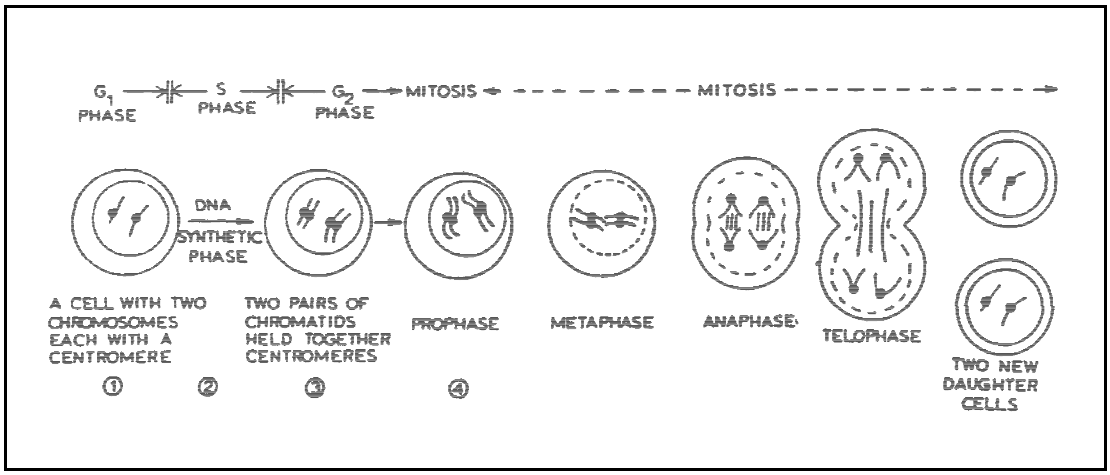


Fig. 5-1. Chromosome replication and the mammalian cell cycle showing mitosis for somatic cells.

The growth kinetic state of a cell population depends upon how many cells are passing through their proliferative cycle and how long that cycle is. The cell cycle is defined as the interval between the midpoint of mitosis in a cell and the midpoint of the subsequent mitosis in both daughter cells. The type

of damage to the chromosome is dependent upon the location of the cell in the cell cycle.

Looking at the cell cycle, there are four phases in the life of the cell—Gap I(G_1), Synthesis(S), Gap II(G_2), and Mitosis (M) (see Fig. 5-1). Progression through the cell cycle is based on the sequential transcription and translation of the cell cycle genes. G_1 may be extended into G_0; however, G_1 cells are already committed to DNA synthesis and division, whereas G_0 cells need a stimulus to enter the cell cycle.

During the S phase, DNA is replicated through the production of sister chromatids. G_1 and G_2 are both lacking in this DNA synthesis. G_1(Gap) is the phase in which the cell "decides" whether to divide. Some cells are permanently arrested in this state. G_2, which is shorter than G_1, is the phase directly before mitosis. Cell division occurs in the mitosis phase.

The length of the cell cycle varies due to variations in the length of G_1 for the cells. M, S, and G_2 vary comparatively little between different cells in different circumstances.

The following principles usually apply to the cell cycle in irradiated cells.

1. Cells are most sensitive at or close to mitosis.
2. Resistance is greatest in the latter part of the S phase.
3. If G_1 has appreciable length, a resistant period is evident early in the G_1 phase, followed by a sensitive period towards the end of G_1
4. G_2 is usually sensitive, perhaps as sensitive as the M phase.
5. The radiosensitivity of a heterogeneous population of cells is dominated by the most resistant component.

Cell cycle sensitivity may be due to changes in the formation of the DNA content during the S and M phases, as well as variations in the level of the sulfhydryl compounds in the cell, which serve as natural radioprotectors. However, cell cycle sensitivity may also be due to the presence or absence of a class of proteins called *cyclins*.

Cell Cycle Controls

According to recent research, starting with the G_1 phase, and then at specific times in the cell cycle, the concentration of cyclins increase in the nucleus. Cyclins are a family of closely-related proteins, consisting of eight types (types A-H). Cyclins form cyclin-Cdk complexes, which is the main control element that regulates the progression and activity of each phase in the cell cycle. The decision to end cell cycle progression occurs at the cell cycle checkpoints.

Each checkpoint monitors different aspects of DNA replication and chromosome segregation. Each regulates a different phase of the cell cycle. Ionizing radiation triggers the checkpoints in G_1, S, and G_2; however, the G_1 checkpoint can permanently stop the cell cycle.

Three cellular responses can occur at the G_1 checkpoint:

1. *Apoptosis* - Apoptosis is a metabolically-activated form of cell death, which serves to eliminate cells which have sustained an unusually high level of DNA damage.

2. *Cell senescence* - Cell senescence acts as an internal constraint on the life-span of a cell line. It is a quiescent state that is triggered after a cell has undergone a finite number of divisions.

3. *G_1 arrest* - In this response the cell is permanently stopped in the G_1 phase.

Each of these three responses involves the critical protein p53, a transactivating protein which initiates the transcription of other genes. A mutation in p53 can lead to carcinogenesis, evidenced by the fact that 50% of human tumors have cells with mutated p53. Such a mutated cell can become the "seed" of cancer within an otherwise healthy body.

Division Delay

Irradiation of the cell can result in two consequences: division delay and DNA damage, which will be discussed in the next section. Irradiation can produce a division delay which is expressed as a delay in entering mitosis. The maximal delay is achieved when cells are irradiated in the G_2 phase, due to a "checkpoint" which is known as the "G_2 block." The G_2 block is due to a dose-dependent inhibition of the synthesis of proteins for mitosis, such as centriole proteins. The delay of S phase cells is due to depression of DNA synthesis and prolongation of the G_2 period. The delay of cells irradiated in the G_1 phase is merely expressed as a prolongation of both S and G_2 phase. Recovery from the G_2 block is characterized by the reappearance of mitotic cells. The time needed for this to occur is a measure of radiation-induced division delay.

Using the cell cycle, we will look at the three types of chromosomal damage—*chromosome*, *chromatid*, and *subchromatid*. Cells that are in G_2, the phase after synthesis occurs, will have damage of the chromatid type. These chromatid aberrations may follow irradiation later in the cell cycle when each chromosome will have divided into two chromatids held together by a centromere, so that the damage may only be evident in one of two chromatids of the pair. Such a break occurs in a single chromatid arm and leaves the opposite arm of the same chromosome undamaged. One example of a lethal chromatid aberration is the *anaphase bridge*.

If the irradiation is delievered early in the cell cycle, before DNA synthesis has begun, then chromosomes will not yet have duplicated and damage will occur to whole chromosomes. This is visible at the next mitosis as chromosome aberrations. The radiation-induced break will be in a single strand of chromatin. This strand of chromatin will replicate the break in an identical strand laid down during synthesis. Therefore, cells that were in G_1, the phase before synthesis, will have damage of the chromosome type, since these changes will be replicated when the cell enters the synthesis phase.

The most frequent aberrations are exchanges and deletions. The simple deletion is the result of a single break in the chromosome or chromatid and the exchange is a new arrangement following the joining of breakage ends that result from separate breaks.

There is always a strong driving force for the DNA to rejoin. Most of the damage due to single-hit breaks is restored to the original state. Occasionally, the fragments formed in a single hit will rejoin incorrectly. An acentric fragment forms when the large fragment joins end-to-end to form a circular chromosome, leaving a small fragment without a centromere (see Figure 5-2).

In multiple breaks, the terminal deletion is a result of a single break across the chromosome; the remainder of the interchange involves a double break and abnormal rejoining. The centric ring is the most common aberration.

With two hits, dicentric products are formed in G_1, when adjacent chromosomes each suffer one hit and recombine. Dicentric products result when *translocation* (movement of chromosome separated in meiosis) is unequal. The product may have two centromeres (dicentric) which leads to the formation of bridges which are fatal to the cell. The dicentric product will remain in the center of the cell during division, not allowing complete separation of the daughter cells. Ring chromosomes are also produced.

In G_2, at the chromatid level of damage, fragments may recombine, omitting small fragments—*interstitial deletion*. If reordering of the fragments occur, without any loss of material, the process is referred to as *inversion*. Examples of two-hit damage are shown in Figure 5-3. An example of reciprocal translocation is shown in Figure 5-4. The dicentrics are used as the basis for biological dosimetry, because the dicentric is the most consistent index of radiation damage. It represents 60% of all observed unstable aberrations following acute irradiation.

At the chromatid level, such unstable aberrations are likely to be lethal and within a few cell cycles would be selectively eliminated from the natural proliferating population of cells. Stable aberrations are more serious because they can pass through successive cycles. Non-lethal chromosome aberrations include symmetrical translocation and a small interstitial deletion.

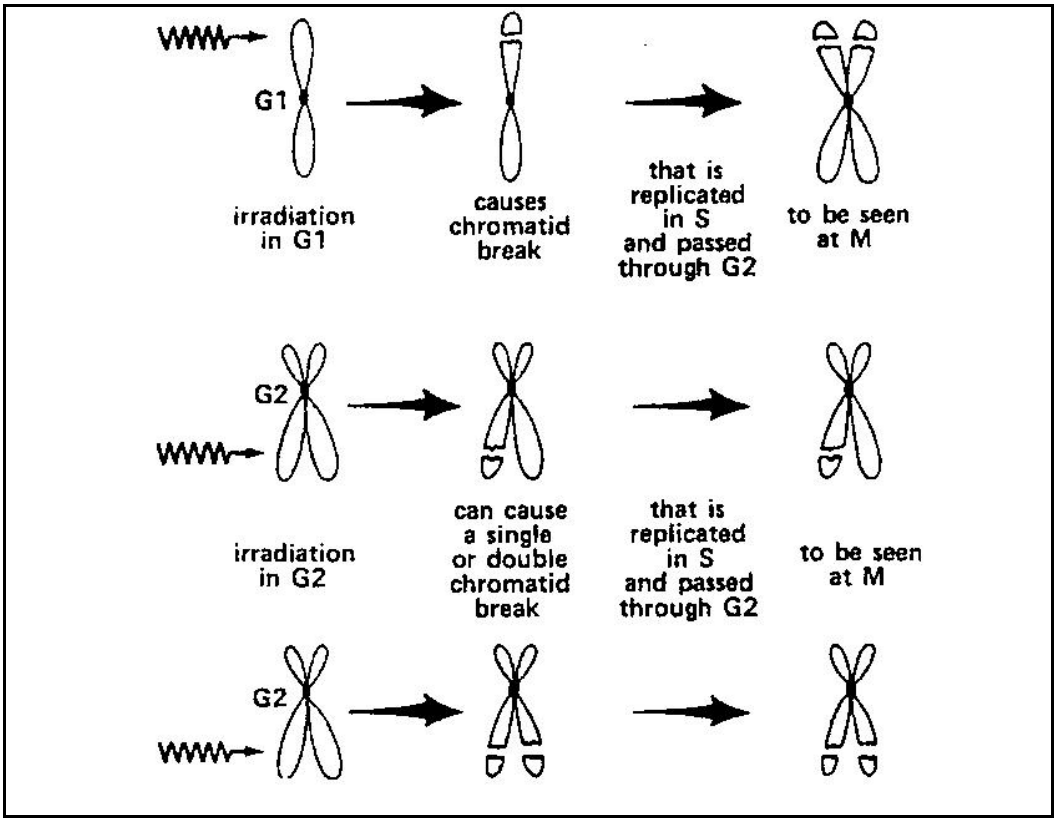


Fig. 5-2. Irradiations during G_1 or G_2 phase of the cell cycle results in single hit aberrations shown above as visualized during mitosis.

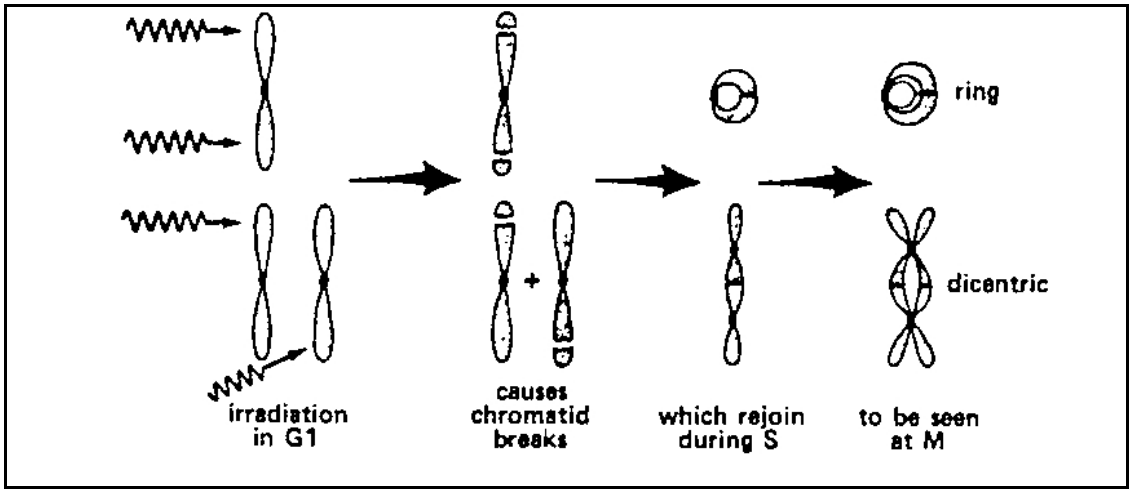


Fig. 5-3. Irradiations during G_1 (or much more rarely G_2) phase of the cell cycle results in multi-hit aberrations shown above as

visualized during mitosis.

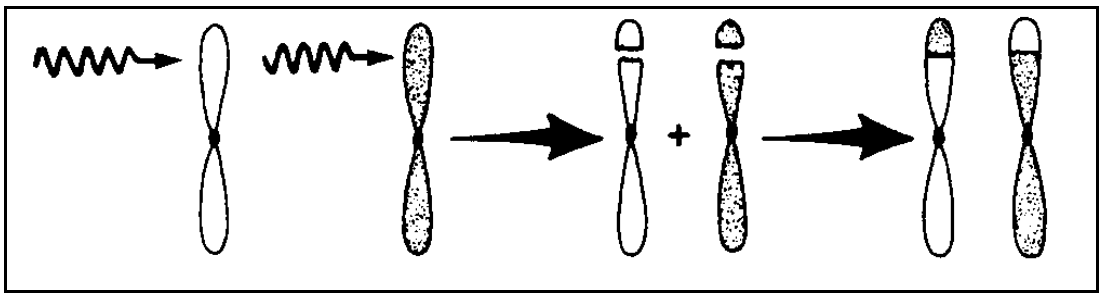


Fig. 5-4. Radiation-induced reciprocal translocation.

Damage due to multiple hits can be extreme. At the chromosome level (in G_1), breaks can form a dicentric product or undergo an isocentric break. An isocentric break occurs at the same location in both chromatids.

G_1: chromosome damage ———> translocation, dicentric chromosome
G_2: chromatid damage ———> interstitial deletion, minute, inversion

Chromosome Aberration Dosimetry

An application of the knowledge of radiation damage to chromosomes is its use in *chromosome aberration dosimetry*. In the event of radiation exposure a blood sample can be examined by a lab specializing in this work and a rather precise estimate of the dose can be obtained in the range of 35 to 500 Rem. This technique requires the services of a highly skilled technician for up to two weeks. Calibration curves enable accidental radiation exposure to be estimated in terms of such chromosome aberrations. The number of cells showing aberration decrease with time, but the chromosome aberrations are still observable after 25 years.

This lesson has explored the effects of radiation on the chromosomes of the cell. Lesson 6 will explain further the effect of radiation on the cell's DNA. Genetic mutations are a the result of chromosome interaction with radiation. Repair mechanisms for this genetic damage will also be explored in Lesson 6.

The response of the cell to radiation is expressed as a survival curve. The target theory model (single and multi-hit) explains how radiation may inactivate the cell. Radiation can either delay the cell cycle or produce chromatid or chromosome damage, depending upon the cell's position in the cell cycle.

Summary

- The interaction of radiation with prokaryotic cells and viruses is described by single hit theory.
- Multi-target, single hit theory explains the interaction of radiation with eukaryotic organisms.
- *Threshold phenomenon* refers to the accumulation of damage in the DNA before cell death occurs.
- There are three primary changes to the chromosome due to irradiation—subchromatid, chromatid, and chromosome level damage.
- The presence of dicentrics in the bloodstream is used for radiation dosimetry.
- The cyclins, which are responsible for checkpoints in the cell cycle, may be inactivated by radiation.
- Division delay is an example of a potential effect of radiation on the cell.
- The p53 protein is commonly mutated by radiation in many cancers.

WRITING ASSIGNMENT - Lesson 5

Complete and submit the following assignment.

Vocabulary

Please write the term and its definition on your paper. Your definition should be in your own words and limited to one or two sentences.

cell survival curve	chromatid	theory
clonogenic survival	inversion	repair-misrepair model
reproductive death	balanced translocation	aptosis
target theory	dicentric product	cell senescence
prokaryotic	hit probability	cyclins
eukaryotic	mean lethal dose	cell cycle
D_{37}	linear-quadratic model	G_2 block
threshold phenomenon	dual radiation action	anaphase bridge

questions

Write short-essay (1 page or less) answers for the following.

1. Why aren't all cells which are alive included in the cell survival curve?

2. What are the four important assumptions made by Lea in the target model?

3. What is the difference between the exponential and sigmoidal cell survival curves?

4. In what type of cells does single hit occur? Multiple hits?

5. Why does the threshold phenomenon occur in the multi-target, single-hit model?

6. When do the three types of chromosomal breaks occur?

7. Which is the most severe break? Why?

8. What are the differences among the linear-quadratic theory, target theory, and dual radiation models?

9. What are the weaknesses in the target theory? Linear-quadratic theory?

10. How does the survival curve differ for densely-ionizing and sparsely-ionizing radiation?

11. Describe briefly how the following survival curves would appear:
    (a) linear quadratic survival curve
    (b) multi-target survival curve
    (c) fractionation of radiation dose

12. What is the importance of the p53 gene? What may happen with radiation exposure?

13. How does resistance to radiation vary throughout the phases of the cell cycle?

14. What is a dicentric? Why is it important in radiobiology?

15. How do chromatid breaks occur? Give an example of such damage.

LESSON 6

Gene Mutations

❖ Preview ❖

READING ASSIGNMENT

Hall: Chapter 11

Bushong: Chapter 35 (pp. 503-505)

Nias: Chapter 18 (pp. 320-324)

LESSON OBJECTIVES

By the end of this lesson you should be able to:

- ❖ Name and explain the three types of genetic mutations.
- ❖ Name several common examples of each mutation type.
- ❖ Discuss the findings of Müller and the Russells.

(continued)

DISCUSSION

This lesson will focus on genetic mutations due to radiation. Lesson Five addressed damage to chromosomes. This lesson will discuss the result of the irradiation of the chromosomes—genetic mutation, focusing on the work of Müller and the Russells. Genes are the functional units of the chromosome, and their expression leads to the production of a specific protein. Repair mechanisms and disorders of these mechanisms will also be studied.

Gene Mutation Classification

A gene is a finite segment of DNA specified by an exact sequence of bases. The number of genes in the human is 0.5×10^5 per haploid set of chromosomes. Chromosome mutations are the result of either an increase or decrease in the number of genes in the nucleus. Point mutations, which result from small alterations in DNA, occur in proportion to dose and are independent of dose rate.

On the whole, genetic mutations are a burden to the population, not a benefit. Radiation-induced mutations add to the spontaneous mutations, increasing the genetic burden. There is no question

- ❖ Explain the importance of the work of Müller and the Russells.
- ❖ Define the concept of doubling dose and genetically significant dose.
- ❖ Discuss normal mutation rates in the human population.
- ❖ Explain the problems associated with the lack of a repair mechanism.
- ❖ Explain how radiation can affect the mutation rate.
- ❖ Discuss the effects of the amount of DNA and dose on mutation rate.

that radiation is deleterious to the species as a whole. Most importantly, radiation does not result in genetic effects that are new or unique, but increases the frequency of some mutations that already occur spontaneously or naturally.

To review briefly, the human *genome* (complete set of chromosomes) consists of 23 pairs of chromosomes—a total of 46 chromosomes. A homologous chromosome pair consists of two chromosomes which are "alike," meaning they have the same type of genetic information. Twenty-two of the pairs are somatic chromosomes. The twenty-third pair consists of the sex chromosomes. The female has two X chromosomes, whereas the male has only one X chromosome. The other chromosome in the male is a Y chromosome, which has very little genetic information on it.

Gene mutations may be classified as dominant, recessive, or sex-linked. A *genetic mutation* is a change in a DNA base leading to the production of an altered protein or no protein product at all.

A *dominant mutation* is one that appears in the immediate offspring if the altered gene is found in at least one of the parents. This dominant mutation need be in the gene of only one of the chromosomes of the homologous pair to be expressed. There are 700 such dominant gene diseases including polydactyly, achondroplasia, Huntington's chorea, and retinoblastoma.

A *recessive mutation* will appear only in offspring that have received the same mutation from both parents. For a recessive mutation to be observed, unless sex-linked, both chromosomes of the homologous pair must carry the altered gene. *This means that the gene must be inherited from both parents; consequently, many generations may pass before it is expressed*. There are nearly 500 recessive diseases, including sickle cell anemia, cystic fibrosis, and Tay-Sachs disease.

Sex-linked mutations occur in the sex chromosomes—female (XX) and male

(XY). Since the male has a dissimilar pair of sex chromosomes that do not contain complementary genes for all the traits, the male will express "recessive" mutations. This type of mutation is called sex-linked. There is more than 80 such sex-linked conditions, including hemophilia, color-blindness, and Duchenne muscular dystrophy.

Mutations occur in both germ cells and somatic cells. Mutations occurring in the sex cells are more disastrous than those occurring in the somatic cells (body cells) because the mutation can be passed to the offspring. Mutations of a somatic cell will merely lead to the death of that one cell. For example, mutation of an epidermal cell (skin) may result in death of that cell or cancer. However, the organism will continue to survive if only this one cell is affected. Its offspring will not be affected.

As a rule of thumb, the genetic effects will be most pronounced in the first generation after irradiation; however, the total number of deleterious effects of genetic mutations following irradiation will be much greater in all subsequent generations.

Radiation can affect future offspring in another way besides mutation—chromosome distribution. Errors in chromosome distribution can result in cells containing too many or too few chromosomes. For example, Down's syndrome results from an extra chromosome 23. Most of the time an incorrect chromosome number leads to embryonic death, accounting for 40% of spontaneous abortions and 6% of stillbirths. Radiation is more effective at breaking chromosomes than in causing errors in chromosome distribution. Such a chromosome imbalance, if it does not cause the death of the embryo, leads to physical abnormalities, usually accompanied by mental deficiency.

Experimental Studies

The early research on the genetic effects of radiation was done by H. J. Müller, who won a Nobel Prize for his studies. He studied the *Drosophila* fruit fly by observing mutations on the X chromosome. The results showed a linear non-threshold response of the mutation rate to radiation dose. This type of response is also known as *stochastic response*. (This type of response has been used by the National Council on Radiation Protection to model the human response to low doses of radiation.) Müller also concluded that the observed mutations were of the *same quality as those which occur spontaneously*. The response observed was independent of dose rate, indicating that the damage is

due to a single hit on a gene.

After World War II, L.B. and W.L. Russell began a large mouse colony which was exposed to radiation dose rates from 0.001 to 0.90 rad per minute and total doses of 1000 rad (10 Gy). They observed specific expressions of genetic information, i.e., the coat color and eye color. These studies have continued with over one million mice, giving the project the common name of the Megamouse Project.

A major conclusion of this study is that there is a dose-rate effect for mammals. This study observed that the mutations were more frequent for mice exposed at a high dose rate than in mice which received the same dose but at a lower rate. This is termed a *dose-rate effect*, as the mutation rate depends upon the rate at which the dose is given, not on the total dose.

The study implies a repair mechanism for radiation damage in mammals. It is important to note that the mutation rate is about 15 times greater than that found in fruit flies. In the target model, this would imply that the actual size of the genome on the chromosomes is about 15 times larger in mammals than in fruit flies.

As has been shown in numerous studies in addition to Russells', there is a relationship between radiation-induced damage and the size of the nucleus, chromosomes, or DNA content. As the DNA content increases between species, the mutation rate per gene multiplies by almost the same factor. This correlation may result from an increased amount of DNA associated with regulating the gene activity as the DNA content increases. This relation is shown in Figure 6-1.

The Megamouse Project led to many other conclusions in addition to that of dose rate. There are two ways to describe the estimated genetic risk of radiation. The first method is to compare radiation-induced mutations with those that occur spontaneously. The results are expressed in terms of doubling-dose. This is the relative mutation risk. The second way of describing the direct or absolute mutation risk quotes the incidence of disorders resulting from mutations in the first generation.

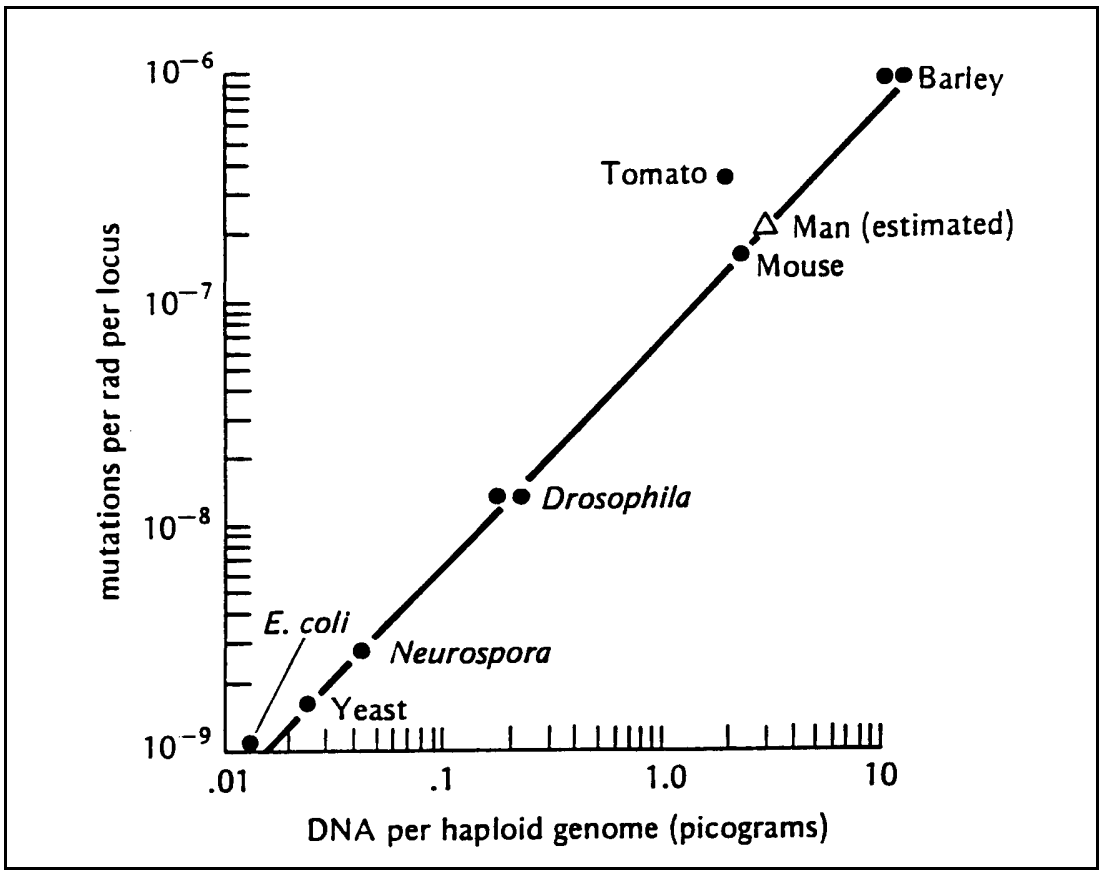


Fig. 6-1. The relationship between the amount of DNA per haploid nucleus in picograms (1 picogram = 10^{-12}g) and the mutation rate per locus per rad. Note: the point for humans is estimated from the mass of DNA per haploid cell and using the straight line on the log-log plot.

Relative mutation risk has been assessed by Russell and Russell in the Megamouse Project. The following major conclusions were reached as a result of these experiences:

1. The radiosensitivity of different mutations varies by a factor of 35—it is only possible to speak of average mutation rates.

2. The male mouse is much more sensitive to radiation than the female. At a low dose rate, almost all the radiation-induced genetic burden in a population is carried by the males.

3. The genetic consequences of a given dose can be greatly reduced if a time interval is allowed between irradiation and conception. Consequently, if persons are exposed to a significant dose of radiation, it is recommended that six months be allowed to elapse between the exposure to the radiation and planned conception to minimize the genetic consequences.

The Concept of a Doubling Dose

The concept of a doubling dose is very useful in describing genetic damage. The *doubling dose* is the amount of radiation needed to produce twice the rate of genetic mutations that would have been observed without radiation. For humans the doubling dose ranges from 50 to 250 rads (0.5 and 2.5 Gy). A more exact estimate of the doubling dose for humans is 1 Gy (100 rads) based on low-dose-rate exposure. *Drosophila* fruit flies have doubling dose 15 times greater than this.

The figure for doubling dose for humans is a calculated quantity, based on the measured mutation rate per locus on the mouse, adjusted for the estimated loci in humans.

The lowest possible doubling dose is 3 rems, the average amount of radiation received from natural sources during the typical reproductive lifetime of 30 years. Estimates of doubling dose from Hiroshima and Nagasaki is 1.56 Sv (156 rems).

The following guiding principles apply to doubling dose:

1. Most mutations, whether spontaneous or induced by radiation, are harmful.

2. Any dose of radiation, however small, entails some genetic risk.

3. The number of mutations produced is proportional to the dose.

4. Risk estimates based on experiments with the mouse are very similar for human values.

Genetically Significant Dose

The *genetically significant dose* is an index of the presumed genetic impact of radiation on a whole population. It is the dose, which if given to every member of a population, should produce the same genetic damage as actual doses received by the gonads of particular individuals. It is a calculated gonadal dose for each person, which is weighted by the expected number of future children for a person of that age and sex.

Mammalian Cell Culture Studies

Several studies have been completed on mammalian cell cultures. In order to observe a mutation in these studies, specific environmental stresses were induced and the mutation was observed when a cell line could live in an environment (such as a media lacking normally needed amino acids or the presence of a drug) in which the cells normally could not survive. By this method, the specific locus mutation rate was found to range from $1.5\text{-}3x10^{-7}$ mutation/rad. Figure 6-2 shows a way in which this mutation could occur.

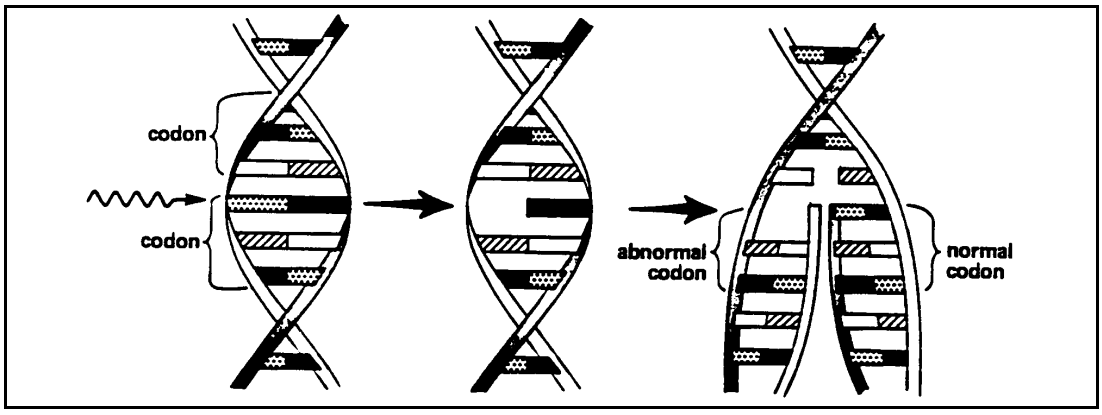


Fig. 6-2. A point mutation caused by radiation is shown. This point mutation creates an abnormal codon, which can cause an a aberrant gene. This is an example of a genetic mutation which can be passed to a daughter cell.

To give you some perspective on the mutations induced by radiation, a short overview of natural mutations and DNA repair is needed. Human mutation rates have been observed from 0.5 to 10 per 100,000 for Huntington's Chorea to neurofibromatosis, respectively. Huntington's Chorea is a dominant disease which does not appear until middle-age in humans, after they have already passed the gene to offspring. Neurofibromatosis is commonly known as Elephant Man's Disease. Similar mutation rates have been observed in such diverse organisms as bacteria and hamsters.

The process of DNA repair may involve enzyme recognition of a distorted section of a DNA strand, excision of the defective sequence, and replacement of this section by a new sequence of nucleotides. This new sequence of nucleotides is formed as a complement to the undamaged DNA strand. Glycolase enzymes are highly specific in removing damaged bases. Endonuclease enzymes nick off sites that are lacking a base or have a damaged base. Polymerases act to refill a new sequence of nucleotides. Ligases will join adjacent nucleotides.

The DNA aberrations which are not directly repaired by excision and replacement may be repaired in a process of "multiplicity reactivation." Figure 6-3 shows this process occurring to form a thymine dimer, which is a common product of UV irradiation.

When these repair mechanisms are not functioning, normal background radiation can cause massive damage to the organism. Xeroderma pigmentosum is a classic example of an inability to repair DNA damage from UV radiation. Humans with the disorder suffer from numerous skin malignancies, resulting in eventual death. Cockayne Syndrome results when ultraviolet radiation inhibits DNA replication. Humans with this disorder suffer from dwarfism, microcephaly, and premature aging.

As a further example of the importance of DNA repair, consider individuals with ataxia telangrectasia, a disorder of DNA repair. Heterozygotes for this disorder are very sensitive to radiation-induced cancer. They are at an increased risk for all types of cancer, with breast cancer in females being prominent. While comprising only 1% of the population, these AT heterozygotes account for 20% of breast cancer occurrence, especially in younger women.

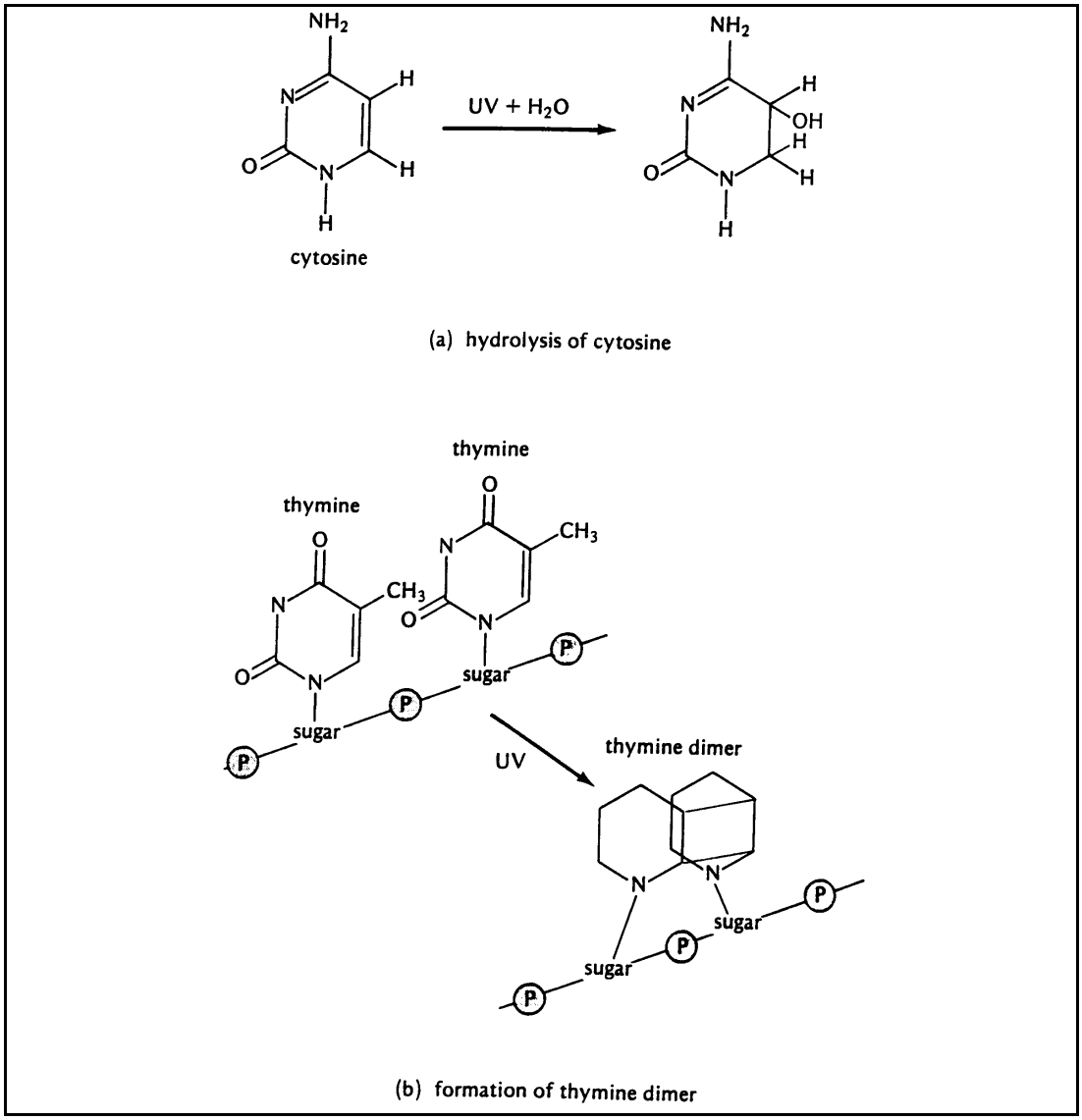


Fig. 6-3. Thymine dimer formation from UV light (b). The hydrolysis of cytosine is also shown in (a).

Risk of Genetic Mutations

In order to put the risk of radiation-induced mutations in perspective, the following facts need to be noted. For a working population, the ICRP estimates the probability per capita for radiation-induced hereditary disorders to be 0.6×10^{-2} per Sv. Therefore, congenital abnormalities are much more important than genetically-transmitted disorders.

It has been estimated that the average American receives less than five rads from artificial radiation sources over a 30-year period. Furthermore, no more than one to six percent of spontaneous mutations in humans may be ascribed to background radiation. The low rate of mutation in the modern environment can be attributed in part to the mechanism for DNA repair. If a single location on a DNA strand is damaged by ultraviolet light, chemicals, or radiation, repair can occur. As a rule, when an acute exposure with a large dose is absorbed, a large proportion of genetic mutations can be avoided if conception is deferred for at least six months.

Summary

This lesson has discussed the irradiation effects on genes. Repair mechanisms, dominant in more complex organisms, are important "fixers" of irradiation damage. Lesson 7 will adress factors, such as oxygen and temperature, which can further enhance or lessen the effects of irradiation on the chromosomes.

- There are three types of genetic mutations: dominant, recessive, and sex-linked mutations.
- The size of the genome of an organism can affect dose-rate effect.
- Doubling dose is also related to the size and repair mechanisms of an organism.
- Repair mechanisms serve to "fix" the genetic mutations caused by background radiation.
- Radiation can induce both genetic mutations and problems with chromosome distribution.
- Genetically-significant dose helps assess the risk of genetic mutations in a population.
- The risk of genetic mutation due to radiation sources is not great.

WRITING ASSIGNMENT - Lesson 6

Complete and submit the following assignment.

Vocabulary

Please write the term and its definition on your paper. Your definition should be in your own words and limited to one or two sentences.

dominant mutation	doubling dose	gonadal dose
recessive mutation	xeroderma pigmentosum	relative mutation risk
point mutation	gene mutation	direct mutation risk
sex-linked mutation	gene	genetic detriment
stochastic response	genetically significant dose	genetic death
frame-shift mutation		

questions

All of the questions below ask for a short-essay response. Please limit your response to one page or less.

1. What are the three types of mutations? Explain the differences between them.

2. Why are germ-cell mutations more damaging than somatic cell mutations?

3. What was the major finding of the Russell and Russell study?

4. What is the importance of doubling dose?

5. What limits the appearance of mutations in the human population?

6. Explain the process of DNA repair.

7. Using Figure 6-1, one can observe that the so-called "simple plants" such as barley and tomatoes have a lower mutation rate than man. Using your knowledge of genetics, why is this so? (Hint: How are the extremely large strawberries different genetically from ordinary strawberries?)

8. Explain why the following statement is true: "Radiation does not result in mutations that are new or unique."

9. What is the impact of chromosome-distribution problems caused by radiation?

10. What were the findings of the Megamouse Project conducted by Russell & Russell?

11. What is the link between radiation, mutation, and breast cancer?

Midterm Examination Information

The midterm examination will cover Lessons 1-6. The exam consists of a series of questions each requiring a short answer.

LESSON 7
Survival Curves

❖ Preview ❖

READING ASSIGNMENT

Hall: Chapters 6 (all), 7 (all), 9 (all), 22 (pp. 397-411), and 25 (all)

Bushong: Chapters 34 (all), 35 (all), and 36 (pp. 516-520)

Nias: Chapters 4 (pp. 60-61), 7 (all), 8 (all), 16 (all), and 17 (all)

LESSON OBJECTIVES

By the end of this lesson, you should be able to:

- Define terms used in understanding survival curves: *mean lethal dose (D_m)*, *threshold dose*, D_q, and D_o.

(continued)

DISCUSSION

This lesson will focus on modifications to the radiation response of the cell, particularly the effects of oxygen and energy transfer on the response of the cell to radiation. Survival curves will be explained in greater detail. Lastly, the effects of sex, age, water, chemicals (radiosensitizers and radioprotectors) on irradiation will be discussed. Dose rate will be addressed, in context with radiotherapy.

Dose-Response Curves

Several clonogenic assays can determine dose-response relationships for cells of normal tissues. The assays for skin colony, testes, kidney tubule, and jejunum crypts can determine the reproductive integrity of individual cells. Bone marrow cells, thyroid cells, and mammary cells all involve transplantation into another site. Skin reactions in pigs, lung response in mice, and spinal cord damage can be used to determine functional endpoints for dose-response curves.

- ❖ Define and explain the four types of radiation damage.
- ❖ Describe the characteristics of the survival curve.
- ❖ Explain the effects of oxygen on radiation response.
- ❖ Describe basic concepts of radiotherapy in regards to oxygen, chemicals, and dose rate.
- ❖ Explain the usage of the terms OER and RBE.
- ❖ Discuss the modification of the radiation response due to water, temperature, age, and sex.
- ❖ Describe the effects of chemicals on the radiation response.
- ❖ Explain the body's response to fractionation and protraction.
- ❖ Explain the relationship between LET and sublethal damage.
- ❖ Differentiate between sublethal and potentially lethal damage at the cellular level.
- ❖ Discuss the importance of fractionation and protraction on the response of an organism.

In general, the response of a tissue or organ to radiation depends on two factors: (1) inherent sensitivity of the individual cells, and (2) kinetics of the population as a whole of which the cells are a part.

In highly-differentiated tissues that have specialized functions, the cell survival curves are irrelevant due to the lack of mitotic future of the cells. The radiation needed to destroy the function of the cell is much greater than that to stop mitosis of the cell.

Survival Curves

The survival curves of mammalian cells can be used to obtain direct information on their response to radiation.

When the logarithm of a typical cell survival is plotted versus dose on a linear scale, several features become evident. At larger doses of radiation, the graph becomes a straight line on this scale. At low doses, a shoulder on the curve is found, which is quantified by the *threshold dose*. The width of shoulder of the survival curve indicates the degree of sublethal damage, which is more readily repaired in the S phase.

As for specific values, the *mean lethal dose*, D_m, is defined as that amount of radiation required to reduce the survival by 37%. It is equal to D_{37} in the linear portion of the curve. A large D_m indicates a radioresistant line of cells, whereas a small D_m is characteristic of cells with a high radiosensitivity. The D_0 is the slope of the exponential portion of the curve, which is the nonlethal dose. The threshold dose, D_q, is a measure of how much damage occurs before it is

lethal. The D_q is a measure of the width of the shoulder. A large D_q indicates that a cell can readily recover. Examine Table 7-1 to note the sensitivity of various cell lines.

The D_0 value is the measure of intrinsic radiosensitivity of a cell type, whereas the clinical radiosensitivity depends upon the size of the shoulder and the cellular environment. This is demonstrated by the shoulder of the survival curves for tissues being larger than those for single cells.

The shoulder of the survival curve is explained by various theories. According to the target theory, the shoulder is due to the interaction of sublethal lesions. The repair model assumes the shoulder is due to the repair of single lesions produced by single tracks of radiation in proportion to dose, a mechanism which may become saturated. Cellular repair enzymes locate the lesions, which may include double and single strand breaks, and fix these lesions, thereby restoring the integrity of DNA. This repair mechanism becomes saturated at high levels of radiation. At higher doses, lesions are lethal due to the saturation of repair enzymes, leading to the survival curve becoming exponential. The more densely ionizing the radiation, the less recovery from the sublethal damage and the smaller the shoulder of the survival curve.

Table 7-1. The reported mean lethal dose (D_0) and threshold dose (D_q) for various experimental mammalian cell lines

Cell Type	D_0 (rad)	D_q (rad)
Mouse oocytes	91	62
Mouse skin	135	350
Human bone marrow	137	100
Human fibroblasts	150	160
Mouse spermatogonia	180	270
Chinese hamster ovary	200	210
Human lymphocytes	400	100

Adapted from: Stewart C. Bushong, *Radiologic Science for Technologists: Physics, Biology, and Protection,* (Elsevier Mosby, St. Louis, 8th ed. 2004), page 512.

The existence of a threshold in cell-survival curves implies that some damage must accumulate before it is fatal to the cell. The larger the value of D_q, the more damage that must accumulate. This damage to cells prior to cell death is called *sublethal damage*. In radiation therapy it is very important to note that when a dose is split into two parts separated by enough time, a threshold is observed for each part of the dose. Thus by properly spacing treatment, it is possible to reduce the damage to healthy cells during radiation treatment. This concept of dose fractionation will be further explored later in this lesson.

Types of Radiation Damage

There are four main types of radiation damage to a cell:

1. *Non-lethal damage* involves a lesion which does not prevent proliferation, but it affects the rate of such proliferation.

2. *Lethal damage* is damage which is irreparable, irreversible, and leads irrevocably to cell death.

3. *Sublethal damage* is damage which is repaired in hours unless additional sublethal damage is added, with which it interacts to form lethal damage. Basically, sublethal damage, which is chiefly evident at low dose levels, is shed after the passage of a relatively short period of time. It has been shown that the repair of sublethal damage reflects the repair and the rejoining interval of double strand breaks before they can interact to form lethal lesions.

4. *Potentially lethal damage* is the damage that can be modified by postirradiation environmental conditions. This type of damage is manifest in those cell populations which are proliferating and are well nourished. This type of damage is only lethal if cells are stimulated to divide before repair occurs. Therefore, if mitosis can be delayed by suboptimal growth conditions, the DNA damage can be repaired. Potentially lethal damage limits the effectiveness of radiotherapy on tumors. There is no potentially lethal damage repair following exposure to high linear energy transfer radiations.

Four Rs of Radiobiology

In radiotherapy, these types of cellular damage are regulated by the four Rs of radiotherapy. The four Rs of radiobiology—repair, reassortment, repopulation, and reoxygenation—are affected by the type of radiation dose.

1. There is a prompt *repair* of sublethal repair damage.

2. There is a progression of cells through the cell cycle during the interval between the split doses, called *reassortment*.

3. There is an increase of surviving fraction due to cell division, or *repopulation*. When the time interval between two dose fractions exceeds the cell cycle, there will be an increase in the number of cells surviving due to cell proliferation.

4. The fractionation of the dose allows greater affect through *reoxygenation* of the tumour, which increases the radiosensitivity.

Cell Cycle Effects

As addressed in Lesson 5, during the cell cycle the radiation sensitivity of the cells can change dramatically. Studies using cells which have their cell cycles synchronized have shown the results found in Figure 7-1 below. To review Lesson 5, the mitosis phase, where the cell divides, is always the most sensitive, while late in the S phase, where DNA synthesis occurs, is the least sensitive. This knowledge is useful in the planing of cancer treatments.

The Effect of Oxygen and LET on Cell Survival

The survival of a cell can be affected by factors other than the radiation dose. The most biologically variable factor that modifies the radiation response is the amount of oxygen in the system. The best clinical radiation sensitizer is oxygen dissolved in the tissues at physiological concentration. In general, any compound that is electron-affinic, such as nitroimidazoles, will tend to be

radiosensitizers. On the other hand, most -SH compounds are protecting compounds, which allow the biological molecule to be restored to its normal state. A measure of the effect of oxygen is *OER* (oxygen enhancement ratio) which is defined by the equation:

$$\mathbf{OER = D_0(anoxic)/\ D_0\ (oxygenated)}$$

where D_0(anoxic) is the dose required to produce the same effect as D_0 (oxygenated), the dose in the oxygenated system.

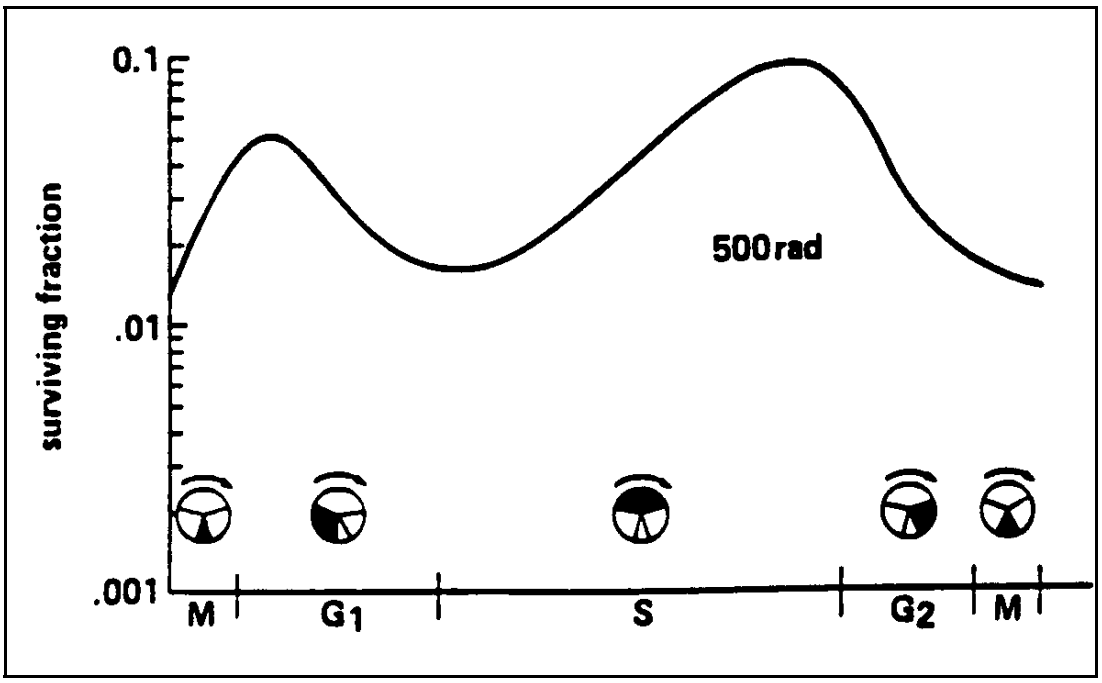


Fig. 7-1. The age-response function for human fibroblasts is shown above for a 500 rad dose. The minimums in the surviving fraction during mitosis (the **M** phase), in the resting state between synthesis and mitosis (the $\mathbf{G_1}$ phase), and in the synthesis phase (**S**), are when the cell is most radiosensitive. The maximums of the surviving fractions occur in the early $\mathbf{G_1}$ phase and in the late **S** phase where the cells are most radioresistant. The most radiosensitive phase is **M** and the most radioresistant is the late **S** phase.

In other words, the ratio of hypoxic to aerated doses needed to achieve the same biological effect is the oxygen enhancement ratio. For a human cell, OER can be as large as 2.3. The exact value varies with the cell cycle, with cells in G_1 having the lowest OER. For sparsely-ionizing radiation, such as x-rays and gamma rays, the OER is 2.5 - 3.0. For densely-ionizing radiation, there is no oxygen effect or the OER is significantly lower. Therefore, the effect of oxygen is reduced as the ionization density increases.

As for the exact mechanism of the oxygen effect, in the competition model, the effects of oxygen are due to the formation of free radicals, which have excess energy to disrupt the bonds or to damage the cell. Recalling Lesson 4, energy deposited by radiation is transferred by direct and indirect means. The majority of radiation effects are due to indirect transfer by the free radicals formed in water radiolysis. Therefore, oxygen increases the indirect radiation response due to the production of free radicals. These free radicals break chemical bonds, produce chemical changes, and begin the chain of events that results in biological damage.

The competition model explains five reactions which lead to the production of free radicals. This model explains the competition between fixation of free radicals by dissolved oxygen and repair by endogenous hydrogen donors.

1. Production of radicals by direct/indirect action

$$R-H \rightarrow RH^{\bullet +} + e^{-} \rightarrow R^{\bullet} + H^{+} + e^{-}$$
$$RH + OH^{\bullet} \rightarrow R^{\bullet} + H_2O$$

2. Chemical Repair (interaction with sulfhydryl compounds)

$$R^{\bullet} + R'SH \rightarrow RH + R'S^{\bullet}$$

3. Damage Fixation (central to oxygen effect)

$$R^{\bullet} + O_2 \rightarrow RO_2^{\bullet}$$

The RO_2 free radical is very toxic to biological structures, as it fixes radioactive lesions.

4. Damage Fixation by chemical sensitizers (reactions that mimic oxygen reactions)

$$R^{\bullet} + X(\text{sensitizer}) + H_2O \rightarrow ROH + X^{\bullet} + H+$$

5. Scavenger Reactions

The superoxide ion ($O_2^{\bullet -}$), which is formed by water radiolysis, is believed to be an intermediate in the oxygen effect. The superoxide dismutase enzyme acts on this radical to form oxygen and hydrogen peroxide, thereby protecting the cell from damage by the free radical. Cells with reduced superoxide dismutase enzymes are much more vulnerable to the effects of oxygen. In summary, oxygen increases the effect of radiation by the action of various oxygenated free radicals, and this increase is quantified by the OER formula.

It is important to remember that as the oxygen concentration increases, the material becomes progressively more sensitive to radiation until in the presence of 100% oxygen, it is about 3 times as sensitive as under complete anoxia.

Oxygen Effect in Tumors

This section will illustrate the practical importance of the oxygen effect in radiotherapy. The presence of a relatively small proportion of hypoxic cells in tumors can limit the success of radiotherapy. Tumors consist of two populations of cells—one well-oxygenated fraction and the hypoxic fraction, which may account for 10-15% of a human tumor. As the tumor is irradiated, the radiation will kill the more radiosensitive outer cells but not the more radioresistant, oxygen-deprived inner cells. As a result, there will be an increase in the supply of nutrients to these inner cells, which will again start proliferating if they have retained their reproductive potential. Therefore, though these cells are only a small fraction of the tumor, they play an important role in the radioresponsiveness of a tumor. Administration of hyperbaric oxygen is used to ensure the radiosensitivity of the tumor. Hyperbaric oxygen administration increases the success rates of radiotherapy for head and neck tumors.

Survival curves are biphasic for tumors, with a steep initial slope for the well-oxygenated proportion of the tumor cell population and a shallower final curve over the higher doses where the radioresistant hypoxic cells predominate. Overall, the most sensitive tumors have much less than 1% hypoxic cells, whereas resistant tumors have more than 10% hypoxic cells.

Linear Energy Transfer

When radiation is absorbed in biological material, ionizations and excitations are localized along the tracks of individual charged particles in a pattern. The amount of energy deposited per unit distance is known as *linear energy transfer* or LET. The effectiveness of radiation in causing damage is enhanced with increasing linear energy transfer. LET is only an average quantity. In fact, this average has very little meaning because the energy per unit length varies a great deal for each particle. For a given type of charged particle, the higher the energy, the lower the LET and therefore the lower its biological effectiveness.

As described previously in Lesson 2, as the LET increases, the relative biological effectiveness (RBE) increases slowly at first, and then more rapidly as the LET increases beyond 10 KeV/μm. This value probably reflects the "target size" and is related to DNA content (the diameter of the DNA double helix). Radiation of this density is most likely to cause double strand breaks.

High LET produces damaging effects through double strand breaks. Low LET radiation produces most of its damage by interaction of two sublethal events. There is little or no shoulder on the survival curve for high LET radiation. The wider the shoulder (higher Dq), the more sublethal damage (due to low LET) can be sustained. The mean lethal dose following low LET radiation is always greater than that following high LET irradiation. The effect of linear energy transfer on OER is shown in Figure 7-2.

Relative Biological Effectiveness

Equal doses of radiation do not produce equal biological effects. This difference lies in the pattern of energy deposition, and is expressed as relative biological effectiveness. *Relative biological effectiveness* or RBE is a measure of the effectiveness of the radiation. The RBE is defined by the equation:

RBE = D_0 (standard radiation)/ D_0 (test radiation)

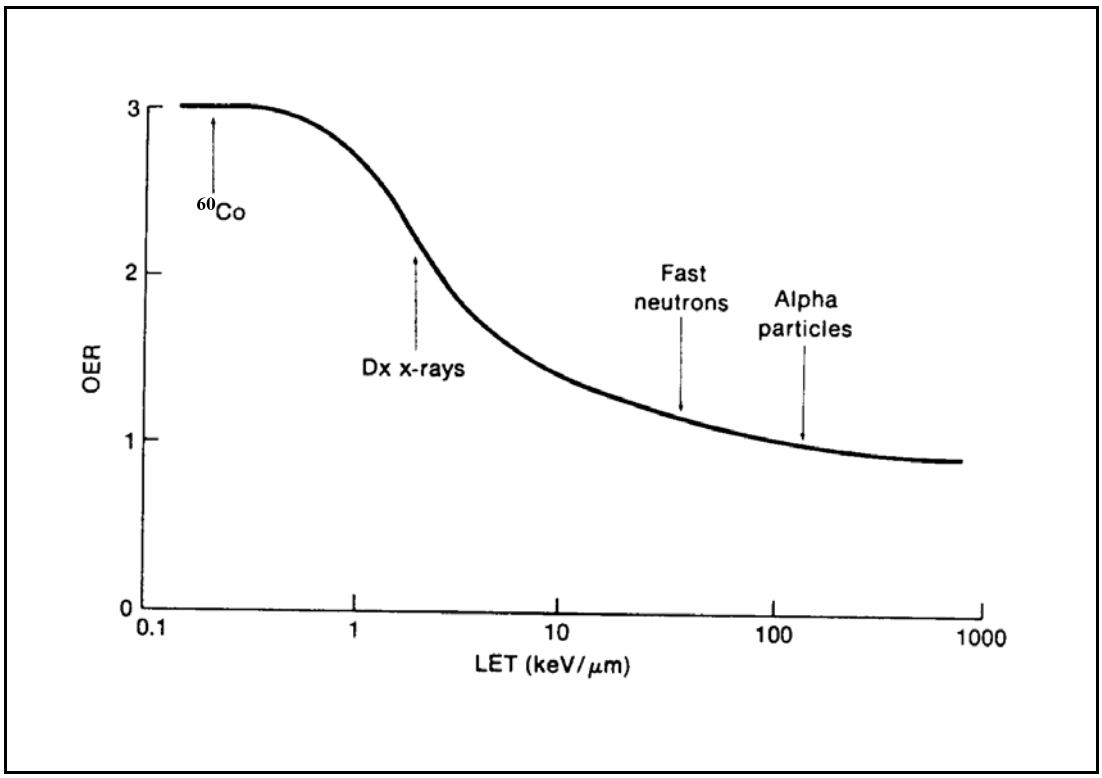


Fig. 7-2. The oxygen enhancement effect is high for low LET radiation and decreases in value as the LET increases.

where D_0 (standard radiation) is the dose of standard radiation required to produce the same effect as the dose of a test radiation, D_0(test radiation). The standard radiation is due to x-rays and gamma rays. As has been described previously, RBE is dependent on both the radiation and the LET. Figure 7-3 below shows the relationship between RBE and LET.

Relative Biological Effectiveness depends on the following factors:

1. radiation quality (RBE)
2. radiation dose
3. number of dose fractions
4. dose rate
5. biological system or endpoint

For example, the RBE for a fractionated regimen is greater than a single exposure because a fractionated schedule consists of a number of small doses. The RBE is large for small doses. Even for a given total dose, the RBE varies greatly according to the tissue. For example, bone marrow stem cells are much more radiosensitive than intestinal crypt cells.

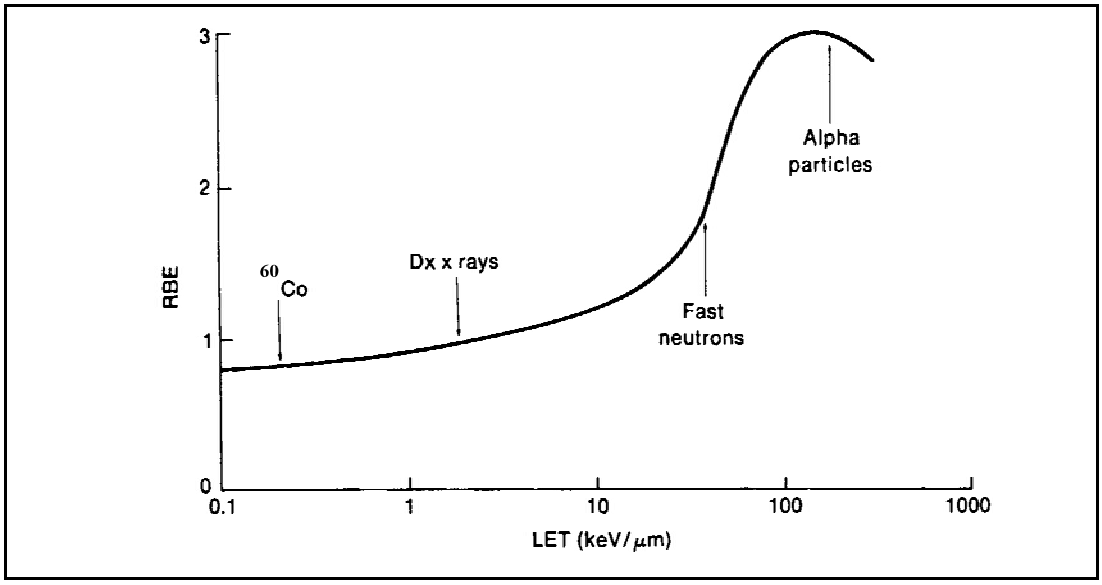


Fig. 7-3. The increase in RBE as the LET increases to a maximum near the LET of alpha particles.

Water

Water transports deposited energy to the biological materials within the cells. Thus, by reducing the water content of biological material, the amount of energy that can be transported is reduced. Due to the lack of water, initial ionization-excitation events must occur directly on the target (i.e., direct effects). In Figure 7-4, the example of arylesterase enzymes illustrates this point. The behavior of the cholinesterase enzyme is thought to be different since it has a large number of thio groups (-SH), as will be discussed in a later section.

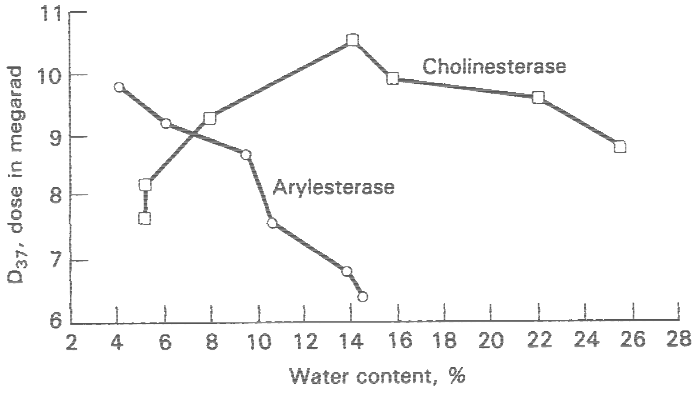


Fig. 7-4. Relative radiosensitivity of two enzymes when they are irradiated under different conditions of hydration. (Augustinsson, Jonsson,and Sparrman, *Acta Chem. Scand*. 15, 1961)

Age

The age of a biological structure is also an important factor in the radiosensitivity of an organism. For humans, the radiosensitivity is greatest in utero when the cells are rapidly dividing. This is due to the increased sensitivity of the cell while in mitosis. A second period of increased sensitivity is in the aged. This is due to a decreased rate of division, and thereby low replacement of cells, in an aged organism. Once a cell is destroyed, the loss will not be replaced—function will suffer.

Sex

Surprisingly, sex is indeed important in radiosensitivity. For humans, women are five to ten percent more radiation resistant than males. Both human sexes have 46 chromosomes, 44 of which are autosomes. The remaining two are sex chromosomes. Women have two X chromosomes, whereas males have an X and a Y chromosome. The Y chromosome has very little genetic information. Recessive traits on the X chromosome will be expressed in the male due to his lack of similar genes in his sex chromosomes. Therefore, women have twice the genetic material in their sex chromosomes (XX vs. XY). The additional DNA could aid in modifying the effects of the radiation.

Chemicals (Radiosensitizers and Radioprotectors)

Chemicals can have either a positive or negative influence on radiosensitivity, being either radiosensitizers or radioprotectors. Most of the true *radioprotectors* are sulfhydryl compounds. Sulfhydryl compounds protect by scavenging free radicals, aiding in the chemical restitution of the target molecule. Thiols (R-SH) are one example of chemicals that decrease radiosensitivity. Other examples of chemicals which protect are cysteine and cysteamine, both of which contain sulfhydryl groups. Seven hundred of these chemicals have been tested to improve survival by up to a factor of two. Unfortunately, all of the chemicals tested to date have strong side effects and are often more damaging than the radiation itself, mainly due to the high concentration required to have any protective effect. They cause nausea and vomiting at levels needed for radioprotection.

More effective radioprotectors have been developed, including WR-638 (Cytaphos), WR-2721 (amifostine), and WR-1607 (d-Con). Amifostine offers protection to the hematopoietic system, gut, and salivary glands. The dose-limiting toxicity is hypotension, sneezing, and somnolence. An important term in conjunction with radioprotection is dose reduction factor, which is the ratio of radiation doses required to produce the same biological effect in the absence and presence of radioprotectors.

Radiosensitizers are chemical or pharmacologic agents that increase the lethal effects of radiation when administered in conjunction with it. Radiosensitizing chemicals increase the transport of energy or increase the damage to the organism. Currently, they offer no gain in radiotherapy because they do not show a differential effect between tumors and normal tissues.

Only two types of sensitizers have a practical use—halogenated pyrimidines and hypoxic cell sensitizers. Halogenated pyrimidines have a differential effect due to tumor cells having a more rapid cell cycle. They weaken DNA chains by being incorporated in place of thymidine. Use of 5-iododeoxyuridine and 5-bromodeoxyuridine, as an adjunct to radiotherapy, began in the 1970s.

Hypoxic cell sensitizers differ from oxygen in being able to diffuse further to hypoxic cells due to not being metabolized. These include TAN, PNAP, and nitrofurans. Misoidazole has been used in several human clinical trials, but results have been disappointing. Central nervous system toxicity reduced the use of the drug at adequate levels. Etanidazole appears to be more promising due to having a much increased dose-limiting toxicity. Anticancer compounds, such as methotrexate, antibiotics, Vico steroids, and alkylating agents are all radiosensitizers.

Temperature

The temperature is clearly a factor in radiation response simply from the chemical nature of the damage, which has an activation energy. The a universal formula for the activation function for a given enzyme is given below:

$$C = \frac{1}{D_{37}} = C_0 e^{-\frac{\varepsilon_0}{RT}} + C_1 e^{-\frac{\varepsilon_1}{RT}} + C_2 e^{-\frac{\varepsilon_2}{RT}}$$

where ε is the activation energy of for the chemical function (T. Brustat, *Biological Effects of Neutron and Proton Irradiations* **2,** p. 404 IAEA, Vienna). The formula has both temperature-independent and temperature-dependent components. The temperature-independent components possibly describe ionization events or other non-threshold chemical reactions.

Dose Rate

If the dose is delivered continuously but at a lower dose rate, it is said to be "protracted." A dose which is delivered at the same dose rate but in equal fractions separated by equal time periods is said to be "fractionated." Dose fractionation is better at limiting damage because tissue repair and recovery occurs between doses.

The following example is a good explanation of the difference between fractionation and protraction:

Protraction: A mouse is given 600 rads at 200 rads/hour for 3 minutes continuously.

Fractionation: A mouse is given 600 rads at 200 rads/min in 12 fractions of 50 rads, separated by 24 hours.

Dose Rate—Protraction

As the dose rate is lowered and the exposure time extended, the biological effect of a given dose is greatly reduced. Since a continuously low dose rate of radiation may be considered to consist of infinitely small fractions, the survival curve will have no shoulder and be shallower than for single acute exposure.

Some cell lines repair sublethal damage rapidly, some more slowly. This is reflected in the survival curves at low dose rates. For example, testis tissue is more sensitive than small intestine tissue. A point is reached at which all sublethal damage is repaired, resulting in a limiting slope.

There are several factors which determine the response of renewal tissues to continual radiation.

1. Cellular sensitivity of the stem cells involved.

2. Duration of the cell cycle (i.e., more damage to cells with a long cell cycle).

3. Ability of some tissues to adapt to the new trauma of continual radiation.

When protraction of radiation dose occurs, there is an increase in recovery from sublethal damage in the surviving cells, leading to more proliferation during the irradiation. As a result of this protracted dose, the radiation may appear to have little or no effect at all. If the dose rate is greatly lowered, there will be time for proliferation of undamaged cells.

At intermediate dose rates, a cell population may only fall to a survival level that is "steady state," due to the balance of continuous radiation damage and the recovery of damaged cells. As a rule, a given dose rate of continuous irradiation will be more effective in cells with a longer cell cycle.

In action, protraction, a method whereby the overall time within the normal radiotherapy range is prolonged, has a sparing effect on the late reactions but a large sparing effect on early reactions. Early-responding tissues are skin, mucosa, and intestinal epithelium; late-responding tissues include the spinal cord.

Dose Rate—Fractionation

The goal of fractionation in radiotherapy is to kill all tumor cells without producing serious damage to the normal surrounding tissues. This is best achieved by giving the total dose of radiation in a specific number of fractions over a time period, generally five treatments a week for six weeks. Repair, reassortment, repopulation, and reoxygenation, the four Rs of radiotherapy, determine the effectiveness of the fractionation. For example, dividing a dose into fractions spares normal tissues because of repair of sublethal damage between dose fractions and repopulation of cells if the overall time is sufficiently long. Fractions also increase damage to a tumor because of reoxygenation and reassortment of cells into radiosensitive phases of the cycle.

With very large tumors, the incidence of late-tissue effects may outweigh the beneficial effects of tumor volume reduction. The fraction size is the dominant factor in determining the late effects while overall treatment time has little influence. By contrast, fraction size and overall treatment time both determine the response of acutely-responding tissues. Therefore, the late effects on lung, kidney, and spinal cord determine the tolerance dosage. Fractionation of the radiation dose produces better tumor control for a given level of normal tissue toxicity than a single large dose.

According to the nominal standard dose system (NSD), the total dose for the tolerance of connective tissue is related to the number of fractions (N) and the overall treatment time (T) by the following formula (Nias, page 289):

$$\text{Total dose} = (\text{NSD})\ T^{0.11}\ N^{0.24}$$

Fractionation can also involve multiple fractions per day—hyperfractionation and accelerated treatment. In hyperfractionation, the treatment time remains the same but the number of fractions are doubled. The intent is to further

reduce late effects and achieve better tumor control. Accelerated treatment halves the treatment time by giving two fractions a day. This process reduces the repopulation in rapidly proliferating tumors. The use of either of these two processes depends on clonogenic cell number doubling time.

The dose rate is often very important in radiation effects on the cell or organism. For some cells, a threshold dose is required before any effect can be seen. By splitting a dose in several parts below this threshold level, a better survival rate occurs than when the dose is applied at once. *Protraction* and *fractionation* are two methods to reduce the effects of the dose delivered.

Summary

This lesson has focused on possible modifications in the radiation dose received by an organism. The survival curves, which illustrate the survival of a population of cells, can show the effects of factors such as sex, age, and dose rate. In Lesson 8, the focus will shift from cells to tissues and organs. The basics of irradiation at the cellular level will also apply to the tissues and organs.

- ❖ Graphing a survival curve gives a great deal of pertinent information such as threshold dose and mean lethal dose.
- ❖ Oxygen has an important influence on the effects of radiation due to destruction of the cell by a free radical.
- ❖ The effects of radiation are influenced by cell cycle position, water, linear energy transfer, age, sex, chemicals, and temperature.
- ❖ The effects of dose rate on radiation is important for therapeutic radiation use.
- ❖ Radiosensitizers and radioprotectors are limited in their use due to toxicity.

WRITING ASSIGNMENT - Lesson 7

Complete and submit the following assignment.

Vocabulary

Please write the term and its definition on your paper. Your definition should be in your own words and limited to one or two sentences.

threshold dose	fractionation	challenge
mean lethal dose	dose modifying effect	potentially lethal damage
sublethal damage	competition model	radiosensitizers
OER	superoxide	methotrexate
RBE	plating efficiency	radioprotectors
thiols	feeder cells	amifostine
protraction	conditioning dose	dose reduction factor

Questions

Anwer each of the short-answer essay questions below in one page or less.

1. What is the effect of temperature on radiation in the following temperature intervals?

   a. $T < 100$ K
   b. $100 < T < 170$ K
   c. $170 < T < 420$ K

2. Why is superoxide or any free radical important in the oxygen effect?

3. What is the main use of split-dose technique?

4. Using the mouse example from this lesson, supply another set of figures to explain fractionation and protraction.

5. How is plating efficiency important in understanding the worth of survival curves?

6. What is the significance of the shoulder in the survival curve?

7. In Figure 7-5 on the next page, label the graph of the survival curve of mammalian cells with the following terms: extrapolation number, quasithreshold, slope, D_0.

8. Explain the relationship between high LET/low LET and sublethal damage.

9. According to the cell cycle, which cell population is most radiosensitive? least radiosensitive?

10. Compare and contrast the four types of cellular damage due to radiation.

11. What are the "four Rs" of radiobiology? Explain each briefly.

12. Explain the oxygen effect seen in tumors during radiotherapy.

13. What are the five factors determining relative biological effectiveness (RBE)?

14. What are the problems which arise in the use of radioprotectors and radiosensitizers?

15. What is meant by hyperfractionation and accelerated treatment? Why are these methods useful?

16. What are the three factors which determine the response of renewal tissues to continual radiation?

17. What is the role of fractionated and protracted radiotherapy in the treatment of tumors with regard to late/early effects?

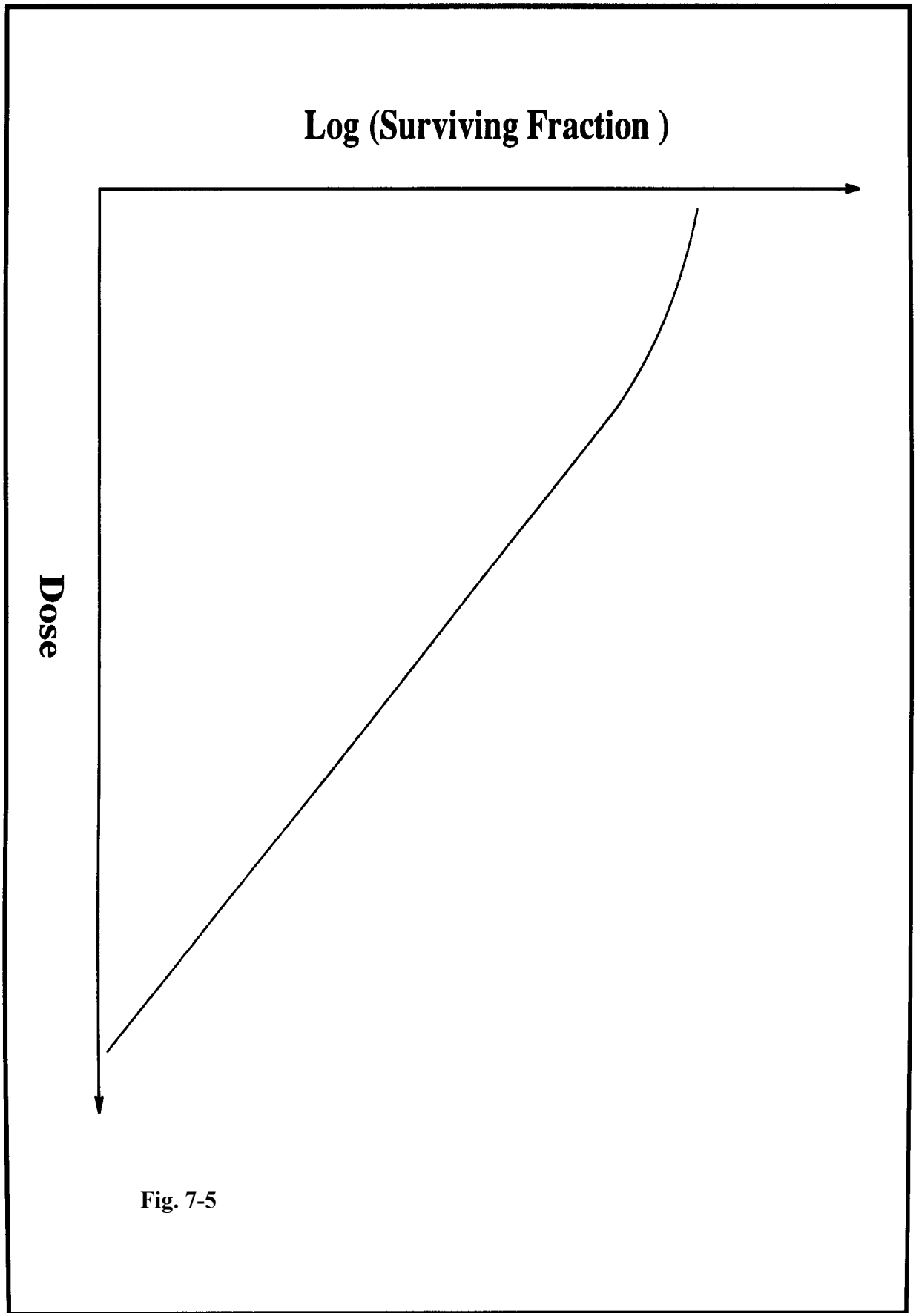


Fig. 7-5

LESSON 8
Effects on Tissues

❖ Preview ❖

READING ASSIGNMENT

Hall: Chapters 12, 13, 19, and 21

Bushong: Chapters 33 (all), 34 (pp. 498-500), and 36 (pp. 520-530)

Nias: Chapters 8 and 13

LESSON OBJECTIVES

By the end of this lesson, you should be able to:

- ❖ Define and explain the Law of Bergonié and Tribondeau.
- ❖ Explain the significance of Casarett's classification of tissue.

(continued)

DISCUSSION

Overview

Lessons 5 and 6 looked at the effects of radiation on the cells. This lesson focuses on *tissues*, collections of cells of similar structure and function. Tissues combine to form *organs*, an overall integrated organization of tissues. Radiation affects the whole body through the hierarchy of the cell - tissue - organ - system organization.

The effects of radiation on a tissue system are dependent on the rate of division or growth kinetics of that tissue. For example, radiation has a much greater effect on a rapidly dividing system (blood-forming organs) than on a slowly dividing system (central nervous system). This lesson will focus on the *nonstochastic* (dose-threshold) effects on various tissues and organs, as well as neoplastic tissue (embryo and fetus).

The Law of Bergonié and Tribondeau

As a historical note, the Law of Bergonié and Tribondeau is of great interest in the development of radiobiology. In 1906, the French scientists Bergonié and Tribondeau made a series of observations of the radiosensitivity of cells of rat testis. In the rat, cell populations with the higher rate of cell division show the earlier response to radiation.

- List the tissues which are highly sensitive, moderately sensitive, and slightly sensitive to radiation.
- Explain the relationship between radioresistance, growth kinetics, and radioresponsiveness.
- Discuss the effects of radiation on digestive organs, liver, kidney, thoracic organs, and lens of the eye.
- Discuss the effects of radiation on hematopoietic system, digestive system, germ cells, epidermis, eye, and central nervous system.
- Describe the effects of radiation on an embryo.
- Explain the increased sensitivity of fetal and embryonic tissue.
- Explain the findings of Hiroshima and Nagasaki, in regards to radiation's effect on embryo development.
- Define and explain the terms *stochastic* and *non-stochastic*.

(continued)

From these observations they formulated a law about the radiation sensitivity of cells and tissues. The radiosensitivity laws can be stated as:

1. Stem cells are radiosensitive. The more mature the cell, the more radiation resistant.
2. The older the tissue or organ, the more radiation resistant it is.
3. The lower the metabolic activity, the higher the radioresistance of the tissue.
4. As the proliferation rate of cells increase and the growth rate of tissue increases, the radiosensitivity increases.

This law has been proved in several different tests, but it does have several important exceptions such as the radiation sensitivity of lymphocytes.

The lymphocyte is extremely radiosensitive, while also being non-dividing and mature.The small lymphocyte breaks the rules in that it does not usually divide, dies an interphase death, and at the same time, is one of the most sensitive mammalian cells.

Casarett's Classificatifon

The classification of cells by Casarett divides cells into four divisions by radiosensitivity, which is affected by the growth kinetics of the cell. Casarett's classification of mammalian cell sensitivity divides the cells into four major categories, numbered I to IV, as shown below:

- ❖ Explain why sterility is one of the classic effects of radiation.
- ❖ Describe the late effects of radiation on the esophagus, small intestine, large intestine, and stomach.
- ❖ Describe the concept of early and late effects.
- ❖ Describe the nonstochastic late effects in humans.

I. Vegetative Intermitotic - cells which divide regularly and have no differentiation

II. Differentiating Intermitotic - cells which divide regularly, some of which are differentiated.

III. Reverting Postmitotic - cells which do not divide regularly.

IV. Fixed Postmitotic - cells which do not divide and are highly differentiated.

(Adapted from Table 8.1, page 168 of Casarett, *Radiation Biology*, Prentice-Hall, 1968)

Specific cell types are divided into the four categories on page 343 of Hall's text. Because this chart is in the text, a slightly different version is shown in Table 8-1.

Radiosensitive Tissue

The sensitivity of a cell to radiation is determined by its state of maturity and its functional role. Immature cells, such as stem cells, are much more sensitive than mature cells due to their high rate of division. The following list shows sensitivity of various cell types in a summary form.

High	Lymphocytes (white blood cells)
	Spermatogonia (sperm-producing cells)
	Erythroblasts (immature red blood cells)
	Intestinal crypt cells (gland cells between villi)
Mid	Spermatids (non-dividing immature sperm)
	Osteoblasts (immature bone cells)
Low	Muscle cells
	Nerve cells

The most sensitive cells are the lymphocytes and the spermatogonia. As a result of radiation therapy, patients may become sterile and susceptible to infection, because of the reduction in these two cell populations. The radiation sensitivity of various human cells is shown in Table 8-1.

Table 8-1. Classification of Human Cell Sensitivity Based on Cell Death

I. Most radiation-sensitive mammalian cells
- A. Erythroblasts (red blood cell precursors). These cells are primitive cells with a high mitotic future and relatively large nuclear volume.
- B. Mature lymphocytes (one of two major classes of circulating white blood cells). Lymphocytes have a large nuclear volume, but divide only under unusual circumstances. These cells are one of the major inconsistencies with the Law of Bergonié and Tribondeau.
- C. Certain spermatogonia (the most primitive cells in the spermatogenic series)

II. Second most radiation-sensitive mammalian cells
- A. Granulosa cells (cells surrounding the ovum) in developing mature ovarian follicles
- B. Myelocytes (in the bone marrow)
- C. Intestinal crypt cells
- D. Germinal cells of the epidermal layer of skin

III. Third most radiation-sensitive mammalian cells
- A. Gastric gland cells
- B. Endothelial (lining) cells of the small blood vessels

IV. Fourth most radiation-sensitive mammalian cells
- A. Osteoblasts (bone forming cells)
- B. Osteoclasts (bone resorbing cells)
- C. Chondroblasts (precursors to cartilage cells)
- D. Granulosa cells of primitive ovarian follicles
- E. Spermatocytes and spermatids

V. Less than moderately sensitive mammalian cells
- A. Osteocytes (bone cells)
- B. Sperm
- C. Superficial cells of the gastrointestinal tract

(continued)

VI. Fairly large dose of radiation necessary to alter these mammalian cells A. Parencymal and duct cells of glands B. Fibroblasts (these form the intercellular fibrous matrix) C. Endothelial cells of the large blood vessels D. Erythrocytes (red blood cells)
VII. Fairly radiation-resistant mammalian cells A. Fibrocytes (connective tissue cells) B. Reticular cells (fixed hematopoetic stem cells) C. Chondrocytes (cartilage cells) D. Phagocytes (scavengers)
VIII. Least sensitive to radiation of all mammallian cells A. Muscle Cells B. Nerve Cells (it may be that the nerve cells are sensitive, but it takes a long time to take effect)
Adapted from R. P. Yaffe and G. L. Helgeson, *Practical Health Physics*, California Book Company, Berkley 1971.

Growth Kinetics and Radiosensitivity

The faster the growth kinetics of a cell population, the earlier the radiation response; however, this radioresponsiveness does not depend upon radiosensitivity of the cells. For example, liver tissue appears to be radioresistant; however, its radio-responsiveness appears slower due to its slower division time.

Tissues that show a response soon after radiotherapy do so because of the faster kinetics of their cell population. There may also be a latent period before the appearance of radiation damage in the tissue. The larger the radiation dose and the larger the volume inactivated, the higher the likelihood of an "avalanche" of cell death which will reduce the cell number below the minimum needed for tissue function, resulting in an earlier appearance of radiation effects. Whereas loss of function is mainly due to loss of parenchymal cells, it may also be due to blood vessel damage and fibrosis. Therefore, radioresponsiveness depends upon a combination of the particular vascular architecture of the tissue and the intricate interaction of cell death, recovery, and repopulation.

It is important to note that overall, radiation has an aging effect on the tissues and organs, in that the organ syndrome occurs in the aged, but radiation increases the incidence and lowers the age when it occurs. This is especially evident in the effects of radiation on the kidney and the lens of the eye, which will be described later in the lesson.

Radiosensitivity of Organs

The radiosensitivity of an organ depends upon the radiosensitivity of the tissues which compose it. The general pattern of radiation damage to organs is the following:

1. inhibition of cell division in mitotically active cells
2. chromosome aberrations
3. hemorrhage and edema
4. removal of debris by phagocytic cells
5. cell regeneration

Hematopoietic Tissue

The hematopoietic system is basically one of the most radiosensitive cell-renewal populations of the organism. The bone marrow varies in structure and cellular composition with age and with anatomical location. It has one of the lowest dose-limiting levels. The hematopoietic system consists of bone marrow (myelopoietic), circulating blood (erythropoietic), and lymphoid tissue (thrombopoietic).

The system produces most of the circulating blood cells. The principal effect of radiation on this system is to depress the number of blood cells in the peripheral circulation.

All cells of the hematopoietic system develop from a single stem cell, *pluripotential stem cell* (see Figure 8-1). The stem cells initiate a variable number of mitoses, during which differentiation and maturation occur before the cells appear in the peripheral blood in a recognizable form. The following cell types are produced by this stem cell, which is located in the bone marrow:

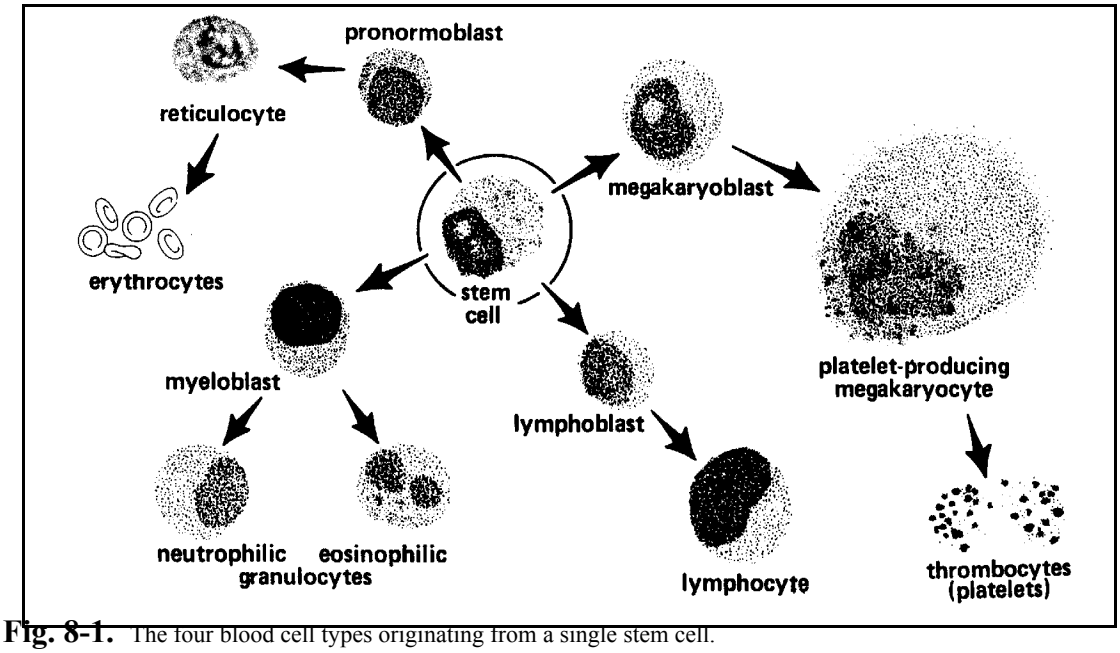


Fig. 8-1. The four blood cell types originating from a single stem cell.

1. Lymphocytes - involved in immune response

2. Granulocytes - scavenger-type cells used to fight bacteria

3. Thrombocytes (platelets) - involved in blood-clotting to prevent hemorrhage

4. Erythrocytes - red blood cells that transport oxygen

After irradiation of the bone marrow, there is an interval before maximum depression of the hematopoietic system, followed by a recovery to the normal level. Therefore, radiation can destroy different cell types needed to combat body infection (white blood cells) due to destruction of a precursor cell.

Anemia, which results from the loss of production of red blood cells, will not appear before the loss of the circulating red blood cells. The timing for destruction of various cell types depends upon the kinetics of each cell type. For example, since red blood cells have relative long life (120 days in man), the effects of anemia are seen later than the effects on the immune system. As is also expected, mature cells are less radiosensitive than undifferentiated precursors. For example, activated T and B cells are less sensitive than are their precursors.

Thoracic Organs

Due to the rapid cell renewal system in the esophagus, radiation effects appear in the esophagus before the lungs. Radiation pneumonitis results from damage to alveolar cells (air sac cells) and capillary cells. Starvation cell death may also occur, which results in early esophageal damage and later lung fibrosis.

The heart, large artery, and large veins are less affected by radiation than the capillaries, which are affected by occlusions. In fact, capillary tissue is the most important limiting tissue in irradiation of a patient.

Thyroid

The normal thyroid is more radioresistant than the hyperactive thyroid. High doses of radiation can permanently damage normal thyroid tissue, leading to hypothyroidism.

Kidney

Due to slow cell turnover, it takes several months for radiation injury to occur in the kidney. Acute radiation nephritis may cause up to 30% mortality; however, even those who recover will have chronic radiation nephritis.

Digestive System

The radiosensitivity of the digestive organs vary, depending upon the sensitivity of the tissues comprising the organ. At high levels of radiation the esophagus, mouth, and stomach become ulcerated. The salivary glands and pancreas are fairly radioresistant. The liver is extremely radioresistant due to its post-mitotic state. The small intestine is the most important site of radiation injury.

The small intestine, consisting of the duodenum (with connection to the stomach and pancreas), jejunum (the main part of the intestine), and ileum (where the small intestine changes to join the large intestine), is the principal site for absorption of digestive products from the gastrointestinal tract. Digestion and absorption is enhanced by the large surface area of the intestine due to its length, intestinal folds, villi, and microvilli. Proteins, carbohydrates, and lipids are absorbed into the blood stream at this location. In contrast, the large intestine functions to recover water from the waste and propel the mass to the rectum.

Again, the small intestine of the gastrointestinal system is extremely sensitive to radiation. Its cell turnover rate (1.4 days) is much greater than other areas of the digestive system, such as lip (15 days), colon (10 days), stomach (3 days), and esophagus (10 days). Again, this increased sensitivity to radiation is due to the rapid rate of cell division in the cells of the crypt and of the related villi. Cells are produced rapidly on the sides of the villus and migrate to the tip, as shown in Figure 8-2. If the radiation dose is high enough, there is rapid cell loss in the crypts and the villi become short and blunted. Radiosensitivity is exhibited as a loss of fluids and electrolytes. Poor absorption of nutrients leads to a high bacterial content in the small intestine. The bacteria cause diarrhea, which results in a loss of fluid and electrolytes, a central feature of acute radiation syndrome, which is discussed further in Lesson 9.

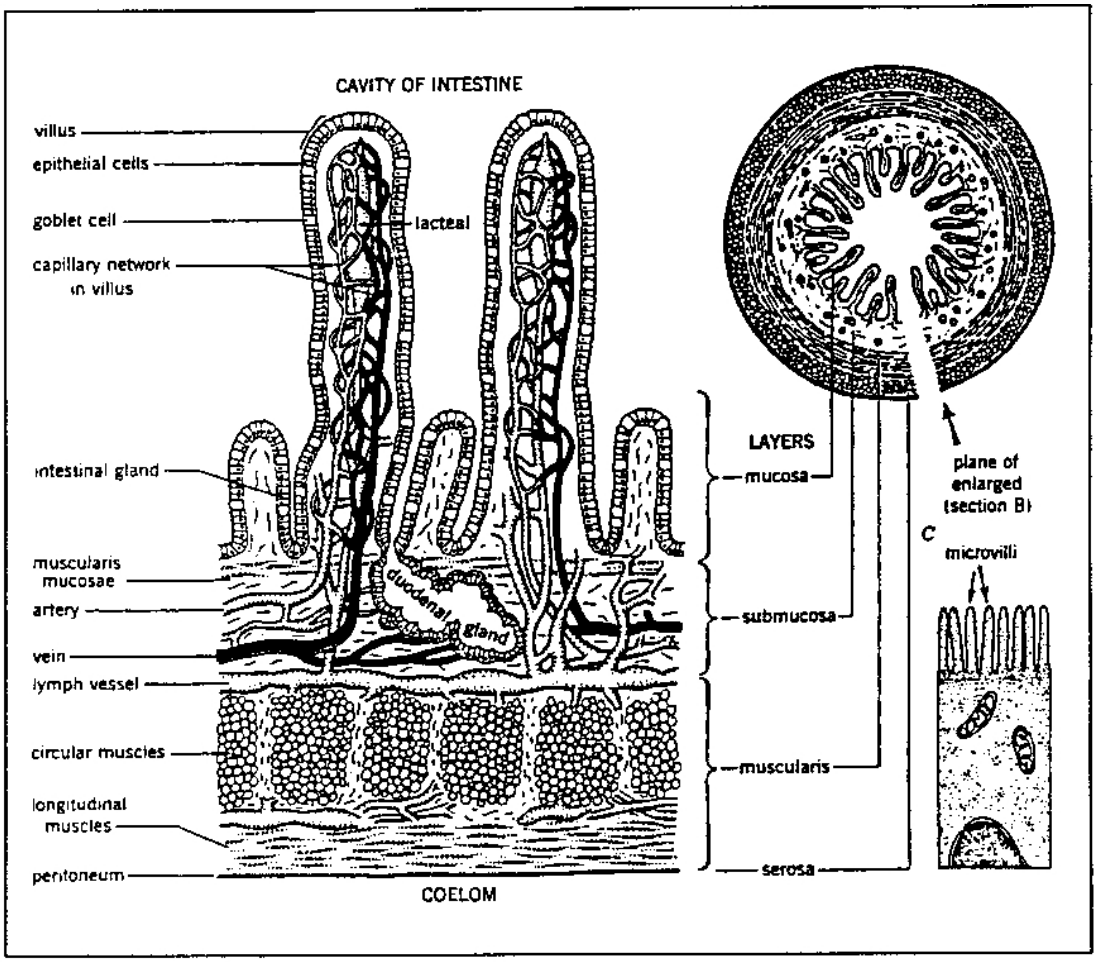


Fig. 8-2. Structure of the small intestine showing the villi which are very radiosensitive due to their rapid division rate.

Male Reproductive System

Spermatogenesis (Figure 8-3), or formation of sperm from spermatogonial cells, is extremely sensitive to radiation. The process of sperm formation, which occurs over 60 days, is primarily sensitive in the intermediate stages. The latter stages of sperm maturation, involving changes from a spermatid to a sperm, are fairly resistant due to the lack of division. The supporting cells of the testes (Leydig and Sertoli cells) are much more radioresistant than the sensitive spermatogonia cells.

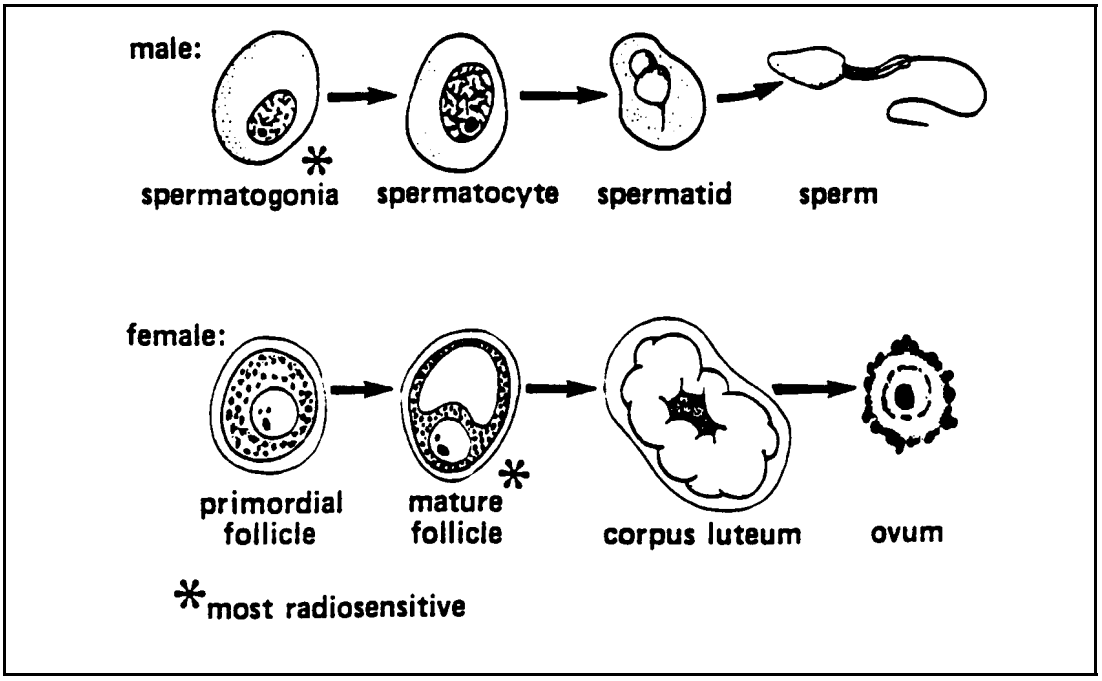


Fig. 8-3. The development of mature sex cells from stem cells.

The effects of radiation on fertility is not apparent immediately due to the postspermatogonial cells being relatively resistant compared with stem cells. The exposed mature sperm cells usually disappear in 2-4 weeks. Sterility follows when these mature cells are depleted and lasts until spermatogonia can repopulate by division. Radiation-induced sterility is not accompanied by changes in hormone balance or libido. Fifteen rads is the threshold that will produce temporary sterility, beginning two months after irradiation and lasting up to twelve months. Roughly five hundred rads (350-600) to the testes will produce permanent sterility. Since male gametogenesis is a self-renewing system, evidence suggests that genetic mutations induced in post-spermatogonial cells are the most hazardous mutations. Interestingly, there is actually a loss in the weight of the testes, peaking at 28 days after irradiation, due to the lack of formation of intermediate sperm forms.

Female Reproductive System

As is true for the male, the female gamete (ovum) is radiosensitive. Unlike the male, the ovaries may atrophy after irradiation, resulting in permanent or temporary sterility. The intermediate follicles of oogenesis are the most sensitive (Figure 8-3). Massive doses (250-600 rads) may lead to permanent sterility. Hormonal changes, similar to menopause, accompany this radiation-induced sterility. Due to the reduced number of oocytes in an older female, the older ovary is more sensitive to radiation than the younger ovary.

Epidermis

The skin, or epidermis, is also radiosensitive due to the rapid division of the basal cells, which are essentially stem cells (see Figure 8-4). The length of the cell cycle and the transit time depend largely on the anatomical site, age, species, and the function. These cells migrate outward, keratinize, and are sloughed off, to be replaced by new cells formed by the basal layer. Damage to these cells produces the earliest evidence of radiation damage—*erythema*. Early erythema is a sunburn-like reddening of the skin, which reaches its peak during the first week. This state is followed by desquamation of the tissues, basically ulceration of the skin. The main erythema reaction involves not only the epidermis, but the dermis and the subcutaneous layers, especially the blood vessels. This appears in a wave-like manner and may lead to dry or moist desquamation. Moist desquamation is the clinical tolerance for radiation therapy. At extreme levels of radiation, necrosis of tissues occur with degeneration extending to the bone tissue.

It is the normal transit time of the basal layer of the epithelium that determines the pattern of radioresponsiveness. As for the hair follicles, the fastest growing hair is the most sensitive to radiation. This is again due to the rate of cell division being greater in faster growing hair. Therefore the list of hair affected from most to least rapid growing, is: beard, scalp, armpit, chest, and pubic. At a higher dose of radiation, hair loss ceases being temporary and is permanent. Hair will often turn white after a moderate dose. The sweat glands will also cease to function at high doses of radiation.

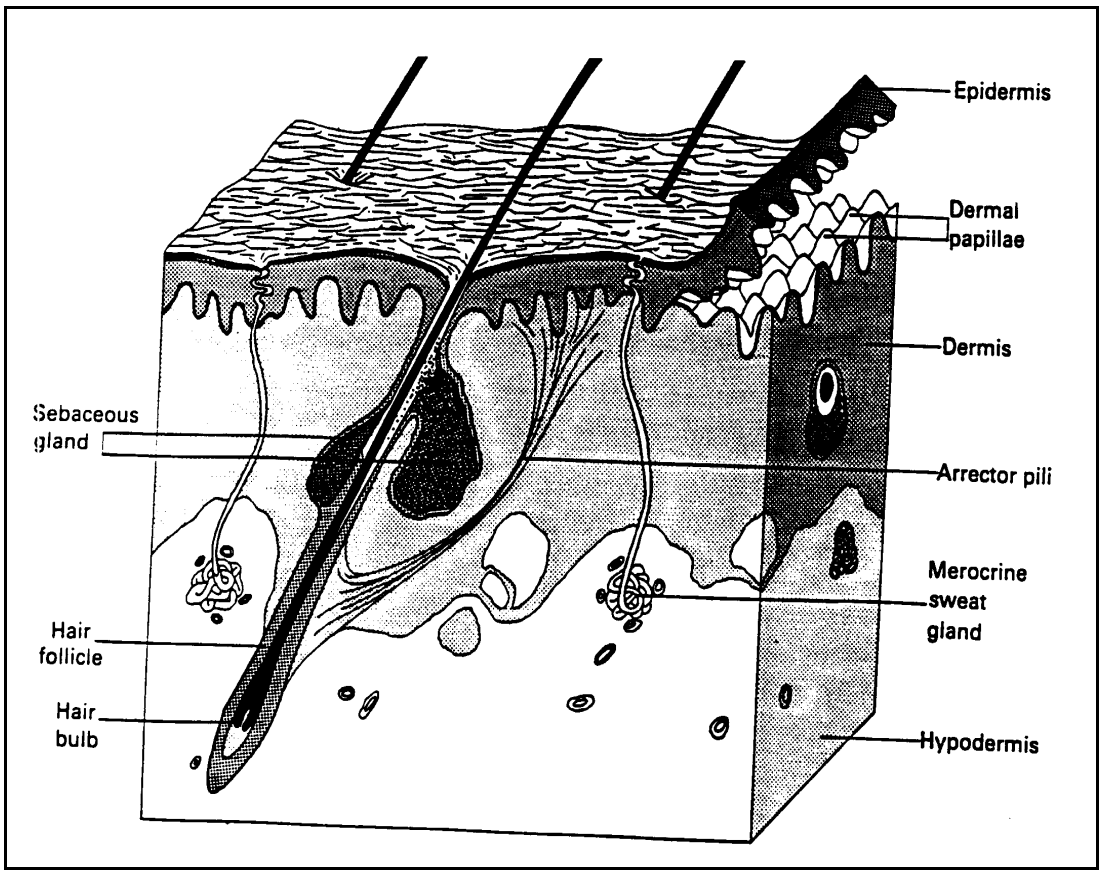


Fig. 8-4. A cross-section view of the skin. Note the basal cells and hair follicles which are most radiosensitive.

Eye - Cataractogenesis

Of all the eye components, only the lens is radiosensitive. This is due to the turnover of the lens cells. The sensitivity of the lens is species-dependent and age-dependent. Neutrons are particularly effective in forming cataracts. Cataracts result from the opacification of these cells. The average latency period for cataracts is 2-3 years.

Central Nervous System

This system was once thought extremely radioresistant because of the low rate of cell division of the neurons; however, this false belief was due to the late manifestation of radiation damage. The spinal cord is much more sensitive than the brain. Upon irradiation, the brain suffers from brain edema.

The earlier mode of injury affects white matter through damage to the supporting glia cells. The later mode of injury is vascular in nature. When the brain is exposed to high doses of radiation in radiotherapy, there is a risk of late brain necrosis. Chronic radiation encephalopathy may occur 3-4 months after radiotherapy. A single very high dose may lead to acute meningoencephalopathy.

Fetal and Embryonic Tissue

Unlike normal tissues which have a resting or G_0 cell population which can replace damaged cells, the neoplastic tissue of an embryo or fetus is composed of rapidly dividing cells that are extremely radiosensitive. The three different periods of intrauterine development—preimplantation, organogenesis, and fetal development and growth—are each affected differently by radiation.

The classic effects of irradiation during pregnancy are the following:

1. Lethal effects, induced by radiation before or immediately after embryo implantation or at high doses during the other stages, expressed as prenatal or neonatal death.

2. Malformations during major organogenesis, when the main body structures are formed.

3. Growth disturbances, induced at all stages of development but especially in the latter part of pregnancy.

4. Carcinogenic effects of radiation are high in utero.

The principal factors of importance in the effects of irradiation in utero are the dose, stage of gestation, and the dose rate.

During *preimplantation (0-9 days in man)*, there are several cell divisions before the fertilized ovum reaches the uterus. The loss of several cells due to irradiation causes death of the organism. Losses at this stage are not detectable in humans. This is the most sensitive stage to lethal effects of radiation. Growth retardation is not observed at this stage, because this is an "all or nothing" effect of radiation due to the small number of and the general nature of the cells.

Organogenesis, running from 10 days to six weeks after fertilization in humans, is the stage in which organs and systems are formed. Radiation administered early in this period would affect the nervous system early and the skeletal system later in the stage, due to the production of a specific defect during the period of organogenesis. Death or malformation can occur from irradiation. This is the most disastrous period for irradiation. The loss of a system, such as gastrointestinal, could be fatal for the organism. If death occurs as a result of irradiation in this sage, it is likely to be neonatal death, occurring at or about the time of birth. Embryos also exhibit the greatest intrauterine growth retardation. This is a weight reduction which is due to cell depletion. Therefore, there is an association between growth retardation and teratogenesis.

The *fetal stage* in humans runs from six weeks to term. Higher doses of radiation are needed to cause death in the fetal stage—smaller head size is a common result in this stage. Most organs are formed and growth is occurring in this period. Further information about these effects is given in Table 8-2 and Figure 8-5.

Irradiation in this stage can cause effects on the hematopoietic system, liver, kidney, and developing gonads. Much higher doses of radiation are required to cause lethality in this period. Although irradiation during organogenesis shows the most temporary growth retardation, irradiation during the fetal stage exhibits the largest degree of permanent growth retardation.

According to data from both medical exposure and Hiroshima/Nagasaki, the most common effects of in utero irradiation are microcephaly (sometimes combined with mental retardation), other central nervous system defects, and

growth retardation. The highest risk of mental retardation occurs at 8-15 weeks when the relevant tissue, the brain cortex, is being formed. Cells killed before eight weeks of gestation can cause small head size without mental retardation. The malformation of body structures, which is expected due to irradiation during organogenesis, is rare in the Japanese survivors.

A great deal of data concerning radiation effects have come from X-ray exposure in expectant mothers. Exposure to medical radiation has led to the following conclusions:

1. Large doses of radiation (250 rads) at 2-3 weeks of gestation do not produce severe abnormalities in most children although many embryos are aborted.

2. Irradiation at 4-11 weeks of gestation leads to severe abnormalities of major organs in most children.

3. Irradiation at 11-16 weeks produces stunted growth, microcephaly, mental retardation, eye, skeletal, and genital organ abnormalities.

4. Irradiation at thirty weeks leads to functional disabilities.

5. Susceptibility to carcinogenic effects of radiation is high during the in utero period. Diagnostic exposure increases the natural cancer incidence by a factor of 1.5 to 2.

Overall, the maximum permissable dose to the fetus during gestation is 5 mSv, with a monthly limit of 0.5 mSv. A dose of 10 rads to the embryo during the sensitive period of gestation (10 days - 26 weeks) is regarded as the cut-off point, above which a therapeutic abortion may be considered.

The “10-day” rule refers to the fact that X-ray examinations of the lower abdomen in women should only be carried out in the first ten days following the first day of the menstrual cycle. Since 1984, it is believed the risk of radiation injury could be greater in the seven weeks before the mother becomes pregnant than in the first two weeks of pregnancy.

In summary, the principal abnormalities produced by irradiation of the embryo are due to damage to many cells and has a threshold dose. Therefore, the effects on the embryo are deterministic (non-stochastic) in nature.

Table 8-2. Effects of Irradiation on the Human Fetus

Fetus Age	Fetus Dose	Type of Abnormality	Frequency
Shortly After Birth	~1 rad	Leukemia	An increase of 300-800 deaths/6 million
Unspecified	1-3 rads	Leukemia	An increase of 30-50%
First half of pregnancy	Diagnostic Dose (200 -250 mrad)	Total Malignancy	Irradiated:control= 9:1
Second half of pregnancy	≤ 5 rads	Eye defect in F_2 generation	Significant
Before 30 weeks (female)	Pelvimetric dose	Altered sex ratio	More males
Unspecified	Diagnostic dose (200-250 mrads)	Neoplasm	Significant
Unspecified	30-250 rads	Microcephalic	61%
		Hydrocephalic	1%
		Mongoloid	0.5%
		Skeletal defect	1.5%

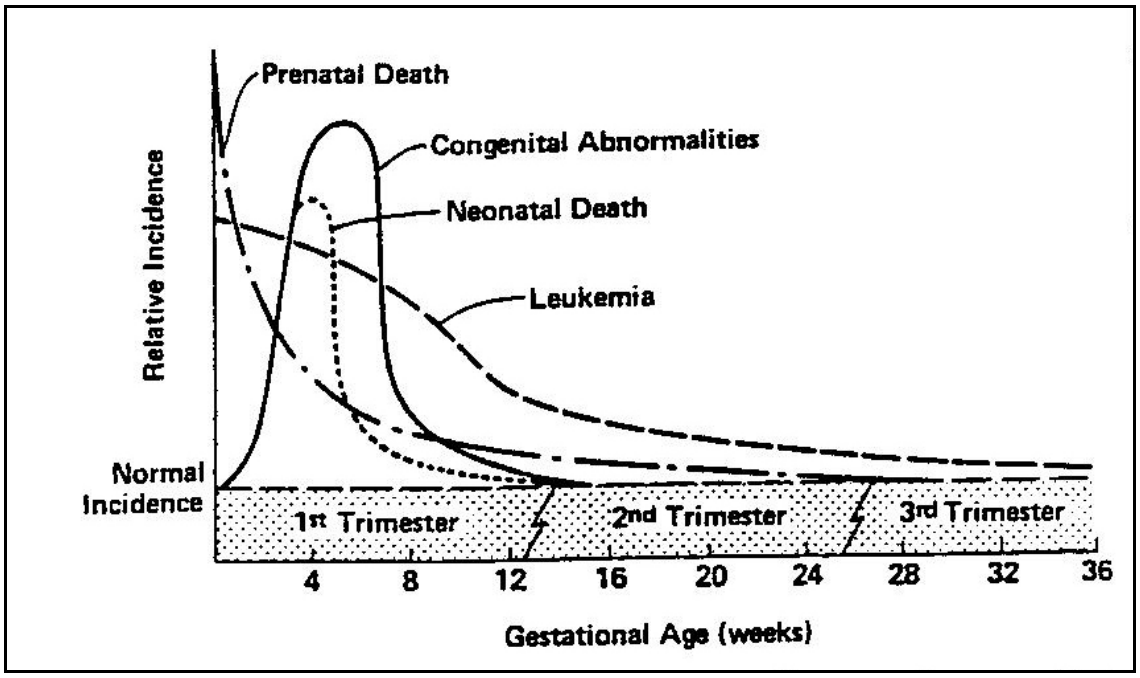


Fig. 8-5. The effects that can be observed after 200 rads exposure at various times after fertilization in humans.

Stochastic and Nonstochastic Effects

Nonstochastic effects are those which have a dose threshold and have a dose-response relationship. Nonstochastic effects have a severity scale associated with dose. Increasing the dose is expected to increase the severity of the outcome. These effects require reduced function of a class of cells essential to maintaining an activity. If a reduction occurs in a cell population, such as epidermal cells, a loss of function will occur. The effects of radiation mentioned in this lesson are nonstochastic.

Stochastic effects are those for which there is no known threshold dose. Stochastic effects would be the production of cancer or genetic defects in egg or sperm. The severity of the response is independent of dose. A stochastic effect signals an event in a single cell that ultimately leads to its irreversible alteration.

Radiologists look at the effects of radiation as *early* or *late effects*. Protraction and fractionation, both discussed in Lesson 7, can affect the appearance of early and late effects. The early effects of radiation are based on the proliferation of cells (division), as evidenced by the effect on testes and intestines.

The esophagus, small intestine, large intestine, and stomach all suffer the same late nonstochastic effects. Irradiation of the organs leads to stricture of the organ (*stenosis*). Stenosis can then lead to blockage of the organ. Fiberatrophy of the tissues also occurs. These late effects are due not to interference with division but to changes in the microvasculature of the cell or cellular DNA.

The liver is radioresistant due to lack of cell division in the mature cells. However, radiation-induced hepatitis can occur. Irradiation of the kidneys results in arteriolar nephrosclerosis. Nonstochastic late effects on the lungs includes radiation-induced pneumonitis. Whereas little is known about the effect on the brain, irradiation of the spinal cord can lead to paralysis. Irradiation of the lens of the eye results in cataracts.

As for stochastic effects, the primary early effect is acute radiation syndrome. The primary importance of late stochastic effects lies in radiation-induced malignancy and genetic effects. Both of these effects, early and late, will be studied in the next lesson.

Summary

- ❖ The effects of radiation on a tissue are due primarily to the rate of division of the cells making up the tissue.
- ❖ The effects of radiation on the sperm and ovaries are especially important because of the possibility of effects on future generations due to genetic mutations.
- ❖ Radiation has an aging effect on kidneys and eyes.
- ❖ The effect of radiation on the skin can be used to estimate the effects of radiation on the body.

- ❖ Embryonic tissue is extremely radiosensitive due to the increased rate of cell division.
- ❖ Irradiation of the embryo can lead to death, organ malformation, or growth deficits.
- ❖ Stochastic and nonstochastic effects differ in dose threshold and dose-response relationship.

WRITING ASSIGNMENT - LESSON 8

Complete and submit the following assignment.

Vocabulary

Please write the term and its definition on your paper. Your definition should be in your own words and limited to one or two sentences.

stochastic effects	stenosis	pre-implantation period
nonstochastic effects	tissue	dry desquamation
cell cycle	organ	arteriolar nephrosclerosis
spermatogenesis	growth fraction	nominal standard dose
organogensis	Hewitt assay	fiberatrophy
erythema	spleen colony assay	avalanche
wet desquamation	gastrointestinal crypt assay	ten-day rule
		microcephaly

Questions

All of the questions below are short-essay. Please try to confine your response to each question to one page or less.

1. What single principle determines the early effects of radiation?
2. What type of cells are most radiosensitive? least sensitive? What determines the radiosensitivity of the cell?

3. What is important about erythema and wet desquamation?

4. How are the stomach and intestines affected by radiation?

5. What stages of spermatogenesis are most sensitive? Why?

6. Why does temporary sterility in men take two months after irradiation to develop?

7. Explain what radiation does to each of the three stages of embryonic and fetal development.

8. Why does anemia develop after irradiation?

9. Explain the importance of the Hewitt assay and the spleen-colony assay.

10. Explain the role of radioresponsiveness of tissue in radiotherapy.

11. What is the effect of radiation on the hematopoietic system?

12. What is the effect of radiation on the nervous system?

13. Explain the statement "Radiation has an aging effect on the body." Cite two examples of this "aging effect."

14. What are the three classic effects of radiation on the developing embryo?

15. What were the principal effects on embryos irradiated during the atomic bombings of Hiroshima and Nagasaki?

LESSON 9
Organs and Organisms

❖ Preview ❖

READING ASSIGNMENT

Hall: Chapters 8 (pp. 129-135), 10 (all), 17 (pp. 288-296 and 306-308), and 19 (pp. 339-355)

Bushong: Chapters 36 (pp. 517-520) and 37 (all)

Nias: Chapters 14 and 15

LESSON OBJECTIVES

By the end of this lesson, you should be able to:

- Define the terms $LD_{50/30}$ and *doubling dose*.
- Name and explain the three stages of acute radiation syndrome.
- Explain the general prognostic signs for acute radiation exposure.

(continued)

DISCUSSION

Overview

This lesson will primarily focus on the stochastic effect of radiation on a specific organ and the overall effect on the organism. Early and late effects (malignancy and genetic problems) will be explored. The effects of radiation on the organs and the organism will be addressed using examples from medicine and various occupations. Carcinogenesis is a late stochastic effect, as compared to the late nonstochastic effects on tissues described in Lesson 8. Various theories of carcinogenesis will be examined in the context of ionizing radiation. The effects to be studied are non-threshold, non-dose-response relationships.

Early Stochastic Effects

The most devastating human response to radiation is death, which occurs at a minimum dose of 100 rads entered over the whole body. Acute radiation lethality is an early effect of radiation not commonly encountered in diagnostic radiology. Acute radiation lethality is measured by the $LD_{50/30}$ in humans and animals. The $LD_{50/30}$ is the dose of radiation to the entire body which will result in death within 30 days to 50% of the subjects irradiated.

- ❖ Discuss the three-stage process of clonal theory.
- ❖ Explain Birenbaum's initiation-promotion hypothesis.
- ❖ Describe specific effects of occupational radiation exposure.
- ❖ Discuss specific effects of medical radiation exposure.
- ❖ Discuss specific effects of nuclear weapon exposure.
- ❖ Explain the late radiation effect of genetic mutation.
- ❖ Describe the basis of the symptoms for acute radiation syndrome.
- ❖ Discuss the study of Furth & Furth on carcinogenesis.
- ❖ Describe oncogenes and their role in cancer.
- ❖ Describe the effects of ionizing radiation on cancer.

The LD_{50} is the dose of any agent or material that causes a mortality of 50% in the experimental groups within a specified period of time. The LD_{50} is a convenient way to smooth out the problems of heterogeneous populations, by reducing the skewing effects due to extreme subjects. The peak incidence of death for humans occurs from days 30-60. Therefore, $LD_{50/60}$ is more commonly used for humans, rather than the $LD_{50/30}$ which is more often used with animals. However, the $LD_{50/30}$ is the most convenient form of the expression.

The best estimate for $LD_{50/60}$ for humans is 3.25 Gy or 325 rem for young, healthy adults. This reflects the observation that larger species are more susceptible to hemopoietic damage than are smaller species. As the whole-body irradiation dose increases, the average time between exposure and death decreases. This time is known as the *mean survival time*. In doses above 500 rem, death from hemopoietic syndrome 3-4 weeks later is common. Survival may be possible if infection, bleeding, or physical trauma are avoided during the blood cell nadir. Bone marrow transplants have been used to try to "rescue" patients who have received a dose between 800-1000 rads.

Acute Radiation Syndrome

The early stochastic effects of radiation are found in acute radiation syndrome. Early radiation lethality is defined as death occurring within a few weeks that can be attributed to a specific high-intensity exposure to radiation. Thirty people died of acute radiation exposure at Chernobyl in April 1986. In fact, much of the recent information on dose levels were obtained by the Chernobyl accident in 1986. The syndrome consists of three stages—prodromal stage, latent period, and manifest illness stage.

The nature of radiation lethality, the timing of death, and whether death occurs at all depends upon various cell populations, specifically their depletion and their ability to recover to a normal level. It is the balance between the gradual removal of the aging mature cells and the arrival of the new mature cells that will determine whether the tissue remains intact enough for continued integrity of the tissue and the life of the affected human.

The *prodromal* stage, occurring from a few hours after the irradiation to day one or two, consists of acute symptoms, which last for a limited period of time. This period can extend for four weeks. The various symptoms of this syndrome vary with respect to the time of onset, maximum severity, and duration, depending on the size of dose. Often a severe prodromal response indicates a poor clinical prognosis. Symptoms include both gastrointestinal and neuromuscular symptoms.

During the *latent* period, the patient will be free of visible effect; however, the lethal effects of the manifest illness stage are developing even though the human appears symptom free.

During the *manifest illness* stage, the clinical signs and symptoms occur. There is a decrease in red blood cells, white blood cells, and platelets. This is due to the radiation's effect on the precursor blood cells. The gastrointestinal symptoms are nausea, vomiting, and diarrhea. The diarrhea and dehydration are due in part to the destruction of the villus cells. Neuromuscular symptoms include apathy, sweating, fever, and headache.

These symptoms demonstrate how problems with the division of cells in the tissue can lead to the illness of the organism. It is due to the different cellular responses that gastrointestinal syndrome occurs before the hemopoietic syndrome. Since hemopoietic stem cells are more radiosensitive than gut cells, survivors of the gastrointestinal syndrome may still die from the hemopoietic syndrome.

Syndromes of Acute Radiation Exposure

There are three dose-related syndromes in acute radiation sickness: *hematologic syndrome*, *gastrointestinal syndrome*, and *central nervous system syndrome*.

The *hematopoietic syndrome* appears at a radiation level of 300-900 rads. The symptoms of this syndrome occur later because mature circulating cells die off and are not then re-supplied by the destroyed precursor population.

The first phase of the hemopoietic phase is due to the lesions of the blood-forming organs, leading to hemorrhage and anemia. The bone marrow, spleen, and lymph nodes atrophy. During 5-6 weeks, infection is important due to destruction of lymphocytes and granulocytes, lack of antibody production, and ulcerations permitting bacteria entry. If the patient survives, convalescence begins after two months.

The *gastrointestinal syndrome* arises at the higher dose of 500-1200 rads. This syndrome may result in death in 5-8 days after irradiation. This syndrome predominates at low whole-body doses, in particular doses to the abdomen. The symptoms include nausea, vomiting, prolonged diarrhea, dehydration, weight loss, and complete exhaustion. Death is due to destruction of the functioning cells of the villi in the small intestine. Loss of the intestinal barrier leads to a bacterial invasion of the bloodstream and the peritoneal cavity, release of proteolytic enzymes, and the loss of water and electrolytes. Symptoms of gastrointestinal origin may disappear after 2-3 days and recur by the fifth day due to loss of the intestinal cells. At this time, peristalsis will end and severe paralytic ileus may occur. Circulation failure, coma, and death may follow. However, some victims may survive this phase due to fluid replacement therapy and antibiotic treatment.

The slowly-dividing cells of the central nervous system are not affected until the immense dose of 10 K-100 K rads. The *cerebrovascular syndrome* results in death 24-48 hours after exposure. The modes of death in the gastrointestinal and hemopoietic syndromes are due to the depletion of stem cells of a critical self-renewing tissue. The exact cause of death in the cerebrovascular syndrome is unclear. Some believe neuronal damage secondary to vascular damage, edema, and increased intracranial pressure may cause the symptoms.

At doses which bring on this syndrome, all three syndromes will occur given enough time; however, the cerebrovascular damage brings death very quickly before the other syndromes are observed. This symptoms again include the loss of movement, respiratory distress, disorientation, seizures, and coma. Refer to Table 9-1 and Figure 9-1 for a summary of information on the three syndromes.

Prognosis

In general, prodromal nausea and vomiting are more prolonged at high doses. Early CNS symptoms indicate a very high and lethal dose. The longer an individual survives after the first 2-3 weeks, the better the prognosis. Those showing the CNS syndrome will die. Those with continual nausea, vomiting, and diarrhea will probably die. Those with brief nausea and vomiting will probably survive.

The very young and the very old are more radiosensitive than the middle-aged and young adults. Females are also more radioresistant than males. The three syndromes of acute radiation syndrome require different levels of radiation for their emergence.

The lymphocyte count is valuable as a criterion for judging radiation injury. The total white cell count is of particular value for following the patient throughout the course of the syndrome.

When only the lower body is irradiated, a higher dose is tolerated and the gastrointestinal tract is the primary target. When only the upper body is irradiated, an even higher dose is tolerated, and the bone marrow syndrome is more common. Survival is more likely if the radiation dose is protracted and if only part of the body is exposed. When a very large volume of tissue is irradiated, damage will be evident after a relatively low dose.

(continued)

Table 9-1. Major Forms of Acute Radiation Syndrome in Humans

Time after Irradiation	Cerebral and Cardiovascular form (20,000 rad)	Gastrointestinal form (2000 rad)	Hemopoietic form (400 rad)
First day	nausea vomiting diarrhea erythema disorientation agitation ataxia weakness somnolence coma convulsions shock death	nausea vomiting diarrhea	nausea vomiting diarrhea
Second week		nausea vomiting diarrhea fever emaciation prostration death	
Third and fourth weeks			weakness fatigue anorexia nausea vomiting fever hemorrhage epilation recovery(?)

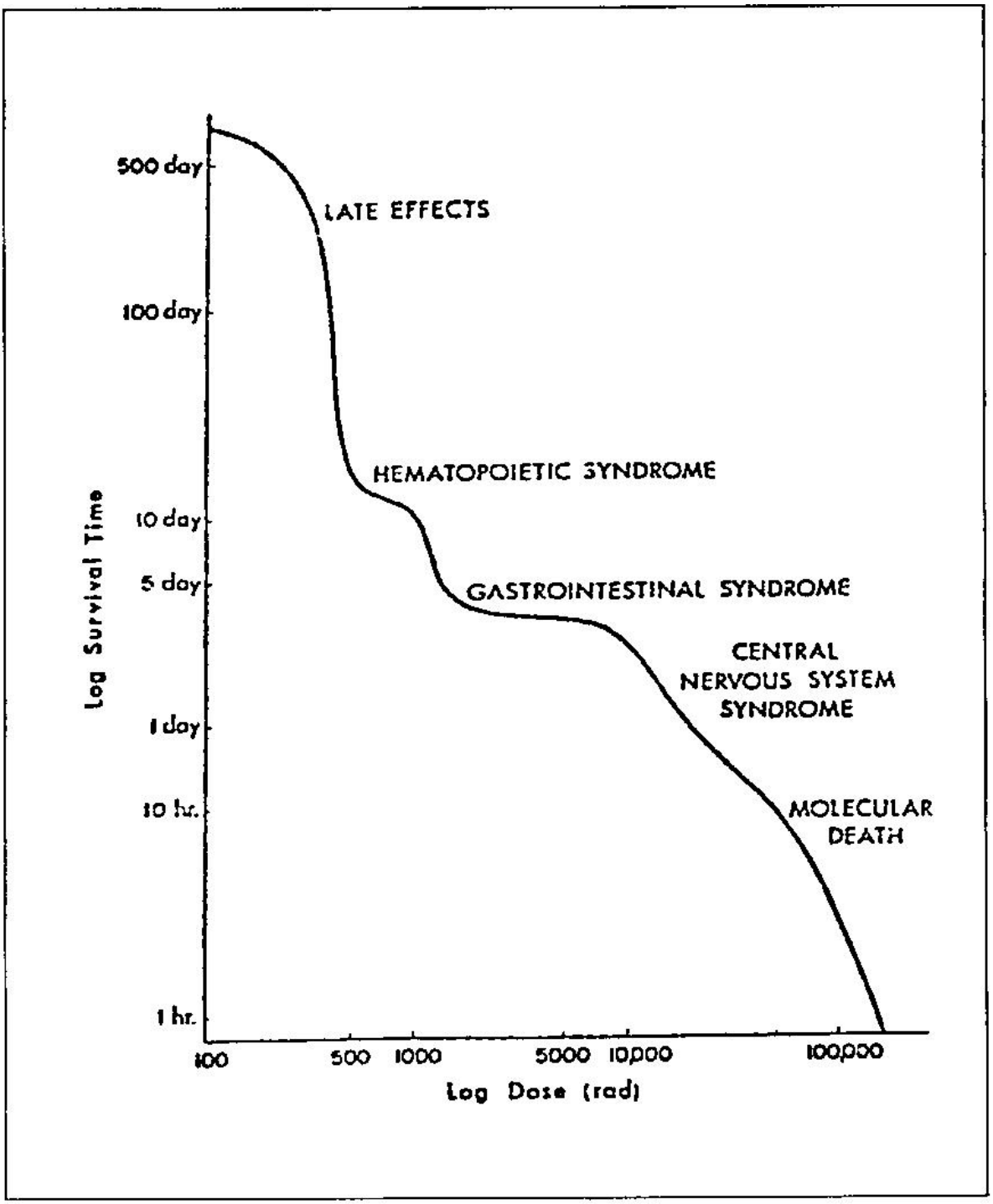
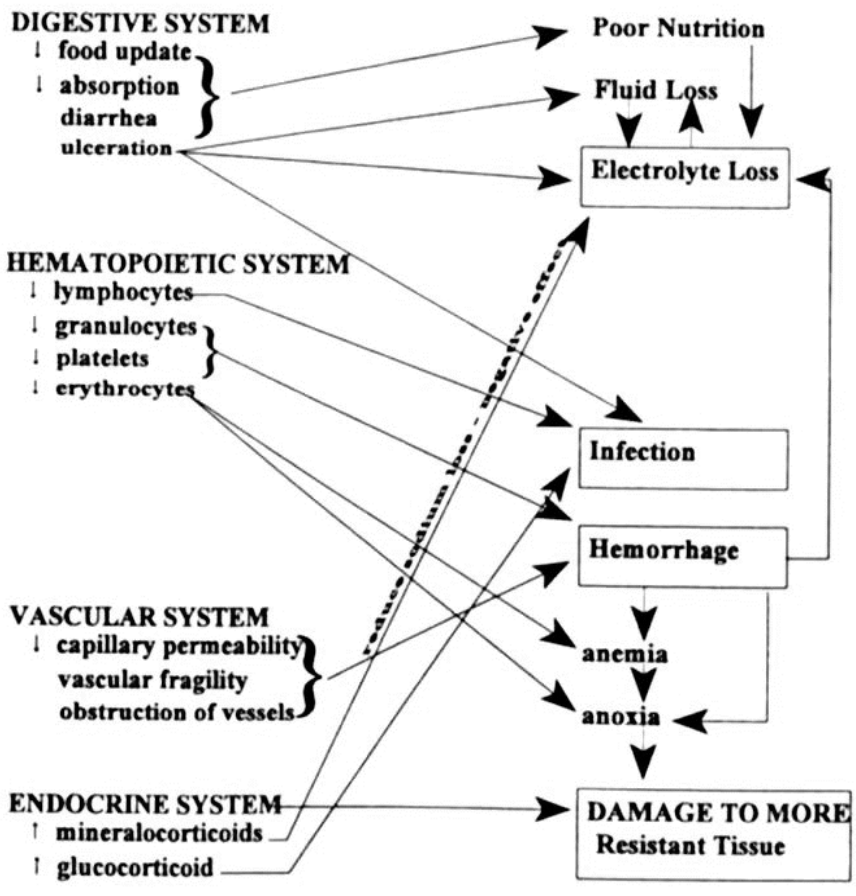


Fig. 9-1. The relationship between the mean survival time and dose. The syndromes are shown which are dominant in the various dose regions.

The dose necessary to produce a given syndrome and the mean survival time are the principal quantitative measures of human radiation lethality. Table 9-2 illustrates a summary of the interrelationships of the acute radiation syndrome. For example, electrolyte loss is due to two factors—hemorrhage of the vascular system and diarrhea of the digestive system. These factors interact to enhance the effects of each other. The effect of various dose rates is summarized in Table 9-3.

Table 9-2. Interrelationships in the Acute Radiation Syndrome



The response to radiation is noted with the arrows. An up arrow means increase in that factor with irradiation and a down arrow means a decrease in that factor with irradiation.

Adapted from R. P. Yaffe and G. L. Helgeson, *Practical Health Physics*, California Book Company, Berkley 1971.

Table 9-3. Biological Effects as a function of dose	
Approximate Dose	Effect on Humans
0.001 r/day	Natural Background Radiation
0.01 r/day	Permissible dose range, 1957
0.1 r/day	Permissible dose range, 1930-1950
1.0 r/day	Illness in 3 to 6 months [not certain] Death in 3 to 6 years [extrapolation from animal data]
10 r/day	Illness in 3 to 6 weeks [not certain] Death in 3 to 6 months [extrapolation from animal data]
10 r instantaneously	Few or no effects
10^2 r instantaneously	Mild irradiation sickness in some people No death
10^3 r instantaneously	Disruption of the blood forming and gastrointestinal tissue 100% death in 30 to 60 days.
10^4 r instantaneously	Disruption of the central nervous system Death in minutes to hours
10^5 r instantaneously	Spastic seizures, sperm mobility ceases Death in seconds
Adapted from R. P. Yaffe and G. L. Helgeson, *Practical Health Physics*, California Book Company, Berkley 1971.	

Late Stochastic Effects - Carcinogenesis

Cancer is a gross distortion of cell behavior caused by numerous gene mutations and numerous abnormalities in the production and functioning of proteins. The cellular basis for cancer is discussed in Lesson 3. Cancer is a class of diseases, all pertaining to unlimited cell growth that is potentially fatal. Cancer initiates from a single cell that has been transformed due to a particular change in its DNA. Ninety percent of human cancers are carcinomas.

A neoplastic cell is hyperresponsive to growth factors, underresponsive to growth inhibitors, and has an increase in metabolic transport capabilities. A cancer cell tends to have an irregular shape, an abnormally appearing nucleus, is more mobile, is invasive, and shows genomic instability. In a benign tumor, the neoplasm remains as a well-defined cluster and does not spread to neighboring cells. A malignant tumor is capable of invading surrounding tissues, due to disruption of intracellular adhesion, which enables invasive tumor cells to insert themselves between cells of surrounding tissue and to migrate. As it spreads throughout the body, the tumor can invade and destroy tissue until the organism is so compromised that death results.

Carcinogenesis is the primary late effect of radiation. Unlike early effects which are due to the radiation's effect on division, the late effects are possibly due to changes within the cell's DNA or microvasculature. Radiation carcinogenesis has mainly been studied in experimental animals, such as the landmark study by Furth & Furth (1936) on mice. However, carcinogenesis in various occupational groups, which will be described later in the lesson, do demonstrate the stochastic nature of cancer. These and other studies have led to a dose-response curve (Hall: Figure 10-5, page 152). The graph shows that incidence vs. dose curve rises sharply for low doses. There is a maximum value of incidence above which incidences decrease. At this saturation point, the number of cells remaining alive to produce a tumor are greatly reduced.

As for general information about radiation-induced carcinogenesis, the time interval between irradiation and the appearance of a malignancy is the *latent* period. Leukemia has the shortest latent period. Tumors may not appear for 20-50 years, due to the effects of age of expression.

In general, those exposed at an early age are more susceptible to radiation-induced carcinogenesis than those exposed at older ages. For example, breast cancer is more common in young females exposed to radiation. There are exceptions to the rule. For example, susceptibility to radiation-induced leukemia is constant throughout life; whereas, susceptibility to respiratory cancer increases in middle age.

The following three sections will examine the prominent theories dealing with the development of cancer in an organism—oncogenes, cooperating genes, and suppressor genes.

Clonal Theory/ Oncogenes

Although a virus causes cancer by inserting an oncogene from its own genome into that of the cell, the mechanism of transformation by radiation is to cause changes in a normal proto-oncogene native to that cell. These changes cause the proto-oncogene to be activated. The proto-oncogenes are present in every cell and may serve to regulate cell growth and differentiation. They act in a dominant manner. Cells containing this activated oncogene become transformed, evidenced by a lack of contact inhibition.

The radiation causes activation of the proto-oncogenes in three ways:

- point mutation,
- rearrangement or translocation of a chromosome which places an oncogene near a promoter sequence,
- gene amplification.

The studies support a three-stage process in the development of cancer due to changes in the proto-oncogene:

1. Transformation of cell with lack of response to growth control mechanisms,

2. Invasion of transformed cells to surrounding tissues,

3. Migration of cells to other body locations to establish a tumor (metastasis).

This process is known as the *clonal theory*, which assumes that a single radiation interaction alters the DNA of a single cell, thereby producing cancer in the cell.

Studies on animals and observations of human patients have shown that perhaps the clonal theory is too simplified. Levels of hormones are extremely influential in cancers of endocrine glands (ovaries, pituitary, etc.). Murine leukemias, leukemia in rats and mice, are dependent on viruses. Immunocompetence is an important modifier in the survival of the cancerous cell.

Initiation - Promotion Hypothesis/Cooperating Genes

There is typically a latency, or waiting period, between the radiation event and the cancer, depending on the type of malignancy. This can be explained by Berenblum's *initiation-promotion hypothesis*. The first step—*initiation*—is the step in which the cell is altered or activated. During the second step—*promotion*—the exposure of the cell to various agents leads to the expression of the cancer.

Since the two steps of initiation and promotion are involved in carcinogenesis, two cooperating oncogenes are needed for expression of the malignant phenotype. For example, the combination of myc and ras might be required for cancer to develop. Myc oncogenes confer immortality, whereas ras oncogenes confer loss of contact inhibition.

Suppressor Genes Theory

Normal cells contain a gene to suppress the neoplastic potential of tumor cells. This suppressor gene may be located on chromosome 11. Mutation of the suppressor gene p53 may result in cancers of the lung, esophagus, breast, liver,

and brain. Loss of the protein p105Rb may lead to retinoblastoma. Somatic homozygosity may also result in an increased incidence of retinoblastoma, colon cancer, etc. Most suppressor genes are recessive.

Other Theories of Carcinogenesis

There are two other theories of carcinogenesis which deserve note. The somatic-mutation hypothesis deals with the damage of the cell due to radiation. However, the viral hypothesis states the possibility of a virus weakening the cell, thereby leading to vulnerability for cancer development. Another similar theory views a virus as the direct cause of the cancer.

Effect of Ionizing Radiation on Cancer

This section will discuss the actual effects of ionizing radiation on tumor suppressor genes and oncogenes. Ionizing radiation is an activator of oncogenes and an inactivator of tumor-suppressor genes. Oncogene activation promotes cellular proliferation, and the checks on this proliferation are removed through the inactivation of tumor suppressor genes. Specific oncogenes and tumor suppressor genes have been correlated with specific cancers; therefore, genetic mutations do lead to cancer. More than seventy oncogenes and a dozen tumor-suppressor genes have been identified.

The oncogenes are activated by the mutation or amplification of normal proto-oncogenes, which are genes that are part of regulatory pathways that exert influence through phosphorylation of target proteins, formation of protein-protein complexes, or regulation of transcription of target genes. Oncogenes are dominant, positive regulators that stimulate cell growth. Oncogenes may be activated through a variety of cytogenic events, such as large chromosome deletions, inversions, and translocation. For example, the ras oncogene is mutated in about 30% of all human cancers, including bladder and colon cancer. Human B-cell lymphomas are due to translocation of bcl-2 proto-oncogenes in 85% of leukemia cases. The cyclin-D1 oncogene is an amplified gene associated with parathyroid cancer. The ret oncogene is associated with papillary adenocarcinomas of the thyroid, the major type of thyroid cancer found among atomic-bomb survivors, including children affected by the Chernobyl accident.

The bcr/abl oncogene is strongly linked with a major form of radiation-induced B-cell leukemia called chronic myelogenous leukemia.

The normal role of tumor suppressor genes, which act in a complementary fashion with proto-oncogenes, is to inhibit cell growth, with their protein products acting as stops on the cell cycle. Tumor suppressor genes may be inactivated through the induction of point mutations, chromosome rearrangements, or the loss of part or all of a chromosome. The p53 gene, involved in the G_1 checkpoint, is mutated in over 50% of all human cancers. Mutations of the core domain of the DNA binding region of p53 are correlated with human cancer. A mutation of rb can lead to retinoblastoma, a rare childhood cancer of the retina.

Therefore, the ionizing radiation serves to inactivate tumor suppressor genes and to activate proto-oncogenes through the following means. Most single strand breaks are repaired without the loss of information and only a slight risk of genetic mutation. Base alterations and basic sites can cause single base changes known as point mutations, which are easily repaired. Although single-strand breaks, basic sites, and base alterations are induced by both ionizing radiation and normal metabolism, the double strand break is caused preferentially by ionizing radiation. The risk of double strand breaks is low; for example, background radiation levels would produce only one double strand break per 10 cells per year. Double strand breaks are difficult to repair and may result in the loss of genetic information due to the lack of a complementary DNA strand; however, a process called homologous recombination may act to restore the double strand break.

Occupational Exposure

Organ-specific radiation cancers can be found clustered in various occupations, medical exposures, and environmental hazards. As is shown by Hall in Figures 10-5 to 10-8 on pages 152-155, the sensitivity for radiogenic cancers varies greatly with the organs affected. The two organs now believed to be the most sensitive for cancer are the female breast and the lung.

Radiology

Radiologists of today do not have a shortened life span; however, they were at much greater risk from the 1930s to 1950s before modern procedures existed. Until about 1950, radiologists in the US were observed to have excess cancer mortality, especially leukemia, lymphoma, and multiple myelomas, when compared to practitioners in other medical specialities. According to a survey in 1956 of 80,000 obituaries of doctors, the mean age of death of radiologists was 60.5 years, as compared to a mean age of 65.7 for doctors not exposed to daily radiation.

Uranium Miners

One of the decay products of uranium is radon (Rn), which is a gas emanated by the rocks to the air. Exposure to radon in the mines leads to lung cancer. Radon was inhaled by the miners, depositing atoms of radioactive material in their lungs. Studies involving the pitchblende miners in Saxony indicate that alpha radiation produces the tumors in the lungs. The average exposure of the miners is 15-20 years; in addition, it is difficult to separate the effects of radon from the effects of cigarette smoking. One study of uranium miners around the world showed an 80% increase in lung cancer deaths over what was seen in unexposed miners. Radon will be further discussed in Lesson 11.

Radium Dial Painters

In the 1920s and the 1930s, watch dials were painted with luminous paints containing radium, which were ingested by the watch workers. This led to bone cancer due to the intense alpha radiation. The radium acted chemically as calcium and was deposited in the bone. This group of workers had bone sarcomas and carcinomas of the epithelial cells of the sinuses. It was the dangers faced by the radium-dial painters which revealed the danger of occupational exposure to radiation. In one study of this population, of 154 subjects who received skeletal doses of greater than 20,000 rem, 62 subjects developed skeletal tumors.

Medical Exposure

Radium Injections

Excess cancer was also due to injection of radium, which was widely taken in Germany (1944-1951) for its alleged curative power. The radium was later deposited in bone, leading to an incidence of bone sarcoma 280 times that of an unexposed population.

Ankylosing Spondylitis

Ankylosing spondylitis is a disease of the spine. This arthritis-like condition, in which patients walk hunched over, was treated by radiation in the 1940s and 1950s in Great Britain. There is a higher risk of leukemia in these patients. These patients also had increased malignancy due to non-Hodgkin's lymphoma and cancers of the esophagus, lung, bone, breast, and brain.

Women with Tuberculosis

Women, in both Nova Scotia and New England, who received fluoroscopic therapy for tuberculosis have a higher rate of breast cancer. Patients receiving radiotherapy for postpartum mastitis also showed an excess incidence of breast cancer.

Children with Enlarged Thymus

Thymic enlargement occurred in two populations of children in the 1940s and 1950s and was treated with radiation in Ann Arbor, Michigan, and Rochester, New York. Twenty years after irradiation of the thymus, an increase occurred in the rate of thyroid cancer. Both malignant and benign thyroid tumors have been observed. Thyroid cancer has also been observed in those with tinea capitis (ringworm of the scalp), a condition once treated with X-rays.

In Utero Diagnosis

The embryo becomes less sensitive to radiation effects as development moves on but is most sensitive during the first trimester (organogenesis). Radiation causes an increase in childhood malignancy, mental retardation, skeletal and organ abnormalities, and central nervous system problems, as can be seen in Table 8-2 (previous lesson). Studies indicate a strong link between excess incidence of leukemia and children irradiated in utero.

Nuclear Weapon Detonation

Hiroshima and Nagasaki

Hiroshima and Nagasaki survivors have a statistically significant increase in leukemia, breast, thyroid, and skin cancer. There was a great increase in incidence of leukemia in the residents of these cities after the dropping of the bomb, having its peak incidence five years afterward. Of nearly 300,000 people, 100,000 were killed from the blast and its early effects. Of the survivers, 100,000 were unaffected, whereas the remainder suffered from late effects (leukemia, breast cancer). There was a fifteen percent increase in general mortality of those people who had been within 1200 meters of the hypocenter of the atomic bomb (see Figures 9-2 and 9-3).

The best study on radiation induction of cancer in humans is the Life-Span Study of Survivors of the atomic bomb attacks on Hiroshima and Nagasaki, which followed 80,000 individuals over the period 1958-1987. These subjects represent all ages, both sexes, and a wide range of doses. Of this population, only 0.35% (500 people) died from radiation-induced solid cancers. Likewise, only 0.087% (75 people) have developed radiation-induced leukemia. Statistically significant non-carcinogenic prenatal effects have been observed, including severe mental retardation, small head size, and low intelligence scores. The IQ downward shift in embryos, during 8-15 weeks after conception, is estimated to be approximately 30 IQ points per 100 rem.

Human Radiation Experiments

Plutonium injections started in April 1945 and continued for two years, involving 18 people with short remaining lifespans due to age or disease. The purpose of the experiment was not to observe radiation effects but to determine the excretion rate of plutonium over time for known intakes. None of the subjects died of causes that could be related to plutonium injections. The controversy arises as to whether the subjects were informed that they would be ingesting radioactive material.

Other human radiation experiments involved tracer studies. Forty-two people ingested iodine-131 and iodine-125 in order to improve diagnosis of thyroid disease and estimate doses due to radioactive fallout. In addition, tritium was ingested by three volunteers at Los Alamos.

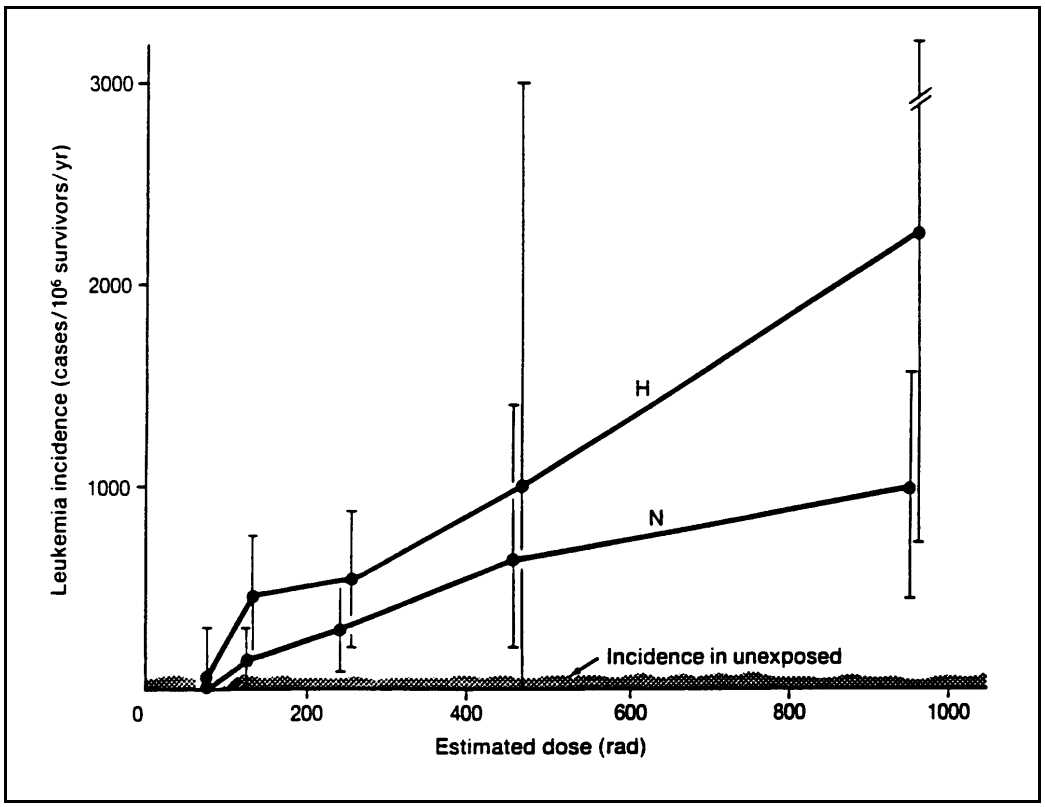


Fig. 9-2. Data on leukemia incidence following the use of nuclear weapons at Hiroshima (H) and Nagasaki (N). This data is consistent with a non-threshold linear dose response. A threshold is not ruled out by this data, however, due to the large error bars.

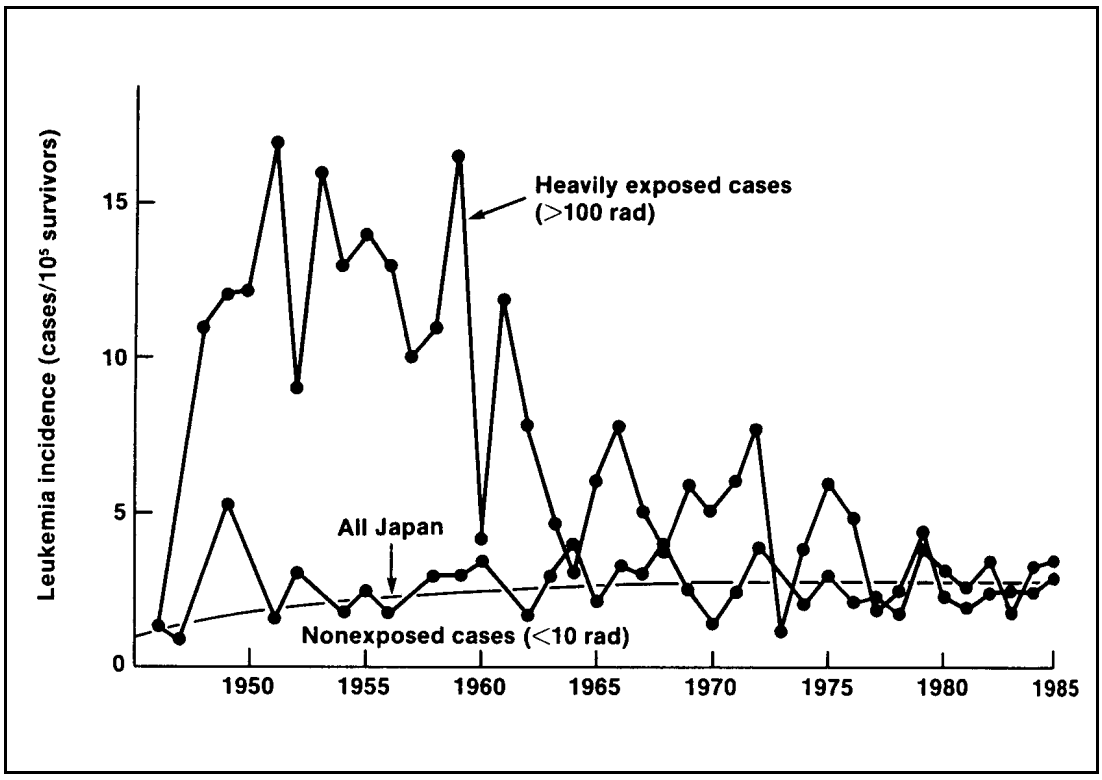


Fig. 9-3. The leukemia incidences in heavily exposed (> 100rad) cases versus time. The rapid (less than 15 years) response to the radiation is unusually rapid compared with the normal latency period of 20-30 years for typical cancers.

Marshall Islands

Marshall Island inhabitants suffered from the effects of radioactive fallout in 1954. There was an increase in children with mental retardation, childhood abnormalities, and childhood malignancy (leukemia).

Late Stochastic Effect - Genetic Mutation

The other late radiation effect is genetic mutation. As for radiation-induced genetic mutations, we have no substantive data on humans. Müller's experiments on Drosophilia, as discussed in Lesson 6, concluded that the radiation does not alter the quality of mutations but rather increases the frequency of them. *Doubling dose* is the dose of radiation that will produce

twice the frequency of genetic mutations as would have been observed without the radiation. Data from mice leads to the conclusion that mammals have some capacity to repair genetic damage. Most radiation-induced mutations are recessive, meaning they must be present in both male and female to produce the trait as discussed in Lesson 6.

Summary

In summary, this lesson has looked at the stochastic effects of radiation. Acute radiation exposure involves the appearance of three syndromes—cardiovascular, gastrointestinal, and cerebrovascular. The late stochastic effect of cancer may be mediated by oncogenes, tumor suppressor genes, cooperating genes, and viruses, all of which are affected by ionizing radiation. Occupational exposure and the events of Hiroshima and Nagasaki deal with carcinogenesis in various organs. Another prominent late stochastic effect is genetic mutation.

- ❖ Acute radiation sickness is an early stochastic effect.
- ❖ Carcinogenesis and genetic mutations are a late stochastic effect.
- ❖ Stochastic effects are non-threshold, dose-response relationships.
- ❖ Occupational exposure has led to many late stochastic effects in people, such as lung cancer, bone cancer, and leukemia.
- ❖ The three main syndromes of acute radiation exposure are cerebrovascular, gastrointestinal, and cardiovascular.
- ❖ According to the oncogene theory, the ras oncogene is mutated in 30% of all human cancers.
- ❖ According to the tumor suppressor theory, the p53 gene is mutated in 50% of all cancers.
- ❖ The events of Hiroshima and Nagasaki are among the primary sources of information for radiation exposure.

WRITING ASSIGNMENT - Lesson 9

Complete and submit the following assignment.

Vocabulary

Please write the term and its definition on your paper. Your definition should be in your own words and limited to one or two sentences.

$LD_{50/30}$
acute radiation syndrome
carcinogenesis
prodromal stage
latent stage
clonal theory
metastasis
initiation-promotion
ankylosing spondylitis
recessive traits
doubling dose
murine leukemia
proto-oncogene
oncogene
tumor-suppressor gene
p53 gene
ras oncogene
cancer
benign tumor
Life-Span Study

Questions

Answer each of the following short-answer essay questions in one page or less.

1. What is the course of illness for acute radiation syndrome?

2. What is the basis of acute radiation syndrome?

3. What is the basis for late stochastic effects? What are these effects?

4. What are the three stages in the clonal theory?

5. What are some problems with the clonal theory?

6. What organs are affected by radiation cancers in the following populations?

    a. radium dial painters
    b. people with ankylosing spondylitis
    c. uranium mine workers

7. What were the effects of radiation exposure on the inhabitants of Hiroshima, Nagasaki, and the Marshall Islands?

8. What is the importance of nominal standard dose in the field of radiology?

9. What is the main difference between mutations due to radiation and those due to natural effects?

10. Why is a victim not cured if he has survived for ten days after radiation exposure?

11. What are some general guidelines for the prognosis of those experiencing extreme radiation exposure?

12. What is the danger in the latent period?

13. Why are infectious organisms so destructive in the hematopoietic syndrome?

14. How can ionizing radiation lead to an increase in cancer, according to the popular cancer theories?

15. In what ways has radiation resulting from medical exposure contributed to cancer deaths?

16. What is the controversy surrounding the plutonium experiments and nuclear fallout?

17. What is the danger of nuclear fallout?

LESSON 10

Risk Estimation; background Radiation: NATURAL AND ARTIFICIAL

❖ Preview ❖

READING ASSIGNMENT

Hall: Chapters 14 and 15

Bushong: Chapters 36 (pp. 517-520) and 37 (all)

Nias: Chapters 18, 19, and 20

LESSON OBJECTIVES

By the end of this lesson, you should be able to:

- List the relative contribution of radiation sources to natural background radiation.
- Define and contrast *relative risk*, *excess risk* and *absolute risk*.

(continued)

DISCUSSION

Introduction

Work in radiobiology has focused on the dose response of biological systems to radiation. Guidelines for exposure limits have been formulated from various committees, using various risk models. These efforts are intended to improve therapeutic radiology procedures and to determine the response to low-level radiation. This lesson will focus on estimating risk and on the sources of background radiation, both artificial and natural. Various sources of background radiation, such as cosmic rays and even ceramic cookware, will be introduced. You will also have an opportunity to determine your personal background radiation level.

An Organism's Response to Radiation

The response of an organism to radiation (the dose response) can have several shapes. The dose response can be linear or nonlinear and threshold or non-threshold. To observe effects due to low dosages, very large numbers of animals need to be irradiated. This is necessary to obtain reasonable statistics on these rare events. Usually, the estimate

- Discuss the three sources of natural background radiation.
- Explain the concept of exposure limits.
- Explain the importance of the radon problem.
- Discuss the three sources of artificial radiation.
- Discuss the complexities of radiation used in medical exposure.
- Explain the importance of doubling dose.
- Explain the role of geography in external terrestrial radiation.

of radiation effects at low dose is based on studies of large numbers of animals at higher doses and extrapolated to the low dose. For this extrapolation, a linear, non-threshold mode is used to estimate the response at lower doses. Recent work by the committee on Biological Effects of Ionizing Radiation (BEIR) has found that after reviewing the literature extensively, a quadratic non-threshold behavior described the data better than a linear, non-threshold response at low energies. However, since the linear, non-threshold response is a conservative estimate of the response, this has been kept as the standard for estimation of risk at low doses.

Risk Models

There are three models which deal with risk due to radiation exposure—absolute risk, relative risk, and time-dependent relative risk models.

In the *absolute risk* model, radiation induces a group of cancers above and beyond the natural incidence

and is unrelated to it. In the *relative risk* model, the effect of radiation is to increase the natural incidence of cancer at all ages subsequent to exposure by a given factor. This model predicts a large excess number of cancers appearing late in life after irradiation. In the *time-dependent relative-risk* model, it is assumed that the excess incidence of cancer is a function of dose, $(\text{dose})^2$, age at exposure, and time since exposure. This model has been useful in understanding epidemiology data from such events as the Hiroshima and Nagasaki atomic bomb exposures and the exposures from the Chernobyl disaster.

The various models are expressed in formulas that allow for estimation of risk. For example, relative risk is defined as the ratio of observed cases to the expected cases:

$$\textit{relative risk} = \frac{\textit{observed cases}}{\textit{expected cases}}$$

The relative risk is computed by comparing the number of persons in the exposed population showing a late effect with the number who developed the same late effect in an unexposed population. A relative risk of 1 indicates no risk at all. A relative risk of 1.75 would indicate the frequency of the late response is 75% higher in the irradiated population. A relative risk of less than 1 indicates a protective benefit.

EXAMPLE 1:

In a study of radiation-induced leukemia following diagnostic levels of radiation, 237 cases were observed in 100,000 people. The normal incidence of leukemia in the United States is 150 cases per 100,000. What is the relative risk of the radiation-induced leukemia?

Answer: Relative Risk = Observed/Expected
= 237/150
=1.58 (i.e., 58% higher in irradiated population)

Excess risk can also be calculated. *Excess risk* is the difference between the observed cases and the expected cases:

$$\textit{excess risk} = \textit{observed cases} - \textit{expected cases}$$

The excess cases found are assumed to be radiation induced.

EXAMPLE 2:

Forty cases of skin cancer were observed in a population of 1000 radiologists. The incidence in the general population is 0.5/100,000. How many excess skin cancers were produced in this population?

Answer: Excess Cases = Observed - Expected
= 40 - .005
= 40 (All 40 represent risk)

The last calculation involves *absolute risk*. Absolute risk is often reported in number of cases/10^6 persons/rad/year. The NRCP reports absolute risks in units cases/Sv/lifetime, i.e., the chance of a fatal cancer is 10^{-2}/Sv/lifetime/ person. To determine the absolute risk factor, a linear dose-response relationship is assumed. Since there are several ways of reporting the risks, care must be taken when discussing the risk with radiation workers and the general public to state the risk so there is no misunderstanding. Using an example of an induced cancer with 100 observed cases and 90 expected cases for a dose of one rad in a year in a population of 1 million, the relative risk would be 1.11, the excess risk would be 10 cases/rad/10^6 people/year, and the absolute risk would be 100 cases/rad/10^6 people/year. Which statement of the risk would you take to most correctly state the problem? Remember in none of these statements of risk can you understand the size of the increase and its relative magnitude. Three different ways of presenting the risk of radiation are shown in Tables 10-1, 10-2, and 10-3.

EXAMPLE 3:

The absolute risk for radiation-induced breast cancer is 6 cases/10^6 persons/rad/year for a 20-year period. If 100,000 women receive 1 rad during mammography, what total number of cancers are expected to be induced?

Answer: $6/\ 10^6\ \ (10^5)\ (1)\ (20) =\ 12$ cases

Table 10-1. Relative contribution of individual tissues and organs to the probability of fatal cancer and total detriment.

Tissues and Organs	Probability of a fatal cancer (10^{-4} rem^{-1})		Total detriment (10^{-4} rem^{-1})	
	Whole Populations	Workers	Whole Populations	Workers
Bladder	0.30	0.24	0.29	0.23
Bone Marrow	0.50	0.40	1.04	0.83
Bone Surface	0.05	0.04	0.07	0.06
Breast	0.20	0.16	0.36	0.29
Esophagus	0.30	0.24	0.24	0.19
Colon	0.85	0.68	1.03	0.82
Liver	0.15	0.12	0.16	0.13
Lung	0.85	0.68	0.80	0.64
Ovary	0.10	0.08	0.15	0.12
Skin	0.02	0.02	0.04	0.04
Stomach	1.10	0.88	1.00	0.80
Remainder	0.50	0.40	0.59	0.47
Total	5.00	4.00	5.92	4.73
	Probability of severe genetic effects			
Gonads	1.0	0.6	1.33	0.8
Grand Total			7.25	5.53

Adapted from: NCRP Report No. 116 "Limitation of Exposure to Ionizing Radiation", (National Council on Radiation Protection and Measurements, 7910 Woodmont Avenue Bethesda, MD 20814, 1993) Table 7-2, page 32.

Table 10-2. Risk factor consequence in life shortening

Risk Factors of disease, occupation, or other conditions.	Expected days of life lost
Being male rather than female	2800
Heart disease	2100
Being single	2000
One pack of cigarettes a day	1600
Working as a coal miner	1100
Cancer	980
30 pounds overweight	900
Stroke	520
All Accidents	435
Service in Vietnam	400
Motor vehicle accidents	200
Average Occupational Accidents	74
Speed limit increase from 55 to 65 mph	40
Radiation Worker	12
Airplane Crashes	1

Adapted from S.C. Bushong, *Radiologic Science for Technologists: Physics, Biology, and Protection*, 7th ed. (Elsevier Mosby, St. Louis, 2004) Table 37-2, page 534.

Table 10-3. Yearly Average Risk of Death from Various Causes.	
Cause	Your chance of dying this year
All causes(all ages)	1 in 100
20 cigarettes per day	1 in 280
Heart disease	1 in 300
Cancer	1 in 520
All Causes (25 year old)	1 in 700
Stroke	1 in 1200
Motor vehicle accident	1 in 4000
Drowning	1 in 30,000
Alcohol (light drinker)	1 in 50,000
Air Travel	1 in 100,000
Radiation, 100 mrad	1 in 100,000
Texas Gulf Coast Hurricane	1 in 4,500,000
Being a rodeo cowboy	1 in 6,200,000
Adapted from S.C. Bushong, *Radiologic Science for Technologists: Physics, Biology, and Protection*, 7th ed. (Elsevier Mosby, St. Louis, 2004) Table 37-6, page 543.	

Exposure Limits

The risk models are used to aid the various regulatory committees in imposing limits. The earliest limits on radiation were based on preventing the onset of obvious effects such as skin ulcerations, which appeared after intense exposures to radiation. Later limits were based on preventing delayed effects, such as cancer. In 1902, the first dose limit of 10 rad was recommended. In 1924, a "tolerance dose rate," a dose that could be tolerated indefinitely, was determined. Essentially, early limits were a judgment call based on the absence of observed biological harm.

The ICRP (International Commission on Radiological Protection) and UNSCEAR (United Nations Committee on the Effects of Atomic Radiation), and NCRP (National Council on Radiation Protection and Measurements) estimate the risk associated with exposure to low levels of radiation and recommend dose limits for radiation workers and the general public. They have estimated the low-dose/low dose-rate risk by extrapolation of risks obtained from high-dose/high dose-rate atomic bomb survivor data and other radiation studies. These other studies include radiation accidents, occupational exposures, and medical exposures. There are several means of obtaining extrapolations:

1. Linear-dose response, no threshold hypothesis (LNT)

   This most common model implies that the risk is proportional to dose all the way down to zero dose. It is calculated by extrapolating the straight line drawn through the high-dose data all the way down to zero. This model is equivalent to a stochastic model of radiation effects. As mentioned earlier, the LNT is the standard for estimation of risk at low doses.

2. Threshold

   This model assumes there is some value of dose below which there is no effect.

3. Sublinear

   This model assumes that the effect per unit dose at low doses is less than at high doses.

4. Superlinear

   This model assumes that the effects per unit dose at low dose is greater than at high doses.

5. Adaptative Response (Radiation Hormesis)

   This model assumes that very low doses have a protective effect on the organism.

Although all of these models have valid points, the results of most animal and cellular experiments favor the LNT or sublinear hypothesis.

The three organizations use the LNT hypothesis as a conservative basis for estimating risk. The risk factor for doses less than 20 rem or 0.6 rem/hr is set equal to one-half the risk factor for high doses (1.2×10^{-3}/rem). Therefore, the risk factor for radiation-induced cancer mortality is 6×10^{-4} per rem for the general population. The risk factors for low dose or low dose-rate radiation exposure is 5×10^{-4} per rem for the general public and 4×10^{-4} per rem for workers, both values applied to exposures in excess of natural background levels.

The annual dose limits recommended by the NCRP are, for occupational exposures, 5 rem for stochastic effects, 15 rem for the lens of the eye, and 50 rem for all other organs. It is recommended that a worker's lifetime effective dose not exceed one rem multiplied by the worker's age in years.

The most objective method of comparing the risks of radiation with those of other hazards is to study mortality statistics from equivalent groups in the population. It is recommended that the general population should not receive an annual dose to the whole body greater than 5mSv over a period of thirty years. Basically, for those exposed to radiation as their occupation, the dose is ten times higher than that for the general population. As a rule, the dose can usually be kept within one tenth of the recommended limit. The limits are higher for individual organs than for the whole body, due to "weighting factors" of the organ exposed.

The ICRP recommends that the public should not receive an additional dose of 1 mSv/year above the background radiation; however, the natural background radiation already amounts to twice this level (2.2mSv/ year). Overall, the most basic principle of radiation protection is to keep radiation sources as low as reasonably achievable (ALARA).

Latent Period

The calculation of risk is complicated by the fact that most radiation effects do not show themslves immediately. There is always a long latent period between the time of irradiation and the clinical appearance of cancer. The latent period is shorter for leukemia than other cancers, with a minimum period of 4-5 years and a mean of eight years. This compares with a minimum of ten years and a mean of 15 years for the appearance of other cancers. It is important to remember that the risk of cancer/leukemia from radiation depends not only on the total dose but on dose rate. High LET radiations are more effective in producing transformation of cells than low LET radiation.

Doubling Dose

A useful concept in radiobiology is the *doubling dose* (also discussed in Lesson 6) in relation to genetic mutations. The doubling dose is defined as the dose of radiation required to double the natural incidence of a genetic effect. This is very useful as it gives an automatic perspective on the process. The U.N. Scientific Committee on the Effects of Atomic Radiation, UNSCEAR, reviewed a study of 750,000 live births and concluded that the spontaneous mutation rate is 10.5%. Further, most of the genetic effects are believed by the Biological Effects of Ionizing Radiation committee (BEIR) to have a doubling dose of 50 to 250 rem. There has not been any observance of statistically significant hereditary health effects of ionizing radiation in humans.

Species Risk

The lesson has focused on the risk for humans. However, the risks and effectiveness of radiation also varies with other species.

Species which reproduce asexually are more radiation resistant than are sexually reproducing species. Whereas sexual reproduction requires at least two survivors, asexual reproduction can proceed with only one individual.

Short-lived species with a short gestation period are more susceptible than long-lived species, due to rapid cell division in the former. Embryonic, young, and very old are more radiosensitive. Warm-blooded animals are more radiosensitive than cold-blooded organisms.

Overall, large herbivorous mammals are the most radiosensitive due to their characteristics of being warm-blooded, sexual, and exposed most of the time. The following organisms are ranked in radiosensitivity from greatest to least—large mammals, smaller mammals, birds, plants, one-celled animals and plants, bacteria, and viruses. Man is ranked among the large mammals in radiosensitivity.

Background Radiation: Natural and Artificial

An average American receives 360 millirems of ionizing radiation every year, 300 millirems per year (78%) from natural sources. The dose to which a human is exposed each year comes from three main sources: natural sources, enhanced natural sources, and man-made sources. 18% percent of radiation comes from artificial sources, the majority of which is due to medical procedures, while the remaining 4% comes from natural background radiation.

Enhanced natural sources are sources in which human activity has increased the level of individual exposure. They are natural in origin and include such activities as air travel at high altitudes and phosphate mining.

Man-made exposure is due to X-rays, radiopharmaceuticals in medicine, accidents in nuclear power plants, and atmospheric testing of nuclear weapons. Of these sources, the most significant exposure is medical. The exposure due to fall-out from 1959-1962 never reached more than a small fraction of that from medical diagnosis. The overall effective dose from medical radiation is less than half that from natural background radiation. These sources will be explored in depth later in the lesson. A personal radiation dose chart is included for you on pages 163-164 so that you can estimate your individual dose from background radiation.

Natural Sources

The sources of background radiation are summarized in Table 10-4. Natural radiation comes from the following sources:

1. cosmic radiation

2. external terrestrial radiation

3. internal terrestrial radiation.

These natural sources affect all of the world's population all the time. The natural background annual, world-wide, average whole-body effective dose is 238 mrem, a value which varies widely among locations. In contrast, the dose associated with internal radiation (due mainly to potassium-40) varies much less from person to person. Epidemiological studies have generally failed to find a statistically significant correlation between cancer mortality and levels of background radiation. The hypothetical risk associated with the dose from natural background radiation is merely a small fraction of risks faced by all humans each day, such as car wrecks.

We will now look at the three sources of natural radiation more closely.

Cosmic radiation is due to an ionizing component and neutrons. The primary cosmic rays have the same composition as the atomic abundance in the solar system. The energy of the primary cosmic rays can exceed 10 TeV (10,000,000 MeV). The primary cosmic ray interacts with the atoms of the upper atmosphere and produces electromagnetic and particulate radiation on earth. The dose rate on the ground varies with altitude, latitude, and longitude. The cosmic ray intensity is least in the equatorial regions and rises towards the poles. The ionizing component consists of protons (75-90%), helium nuclei (10-18%), and ions with an atomic number greater than 3 (1-7%).

In addition to the cosmic ray background, there are also high energy X-rays and gamma-rays present (see Figure 10-1). However, the dose from the electromagnetic radiation in much less than from the particulate radiation.

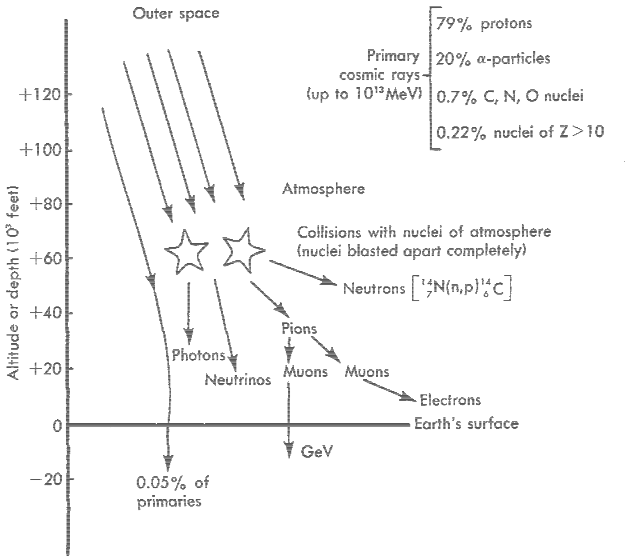


Fig. 10-1. (Source: Arena, Victor, *Ionizing radiation and life*, C.V. Mosby, 1971, Fig. 6-13, p. 110)

Table 10-4. Sources of background radiation both natural and man made.

Radiation Source	Annual Dose (mrad)	Annual Dose (μGray)
Man Made		
Diagnostic X-Rays	40	400
Nuclear Medicine	14	140
Consumer Products	10	100
Other	1	10
Subtotal	65	650
Natural		
Internal Dose	40	400
Terrestrial Nuclides	29	290
Cosmic Rays	29	290
Radon	197	1,970
Subtotal	295	2,950
Total	360	3,600

The dose from cosmic rays is highly dependent on altitude. As shown in Table 10-5, the dose rate increases rapidly with altitude. For example, the average cosmic ray annual dose equivalent in the United States is 26 mrems at sea level, a figure that doubles for each 2000 m increase in the lower atmosphere. The dose at 30,000 feet, normal cruising altitude for jet aircraft, can climb to over 100 mrem/hour during a typical solar flare. A study is underway of aircraft personnel as subjects in a test of individuals exposed to low dose rates.

Table 10-5. The Dependence of Cosmic Ray Dose With Altitude

Altitude(ft)	Dose Rate (mrem/yr)	Example
Sea Level	31	Boston
5,000	55	Denver
10,000	137	Leadville, Co
30,000	1,900	Commercial Jet Aircraft
50,000	8,750	SST airliner
80,000	12,200	Spy Plane
120,000	10,500	Near Earth Orbit

Adapted from Daniel A. Gollnick, *Basic Radiation Protection Technology*, 2nd ed. Pacific Radiation Corporation, Altadena, California (1993).

The *external terrestrial* radiation source comes from components of the earth's soil, rocks, and buildings. The most common radioisotopes in the earth's crust are ^{238}U, ^{232}Th, and ^{40}K. The radioactivity in soils, rocks, and housing building materials is greatly elevated in areas of Brazil, the Burgundy region of France, in Kerala, India, and the Northern Nile delta region of Egypt. Kerala and the Brazilian coast have monazite sands containing thorium concentrations as high as 10%. Uranium, thorium, and their daughters are especially plentiful in igneus rock, such as granite, bituminous shale, and phosphate, rocks which are plentiful in Burgundy. Interestingly, no excess incidence of cancer or genetic anomalies have been observed in these areas. There are widespread geographic variations in the levels of external terrestrial radiation. Reactions of cosmic rays and the particles from the sun result in the formation of some additional radioactive nuclei such as ^{3}H and ^{14}C.

Radon

As mentioned previously, radon is the major component in external terrestrial radiation. Recent surveys of homes in the United States have revealed a very high incidence of radioactive radon gas and its daughter products. *The largest contributor to effective dose is radon for non-smokers in the United States.* Radon is a chemically inert gas which is formed in several of the natural decay chains which start with thorium or uranium nuclei. Due to the chemical properties of radon, it is easily transported to the surface through small cracks in the rocks from the area where it is produced. During the last two decades, there has been a shift to improved sealing of houses, which has understandably exacerbated the problem. The average concentration in the U.S. is 376 mBq/L in the living area and much more in the basement. The current estimate of an average annual dose to the lungs from radon is 197 mrem.

Many variables influence radon levels, including the time of day, the season, geology of the soil, home construction, barometric pressure, humidity, moisture in the soil, and the rate of ventilation in the home. There are two common home radon measurement devices—charcoal canisters and alpha track monitors.

Water is a major source of radon. Water obtained from surface sources, such as lakes and reservoirs, is low in radon; however, water from wells has high concentrations of radon gas.

As explained in the previous lesson, radon contaminates many underground mines, leading to an increased risk of lung cancer. Radon gas leads to irradiation of the surface of the lungs when the gas and its products are inhaled. The radon decays to polonium, which emits alpha particles, which causes “hot spots” of radiation damage. Six to twelve percent of cases of lung cancer are due to radon, amounting to 5,000-10,000 cases per year. The main evidence that exposure to radon increases mortality from lung cancer comes from miners working underground where there are high concentrations of radon decay products. Since lung cancer due to radon is a stochastic effect, the best precaution is to provide adequate ventilation in houses.

Interestingly, radon data shows a negative correlation between radon and lung cancer up to concentrations of at least 7 picocuries per liter, implying that radon exposure has a hormetic effect at this level.

Internal Terrestrial Radiation

The *internal terrestrial* exposure is due to the ingestion of small traces of radioactive materials present in food supplies or inhaled as airborne particles. Radioactive thorium, radium, and lead can be detected in most persons; however, only ^{40}K makes an appreciable contribution. Other radioisotopes involved in internal terrestrial exposure include ^{14}C and ^{226}Ra.

The predominant radioactive element in normal foods and human tissues is ^{40}K. It is concentrated particularly in muscle. We also ingest uranium, radium, and thorium in food we eat. ^{226}Ra is chemically similar to calcium and barium, so it passes easily into the food chain. It is present in all foods, especially cereals and brazil nuts, which concentrate radium. The excess radium concentrates in the skeleton. On a facetious note, some scientists believe it is best to sleep in twin beds so as not to receive additional radiation from each other's body.

Personal Radiation Dose Chart

(Adapted from Personal Radiation Dose, American Nuclear Society, 1990
with further data from NCRP Report No. 93 and NCRP Report No.95
From Roger Eckhardt, "Ionizing Radiation-It's Everywhere!"
Radiation Protection and the Human Radiation Experiments,
Los Alamos Science **23** 48 (1995).

Estimate your annual effective dose in millirem by adding the numbers in the right hand column, including the numbers you choose from each category with a blank space.

Where you live:

Cosmic Radiation at sea level

For your elevation in feet:

500-1000 ft:	2	
1000-2000 ft:	5	
2000-3000 ft:	9	
3000-4000 ft:	15	
4000-5000 ft:	21	
5000-6000 ft:	29	
6000-7000 ft:	40	
7000-8000 ft:	53	
8000-9000 ft:	70	
9000-10000 ft:	107	_____

Terrestrial:

Live in a state bordering the Gulf or Atlantic from Texas east and north:	23	
Live in Colorado Plateau or Rocky Mountain State:	29	
Live anywhere else in the United States:	46	_____

Internal:

What you eat and drink		
Radon: Insert a value for your average radon level (in picocuries per liter x 100) or use the U.S. average of 200 mrem		_____

(continued)

Life Choices:

Live in a stone, brick, concrete, or adobe building:	7
Live within 50 miles of a coal-fired electric utility plant:	0.03
Live within 50 miles of a nuclear reactor:	0.01
Jet airline travel - each 1000 miles traveled annually:	1
Smoke cigarettes - multiply packs per day by 870 (high degree of uncertainty):	
Use a typical distribution of consumer products (U.S. average):	10
Cook and heat with natural gas:	2
Work with commercial fertilizer products (e.g., farming):	1

Medical Exposures:

Receive a diagnostic x-ray (U.S. average):	40
Receive a thyroid scan:	590
Wear a plutonium powered pacemaker:	100
Receive other medical radiation exposure (ask physician):	

Occupational:

If you work with radiation sources, add your annual dose in millirems, or select the 1980 average for exposed workers in your occupation:

Air flight crew: 670	Well logger: 420
Nuclear fuel cycle: 600	Government: 120
Medicine: 150	U.S. Public Health Service: 47
Industry: 240	Open-pit uranium mining: 115
DOE Contractor: 180	Underground mining: 700

Public Exposures from Nuclear Age:

Transportation of radioactive materials:	0.6
Fallout from atmospheric testing:	0.5

Your Annual Effective Dose (millirem):

Sum the numbers in the right column:
(U.S. Average: 360 millirem)

Consumer Products

Many consumer products are radiation sources, such as radioluminous timepieces (containing radium) and smoke detectors (containing ^{241}Am, an alpha source). The main exposure from smoke detectors is to the workers assembling the detector. Static eliminators, which are used to clean negatives and CDs, contain ^{210}Po.

Ceramic dinnnerware is a source of ionizing radiation, due to the glazes containing uranium oxides and sodium uranite. Dental products, such as crowns, and opthalmic glasses, especially rose-tinted glasses, contain radioactive material.

Tobacco products have an above-average concentration of lead ^{210}Pb and ^{210}Po. Smoking of tobacco leads to large exposures of radiation in the lungs, leading to the belief that radiation may be one of the major causes of lung cancer for smokers.

In addition, a masonry home, such as brick, stone, adobe, or concrete, also leads to an increase in radiation exposure.

Artificial Sources of Radiation

The artificial sources of radiation are due to the following:

1. fallout from nuclear testing
2. medical treatment
3. reactors.

It is important to note that these artificial sources only affect a small fraction of the population at any one time.

The fallout from nuclear weapons testing can be found at various levels in the atmosphere and on the ground. The fission products are precipitated out by rainfall in various regions. Although the United States and Russia have stopped open-air testing, tests from China and the France have been conducted since that time. The most important radioisotopes of fallout are those which give external gamma ray doses and those that become internally deposited in the body, either by direct absorption or via a food chain. The production of some of the important radionuclides in nuclear detonations is shown in Table 10-6. Current limits on U.S. and Russian underground testing are at the 200 kiloton levels. Nuclear tests by other countries are not now regulated by treaty.

Many atmospheric nuclear weapon tests were conducted by the United States, Soviet Union, Great Britain, France, and China from 1945 to 1963. Fallout, the radioactive debris ejected into the environment by a nuclear explosion, does not remain in the test site. Rather, they fall onto plants outside the research area and enter the food chain. The radioisotopes ^{131}I, ^{90}Sr, ^{89}Sr, and ^{137}Cs are the most important hazards. Two studies at Los Alamos—Humco I and II—were used to study the effects of fallout, specifically the presence of ^{137}Cs.

Table 10-6. Radioactive Fallout from a 1 Megaton Nuclear Bomb by Radionuclide

^{14}C	3.5×10^{4} Ci
^{24}Na	3.0×10^{11} Ci
^{89}Sr	1.7×10^{7} Ci
^{90}Sr	1.0×10^{5} Ci
^{131}I	7.0×10^{7} Ci
^{137}Cs	1.4×10^{5} Ci
^{239}Pu	3.6×10^{3} Ci

Adapted from Daniel A. Gollnick, *Basic Radiation Protection Technology*, 2nd ed. Pacific Radiation Corporation, Altadena, California (1993).

Chernobyl has been the most recent large source of fallout. The Chernobyl accident occured in Russia in 1986. Thirty-one people died from the accident, and 135,000 people in the region were permanently evacuated. These evacuated people had an average dose of 12 rem, a dose 1500 times greater than that of people near Three Mile Island. Pripjat is a "radiation ghost town." Three million acres of agricultural land has been lost due to contamination.

The artificial background dose due to reactors is still quite controversial. The more accepted estimate is that the dose from the nuclear reactors is less than one percent of the total background radiation. This is difficult to estimate, due to uncertainties about the chance of a catastrophic accident which releases radiation. For instance, the Chernobyl reactor disaster resulted in fallout which increased background radiation not only for the local population, but also for a large part of western Europe.

Occupational Dose

Those who choose to work with ionizing radiation may be exposed to higher doses than the general public. Most workers in nuclear power stations and medical radiation are in a low dose category. The higher dose group includes uranium miners, crews of jetcraft, nuclear reactor workers, and nuclear fuel reprocessing workers.

Medical Use

Medical exposure is one of the most significant external man-made sources of radiation. Medical exposure is primarily due to diagnostic X-ray of the chest, head or other body parts. The therapeutic X-ray delivers much larger doses of radiation. On average, the dose from diagnostic x-rays is estimated at 23 mrem/year (0.23 mSv/year). Nuclear medical diagnostic procedures are estimated to average 14 mrem/yr (140 μSv/yr). Therapeutic radiation, primarily to control cancer, can reach up to 6000 rads per patient.

The medical use of radiation involves offsetting a risk against a benefit. The detriment in regards to the annual collective dose of persons is the following:

4%/Sv fatal cancer
0.8%/Sv of nonfatal cancer
0.8%/Sv heritable effects (mutations)

This risk must be weighed against the benefit that millions receive from improved diagnosis. A dose of one sievert to the population would cause a 5% lifetime risk of fatal cancer.

The two tissues that are dose-limiting for medical radiation procedures are the bone marrow, due to leukaemogenesis, and the gonads, because of genetic effects. In examinations of the lower trunk, the gonads receive a high dose, unless they are shielded with protective devices.

To summarize, there are three potential hazards resulting from medical radiation:

1. heritable effects in future generations
2. risk of cancer or leukemia in patients themselve
3. anomalies or malignancies in irradiated embryos

The dose for medical exposure is not a contributor to the annual dose for an individual.

As shown by the chart (Bushong, p. 5, Figure 1-3; Hall, p. 203, Figure 14-5; Nias, p. 7, Figure 1-4), the dose from natural sources accounts for 82% of the average dose. Radon, by itself, accounts for 55%, being the largest single radiation source. The cosmic and terrestrial sources account for 11% of the total. Internal sources, such as ^{40}K, account for 11%. Manmade sources account for 18% of the dose, the largest being 11% from medical X-rays. Consumer products account for 4% of the dose, whereas nuclear fallout, nuclear power plants, and occupational exposure contribute less than 1% of the total dose. These values for the estimated background will vary depending upon the source of the dose estimates and the assumptions used in making them. A few reasonable alternate choices for the personal radiation dose chart will give you an understanding of the variability of the background radiation.

Summary

In summary, Lesson 10 has dealt with the risk models and exposure limits for radiation. It has examined the various sources of background radiation, both natural and artificial sources. Sources examined in depth included radon, medical exposure, and fallout. You have had also has an opportunity to put the information in perspective by completing the personal radiation dose chart.

- ❖ Dose response curves can differ for organisms of different species.
- ❖ Relative risk, excess risk, and absolute risk are all measures for expressing the risk of an event.
- ❖ Natural background radiation is due to cosmic rays, external terrestrial radiation, and internal terrestrial radiation.
- ❖ Artificial sources of radiation are reactors, fallout, and medical treatment.
- ❖ Using the LNT model of risk, the regulatory committees have calculated exposure limits.
- ❖ Radon, which is the primary source of external terrestrial radiation, has been implicated in lung cancer.
- ❖ Potassium-40 is the main source of internal terrestrial radiation.
- ❖ The use of radiation in medicine is relatively safe; however, the risks and benefits must be assessed.

WRITING ASSIGNMENT - Lesson 10

Complete and submit the following assignment.

Vocabulary

Please write the term and its definition on your paper. Your definition should be in your own words and limited to one or two sentences.

dose response	external terrestrial radiation	latent period
BEIR	cosmic rays	ALARA
relative risk	internal terrestrial radiation	radiation hormesis
excess risk	threshold dose	lifetime effective dose
absolute risk	radioactive isotopes	enhanced natural sources
radon	potassium-40	time-dependent relative-risk model

Problems and Questions

These problems and questions require numerical or short-essay answers. Show your work and circle your final numerical answers. Limit your short-essay answers to one page or less.

1. Why are experiments looking for radiation effects normally done at high radiation dose rates rather than at low dose rates?

2. Given: the risk of dying today is 1 in 10,000, the risk of being hit and killed today if you ride a bicycle is 1 in 5,000, and the risk of dying today if you wear a safety belt and drive defensively is 1 in 20,000.

   What is: the *absolute* risk of dying today, dying today if you ride a bike, and dying today if you wear a seat belt and drive defensively? What is the *relative* risk for the same cases? What is the *excess* risk for the same cases?

3. Using Table 10-3, what is the relative risk of dying in a year assuming that you:

   a. are 25 years old
   b. drink (light drinker)
   c. will have a Gulf Coast hurricane visit you versus 100 mr of radiation?

4. How much background radiation do we get from cosmic rays?

5. How much background radiation do we get from medical uses?

6. What are some important isotopes in natural internal radiation?

7. Why is radon present in homes? It wasn't there when they were first built. Where does it come from?

8. Given the dose of 23 mrem/year from medical exposure and using Table 10-1, what is the probability of fatal cancers for whole populations for breast and colon cancer?

9. Given the dose of 6,000 rads from therapeutic radiation, what is the probability of fatal cancers for stomach, bone marrow, and bone surface?

10. What is the largest source of artificial radiation?

11. Complete the personal dose chart on pages 173-174.

12. What are some of the radiation sources you may be in contact with in your home?

13. What is the role of geography in background exposure? How dangerous is background exposure?

14. What is the importance of exposure limits? Who decides what the limits are?

15. What are the two dose-limiting tissues in medical exposure to radiation? What are the three potential hazards in medical radiation?

16. Why do uranium miners who smoke have one of the highest cancer rates of any occupational group?

17. Place the following radiation sources in rank order (largest to smallest): fallout, cosmic sources, radon, nuclear power plants, internal sources, medical exposure.

Personal Radiation Dose Chart

(Adapted from Personal Radiation Dose, American Nuclear Society, 1990
with further data from NCRP Report No. 93 and NCRP Report No.95
From Roger Eckhardt, "Ionizing Radiation-It's Everywhere!"
Radiation Protection and the Human Radiation Experiments,
Los Alamos Science **23** 48 (1995).

Estimate your annual effective dose in millirem by adding the numbers in the right hand column, including the numbers you choose from each category with a blank space.

Where you live:

Cosmic Radiation at sea level

For your elevation in feet:

500-1000 ft: 2	5000-6000 ft: 29	
1000-2000 ft: 5	6000-7000 ft: 40	
2000-3000 ft: 9	7000-8000 ft: 53	
3000-4000 ft: 15	8000-9000 ft: 70	
4000-5000 ft: 21	9000-10000 ft: 107	_____

Terrestrial:

Live in a state bordering the Gulf or Atlantic from Texas east and north:	23	
Live in Colorado Plateau or Rocky Mountain State:	29	
Live anywhere else in the United States:	46	_____

Internal:

What you eat and drink		
Radon: Insert a value for your average radon level (in picocuries per liter x 100) or use the U.S. average of 200 mrem		_____

(continued)

Life Choices:

Live in a stone, brick, concrete, or adobe building:	7
Live within 50 miles of a coal-fired electric utility plant:	0.03
Live within 50 miles of a nuclear reactor:	0.01
Jet airline travel - each 1000 miles traveled annually:	1
Smoke cigarettes - multiply packs per day by 870 (high degree of uncertainty):	
Use a typical distribution of consumer products (U.S. average):	10
Cook and heat with natural gas:	2
Work with commercial fertilizer products (e.g., farming):	1

Medical Exposures:

Receive a diagnostic x-ray (U.S. average):	40
Receive a thyroid scan:	590
Wear a plutonium powered pacemaker:	100
Receive other medical radiation exposure (ask physician):	

Occupational:

If you work with radiation sources, add your annual dose in millirems, or select the 1980 average for exposed workers in your occupation:

Air flight crew: 670	Well logger: 420
Nuclear fuel cycle: 600	Government: 120
Medicine: 150	U.S. Public Health Service: 47
Industry: 240	Open-pit uranium mining: 115
DOE Contractor: 180	Underground mining: 700

Public Exposures from Nuclear Age:

Transportation of radioactive materials:	0.6
Fallout from atmospheric testing:	0.5

Your Annual Effective Dose (millirem):

Sum the numbers in the right column:
(U.S. Average: 360 millirem)

LESSON 11

Metabolism and Biological Effects of Radionuclide Uptake

❖ Preview ❖

READING ASSIGNMENT

Hall: Chapter 14 (pp. 218-224)

Nias: Chapter 18 (pp. 314-320)

LESSON OBJECTIVES

By the end of this lesson, you should be able to:

- ❖ Name and explain the three ways in which radionuclides may enter the body.
- ❖ Define *biological half-life* and explain the need for this concept.
- ❖ Define *discrimination ratio*.
- ❖ Describe importance of tritium as a radionuclide.

(continued)

DISCUSSION

Radionuclide Entry into the Body

This lesson will deal with the metabolism of radionuclides. Radioactive isotopes are unstable atoms that disentegrate randomly with the emission of ionizing radiation, including alpha and beta particles, gamma rays, or a combination of these. It will introduce the concepts of discrimination ratio, biological half-life, and radiotoxicity. Committed dose and the committed dose formula will be discussed. Important radionuclides and their properties will be discussed. The history and basic concepts of nuclear medicine, in relation to the properties of radioisotopes, will be examined.

Concepts of Nuclear Medicine

The first person to suggest the use of radioisotopes in biology and medicine was the chemist Hevesy. Nuclear medicine was a late starter compared with radiation therapy and X-ray diagnosis. Ten to twelve million doses are administered each year.

In nuclear medicine, the radiation is delivered internally from radioactive isotopes administered to the patient by injection or by mouth. Some isotopes

- ❖ Define effective dose equivalent.
- ❖ List and explain the three critical doses in nuclear medicine.
- ❖ Describe the effects of radionuclides of noble gas, alkali metals, and radium on the human body.
- ❖ Explain the significance of radioactive iodine and its metabolism.
- ❖ Describe the sources of both manmade and natural radiation.
- ❖ Describe the factors which determine radiotoxicity.
- ❖ Rank the radionuclides in order of radiotoxicity.
- ❖ Explain the importance of committed dose.
- ❖ Work problems with the committed dose formula.

are used for their imaging properties, being generally distributed throughout the body. Others are chosen for the property of being localized in a particular organ.

Nuclear medicine using radionuclides is based on the accumulation of the isotope in the organ of interest (the *target organ)*. However, the dose to the critical organ will limit the amount of radioisotope that may be administered.

It is important to remember that the pathway of the radionuclides is determined by the parent element. It is not affected by radioactive decay or energy release. In addition, if the element involved is not normally metabolized, its fate will be determined by the metabolic activity of its nearest neighbor in the periodic chart.

The factors affecting the absorption of a radioisotope are the following:

1. Distribution of the radionuclide within the body and its uptake in certain critical organs.
2. Nonhomogenous distribution of the nuclide even within the critical organ.
3. Biological half-life of the nuclide, which may vary with the patient's age and may be modified by disease or pathologic conditions. For example, variation in the excretion due to disease can influence the radiation dose.

The *effective dose equivalent* recognizes the varying sensitivity of different body tissues. Remember, the dose equivalent is calculated by multiplying the absorbed dose by the appropriate quality factor.

Three doses are critical:

1. The *total body dose*, which will determine the risk of leukemia.

2. The *dose to the critical organ*, due to susceptibility to radiation-induced cancer.

3. The *gonadal dose*, since this is a measure of genetic hazard.

The consequences of a dose are reduced if the radiation is spread over a period of time compared with a single acute exposure.

Radionuclides have three ways in which they enter the body:

1. Inhalation
2. Ingestion
3. Injection

In the process of ingestion, radionuclides may enter the oral cavity directly. However, a significant alternative means of entry is via the mucus formed, containing particulate matter taken in by the tracheo-bronchial tree. After ingestion, the material follows the normal path of the gastrointestinal tract. The radionuclides will be absorbed into the bloodstream (or lymphatic system) or expelled from the body.

In inhalation, there are three distinct regions which retain different-sized particles. The nasopharynx retains large particles, whereas the deep lung is reached by only the smallest of particles. The tracheo-bronchial tree retains particles of intermediate size. As in the gastrointestinal tract, the substances are eventually absorbed into the bloodstream of the organism.

Injection of radionuclides into the body can result from medical procedure or accident. Radionuclides are routinely injected for both diagnostic tests and radiation therapy. During work with radionuclides, injection is possible through trauma to the skin tissue.

Discrimination Ratio

To repeat an important point, the nuclides which are isotopes of natural elements in the body are metabolized the same as the natural element. For example, I, C, K, Na, Ca, and H are all metabolized as the natural, nonradioactive form of the element. For example, the radium ingested by the watch workers, which was described in Lesson 9, was metabolized like its nearest periodic table neighbor—calcium. Therefore, radium was deposited in the bone, as calcium would be in normal metabolism. However, the foreign nuclide is at a disadvantage when compared to the normal element relative to the number of atoms of the same element normally present in your body. The *discrimination ratio* describes the competition between a given radionuclide and its normally occurring stable isotopes.

Biological Half-Life

It is difficult to determine how much of a dose has been administered to a tissue for many reasons. There is a non-uniform distribution of the isotope in body organs. Once in the body, the isotope is undergoing radioactive decay. There are variable and organ-dependent rates of activity equilibrium for the isotope. There are two situations in which knowing the dose administered is important—use of radionuclides in medical diagnosis and administration of exposure to radionuclides in the environment. In these two cases, urine and feces assay are sometimes needed to determine the amount of a radionuclide present. From the assay, a model of the human metabolism of the element assayed can be used to estimate the internal dose.

In order to calculate the doses administered to the body, one needs to use the concept of *biological half-life*. As the formula states:

$$\frac{1}{T_{eff}} = \frac{1}{T_p} + \frac{1}{T_b}; \quad T_{eff} = \frac{T_p T_b}{T_p + T_b}$$

where T_{eff} = effective half-life
T_p = physical half-life
T_b = biological half-life

An example of a biological half-life is the excretion of tritium from humans. When irradiated water is ingested, the amount of tritium present in the urine decreased with a biological half-life of approximately 10 days when water uptake was normal (2.7 liter-day). Further work showed that this half-life is reduced to 2.4 days when water intake was increased to 12.8 l/day. Thus, the biological half-life can be modified by external factors.

To reiterate an imporatant basic point, the half-life is a unique feature of each isotope, as is the type of radiation emitted and the main energy of that radiation. Uranium-238 has the longest half-life and the lowest energy of gamma radiation. Long half-lives present problems to the nuclear power industry, which has to store or process these nuclear waste products without hazard to the public.

Radionuclides in Nuclear Medicine

Many radioisotopes have been used in various capacities in nuclear medicine techniques, including the following: Sodium-24 has been used to measure the circulation time of blood; Iodine-131 has been used to measure thyroid function, leading to a possible diagnosis of hypothyroidism or hyperthyroidism; Iodine-131 can also be used to diagnose both internal bleeding and fat malabsorption; Iron-59 is used to study the formation rate of red blood cells in people with disease (such as anemia) and in healthy people; Chromium-51 is useful in determining the length of red blood cell survival; Potassium-40, which concentrates in the muscle, can be used to measure the body's muscle mass.

Important Radionuclides

The lesson will now focus on several radionuclides of biological importance, many of which have caused malignancies in the previously-mentioned occupational groups.

1. *Tritium (^{3}H):*

   Tritium primarily is present as a result of nuclear weapon testing in the environment. Exposure most likely occurs by ingestion or inhalation of water containing tritium. This water then goes into the human soft tissue mass, possibly being integrated into cells. The biological hazards of tritium in water are low.

2. *Noble Gases - Krypton and Radon*

   These noble gases lack chemical reactivity, limiting any hazards as a result. They are soluble in body fat. Krypton is produced by the nuclear power industry. Radon is widely distributed in the environment, and as was shown in the previous lesson, can cause lung cancer. This is a frequent occurrence for uranium mine workers.

3. *Alkali Metals*

   Potassium, K, is present in all organisms; ^{40}K contributes to the background dose for humans. Cesium behaves as potassium, being absorbed from the gastrointestinal tract to muscle. It is present in the muscle of meat animals, which may be ingested by humans.

4. *Alkaline Earths*

   All these elements act as calcium and are concentrated in bone. Strontium, found in fission products, appears in food cycles where calcium-rich products such as milk and milk products are eaten.

5. *Radium*

   All the decay products of radium are found in the earth's crust (U, Ra, Pb). Ingestion of radium leads to sarcomas of bone, as shown by the experience of the radium dial painters. Treatments with radium in the past led to bony tumors.

6. *Halogens - Iodine*

   Iodine radionuclides are produced by the fission of uranium or plutonium. In nuclear accidents, it is released as a gas and moves rapidly through the food chain as iodine fallout on forage for cows, where it then concentrated in milk, and the milk is then ingested by humans. Iodine has a half-life of only 8 days, so its hazard due to release is short-lived. In the body, iodine is concentrated in the thyroid. To prevent malignancy, a potassium iodide salt is given to compete with radioactive iodine for incorporation in the thyroid. Radioactive iodine-131 is widely used in the treatment of hyperthyroidism, the major benign disease for which radiation is the treatment of choice.

7. *Uranium*

   Uranium, which occurs naturally in the earth's crust, is a nephrotoxic agent, producing severe kidney damage.

8. *Plutonium*

   Plutonium is a man-made element first synthesized by the Manhattan Project. It has been ingested by humans in the past in controversial experiments. Plutonium enters the body by inhalation of aerosols containing the element. It settles in the deep lung or may be deposited in bone. No plutonium-related disease has yet been found in humans.

Radiotoxicity

The radionuclides described above each have different effects on the body, that is, they have different radiotoxicities. The radiotoxicity of the radionuclide depends on the following four factors:

1. energy and type of radiation emitted by isotopes

2. physical half-life of isotopes

3. biological half-life of isotopes

4. whether localized concentration of isotopes occurs in critical organs of the body.

Because internally deposited radioactive isotopes may be accumulated selectively in critical organs, the actual radiation dose will depend upon this factor, as well as the half-life, energy, and type of radiation emitted.

Using the four factors, some of the radionuclides mentioned in this lesson can be placed in the following three levels of toxicity:

Very Toxic:	Ca, Sr, I
Moderately Toxic:	P, S, Fe, Co, Cs
Slightly Toxic:	H, C, Na, K

Calcium and strontium radionuclides are very toxic because they concentrate in bone and have a low turnover rate, i.e., long biological half-life. Likewise, the radioisotope of iodine concentrates in the thyroid. The radionuclides of hydrogen and sodium are among the least toxic because of their high turnover rate and elimination from the body.

These factors can be changed drastically when a radionuclide is used as a label in a biologically active compound. For instance, if ^{14}C-labeled purine is ingested, it will be incorporated in the DNA and RNA. It will have a much longer biological half-life than free ^{14}C, and, when the labeled ^{14}C does finally decay, the damage to the organism will be much greater.

Lastly, a useful concept for the reporting of internal contamination is the committed dose. The *committed dose* is defined as:

$$\int_{t_0}^{t_0+\Delta} D_1(t)\,dt$$

where $D(t)$ is the dose rate for the radionuclide at a given time t, T_0 is the initial date of exposure, and Δt is the time from the initial exposure until the life expectancy of the exposed individual. For current regulations, the committed dose is calculated from the time of exposure to the expected end of life.

An example of this is an exposure to tritium, which has an initial internal dose of 2.0 rem/day. The biological half-life for tritium is 7 days. The committed dose is then

$$\int_{t_0}^{t_0+\Delta t} 2.0\,\frac{rem}{day}\,\exp(-\ln(2)\left(\frac{1}{7\ days}+\frac{1}{(14\ y)(365.25\ day/y)}\right))t\,dt$$

The integral is then easily solved for the Δt of the remaining life expectancy of the exposed individual.

Summary

In summary, radionuclides are an important component of nuclear medicine. The properties of the specific radionuclide, such as half-life and distribution properties, determine the use of the radionuclide in therapy. Radiotoxicity of the element is a critical factor in the use of the radionuclide. Critical organ dose, total body dose, and gonadal dose are values used to limit adverse effects to the patient.

- Radionuclides have three methods to enter the body—inhalation, ingestion, and injection.
- Radionuclides differ in their metabolism from their stable counterparts.
- Radionuclides have different radiotoxicities, depending on the biological and physical half-life, location of concentration, and type of radiation emitted.
- Many of the radionuclides have disastrous effects on an organism, such as cancer and kidney damage.
- Total body dose, critical organ dose, and gonadal dose are all critical values in nuclear medicine.
- Nuclear medicine is a new field in comparison to the older field of radiation therapy.

WRITING ASSIGNMENT - Lesson 11

Complete and submit the following assignment.

Vocabulary

Please write the term and its definition on your paper. Your definition should be in your own words and limited to one or two sentences.

radionuclide	radium	committed dose
discrimination ratio	plutonium	effective dose equivalent
biological half-life	uranium series	gonadal dose
tritium	physical half-life	critical organ

Questions

All of the questions below are short essay. Please try to keep your answers to one page or less.

1. What are the three ways in which radionuclides can enter the body?

2. Why do scientists use the concept of biological half-life?

3. What determines how specific radionuclides are metabolized?

4. Why is it dangerous to humans if a cow eats a radionuclide of an alkali metal?

5. Why are noble gas radionuclides not quite as reactive as other radionuclides?

6. Why does one ingest potassium iodide when exposed to radioactive iodine isotopes?

7. What are the usual uses for the following radionuclides: krypton, sodium, barium, strontium, xenon, and tritium?

8. What is the largest source of natural radiation? How does one handle and lessen the effects from this source?

9. What are some of the consumer products which lead to man-made background radiation? How can one lessen their effects?

10. Why are strontium and iodine much more damaging to the body than tritium?

11. What are the three critical values in nuclear medicine?

12. How does the concept of internal terrestrial exposure relate to radionuclide concepts?

LESSON 12

Course Paper

At this point, you should have written your course paper, following the format suggested by your mentor in response to your assignment in Lesson 3. Remember that the grade for this paper counts 10 percent of your course grade. Present your work in a neat, well-organized fashion and double-check your spelling and grammar. Make and keep a copy of your paper before you mail it, in case of a postal service problem.

Final Examination Information

The final examination will cover all the course material. The format will include both multiple choice questions and a series of questions each requiring a short answer.