Radiation Biology (MPHY 5172)

9/5/2024

Housekeeping Issues

- **Instructors**
  - Jianling Yuan, yuanm033@umn.edu
  - Lindsey Sloan, sloan153@umn.edu

Classic radiobiology
Clinical application

Cancer Biology
Chemotherapy and Immune Therapeutics

Syllabus

Date		Content	Lecturer
9/5	Th	Chapter 1: Physics and Chemistry of Radiation Absorption	Yuan
9/9	M	Chapter 2: Molecular Mechanisms of DNA and Chromosome Damage and Repair (I)	Yuan
9/12	Th	Chapter 2: Molecular Mechanisms of DNA and Chromosome Damage and Repair (II)	Yuan
9/16	M	Chapter 3: Cell Survival Curves (I)	Yuan
9/19	Th	Chapter 3: Cell Survival Curves (II)	Yuan
9/23	M	Chapter 4: Radiosensitivity and Cell Age in the Mitotic Cycle Chapter 22: Cell, Tissue, and Tumor Kinetics (I: Cell Cycle)	Yuan
9/26	Th	Chapter 5: Repair of Radiation Damage and the Dose-Rate Effect	Yuan
9/30 (ASTRO)	M	Chapter 6: Oxygen Effect and Reoxygenation	Yuan
10/3	Th	Chapter 7: Linear Energy Transfer and Relative Biologic Effectiveness Chapter 25: Alternative Radiation Modalities	Yuan
10/7	**M**	**Exam 1 (Covers material up till 10/3; 30%)**	Yuan
10/10	Th	Cancer Biology (I)	Sloan
10/14	M	Cancer Biology (II)	Sloan
10/17	Th	Cancer Biology (III)	Sloan
10/21	M	Chemotherapy & Immune Therapeutics (I)	Sloan
10/24	Th	Chemotherapy & Immune Therapeutics (II)	Sloan
10/28	M	Chapter 8: Acute Radiation Syndrome	Yuan
10/31	Th	Chapter 9: Medical Countermeasures to Radiation Exposure Chapter 11: Heritable Effects of Radiation	Yuan
11/4	M	Chapter 10: Radiation Carcinogenesis	Yuan
11/7	Th	Chapter 12: Effects of Radiation on the Embryo and Fetus Chapter 13: Radiation Cataractogenesis	Yuan
11/11	**M**	**Exam 2 (Covers Chapters 8-13; Sloan Content; 30%)**	**Yuan/Sloan**
11/14	**Th**	Chapter 19: Dose-Response Relationships for Model Normal Tissues	
11/18	M	Chapter 20: Clinical Response of Normal Tissue (Lecture I)	Yuan
11/21	**Th**	Chapter 20: Clinical Response of Normal Tissue (Lecture II)	Yuan
11/25	M	Chapter 21: Model Tumor Systems Chapter 22: Cell, Tissue and Tumor Kinetics (II)	Yuan
11/28	Th	**Happy Thanksgiving! No Class**	
12/2	M	Chapter 23: Time, Dose and Fractionation in Radiotherapy (I)	Yuan
12/5	Th	Chapter 23: Time, Dose and Fractionation in Radiotherapy (II)	Yuan
		The Possibilities of the Perils	
12/9	M	Chapter 26: The Biology and Exploitation of Tumor Hypoxia	Yuan
12/12	Th	Self-Study	
12/16	**Th**	**Exam 3 (Cumulative; 40%)**	**Yuan/Sloan**

ABR Exam – Medical Physics

ABR | American Board of Radiology

Initial Certification for Medical Physics

Part 1 Exam

Last verified on June 5, 2023

The first exam candidates will take is the Part 1 computer-based exam, which consists of a general exam section and a clinical exam section. Both are based on the expected knowledge of a second-year graduate student. The two sections can be taken at different times. For example, a candidate who is prepared for the general section may take it first and postpone taking the clinical section until a later administration.

The general exam section focuses on medical physics at the level of common graduate courses. The clinical exam section focuses on anatomy, medical terminology, and physiology at the level of an introductory course taught in a college of health sciences, as well as radiobiology at the level of an introductory graduate course. The exam also includes ethics and professionalism at the level of the RSNA-AAPM Ethics and Professionalism modules.

ABR Exam – Medical Physics

Part 1: Qualifying - General & Clinical

Day	Session	Number of Questions	Exam Time	Tutorial / Practice (minutes)	Total Exam Time	Break Time[1] (minutes)	Total Time[2]
1	General	130	4 hours and 1 minute	20	4 hours and 21 minutes	25	4 hours and 46 minutes
Required intermission (60 minutes)							
1	Clinical	80	2 hours and 28 minutes	N/A	2 hours and 28 minutes	15	2 hours and 43 minutes
	All	210					8 hours and 29 minutes

[1]You may take more break time; however, your exam time will continue to count down.

[2]This is the total allotted time for the exam. Your total exam time may be less.

ABR Medical Physics Part I Content Guide

- **Radiation Biology**
  - Physics and chemistry of radiation interactions with matter
  - Molecular and cellular radiobiology
  - Tumor radiotherapy
  - Normal tissue response to radiotherapy
  - Time dose fractionation
  - Radiobiological basis of radiation protection
  - Radiation accidents and environmental radiation exposure
  - Diagnosis and medical management of radiation syndromes
  - Deterministic effects
  - Stochastic Effects
  - Radiation carcinogenesis
  - Heritable radiation effects
  - Effects on the developing embryo

On exam 2 and 3, there may be different versions of the cancer biology questions for physics students

Alternatively, there may be additional questions for rad onc residents

ABR Medical Physics Part I Sample Questions

A fetus receives a dose of 2 Gy during weeks 20 to 39 pregnancy. After birth, the child has an increased risk for what condition?

A. Trisomy 21
B. Leukemia
C. Microcephaly
D. Neonatal death

For ionizing radiation, how does the OER vary as LET increases from 1 to 100 KeV/μm?

A. Increases
B. Decreases
C. Remains the same
D. Increases then decreases
E. Decreases then increases

https://www.theabr.org/medical-physics/initial-certification/part-1-exam/content-guide

ABR Exam – Medical Physics

How do I log in to the Exam Readiness Check?

Log in to https://myabr.theabr.org. You will see an option to start the Exam Readiness Check. You will also be sent an authenticated link via email when you register for an exam that will take you directly to the Exam Readiness Check.

Where are the answers to the Sample Questions?

The Answer Key for the Sample Questions can be found here.

What is the point of the Exam Readiness Check and Sample Questions?

The Exam Readiness Check and Sample Questions provide an opportunity for candidates to familiarize themselves with the exam interface and navigation before their exam day. Completing the Exam Readiness Check is important to fully understand the functionality of the exam interface including case navigation, flagging questions, using the image manipulation tools, starting/ending a break, and question content blocking.

How many Sample Questions are provided?

There are 30 Sample Questions.

ABR Exam – Rad Onc Residents

Residents have the option to take the Medical Physics for Radiation Oncology and the Radiation and Cancer Biology parts of the Qualifying Exam at any time after completing 32 months of residency training. With written approval of their program director, this option may be exercised after completion of **24** months of residency. Residents who wish to take the exam early should have their program reach out to the ABR. Residents may take the Clinical Radiation Oncology part of the Qualifying Exam at any time after completion of 44 months of residency.

ABR Rad Onc Residents Exam

2025

Description	Date	Location	Application Period	Registration Opens
Oral Certifying Exam	Week of April 6	Remote	PGY-2	December 2024
Clinical Qualifying Exam	May 15	Remote	PGY-2	February 2025
Biology and Physics Qualifying Exam	June 26	Remote	PGY-2	April 2025
Oral Certifying Exam	Week of October 19	Remote	PGY-2	July 2025

2025 JUNE

SUNDAY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY
1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19 ☆	20 ☆	21
22	23 ☆	24 ☆	25 ☆	26	27	28
29	30					

www.calendar-to-print.com

☆ Protected study time

Radiation and Cancer Biology Exam

Day	Session	Number of Questions	Exam Time	Tutorial / Practice (minutes)	Total Exam Time	Break Time[1] (minutes)	Total Time[2]
1	Biology	100	1 hour and 49 minutes	20	2 hours and 9 minutes	10	2 hours and 19 minutes

[1]You may take more break time; however, your exam time will continue to count down.

[2]This is the total allotted time for the exam. Your total exam time may be less.

ABR Study Guide

I. Interaction of radiation with matter	1% to 4%
II. Molecular and cellular damage and repair	13% to 17%
III. Cellular response to radiation	7% to 10%
IV. Linear energy transfer (LET) and oxygen effect	3% to 5%
V. Tumor biology and microenvironment	3% to 5%
VI. Cancer biology	19% to 23%
VII. Radiobiology of normal tissues	9% to 12%
VIII. Dose delivery	11% to 15%
IX. Combined modality therapy	11% to 15%
X. Late effects and radiation protection	6% to 9%

The ranges above are those generally in effect for the exam to be administered in 2020 and are intended only for guidance in candidate preparation. They do not necessarily represent a precise number of scorable items.

VI. Cancer biology

a. Cell and tissue kinetics
  i. Methods to assess cell cycle kinetics
  ii. Proteins involved in cell cycle control and checkpoint initiation (e.g., CDKs, cyclins, CDK inhibitors)
  iii. Phases of cell cycle and radiation sensitivity
  iv. Cell cycle arrest and redistribution after irradiation

b. Molecular signaling
  i. Main signaling pathways and critical proteins involved (e.g., PI3K/AKT, RAS/ERK, TGF-β, Wnt, Notch, NFkB)
    a) Receptors/ligand (e.g., EGFR, VEGFR, c-MET, HER2, FGFR, ALK)
    b) Kinases
      1). Definition of kinases (e.g., STKs, TKs/RTKs, DSKs)
      2). Common kinases in cancer (e.g., ATM, ATR, Chk1, Chk2, PI3K, MAPK) and corresponding phosphatases (e.g., PTEN)
  ii. Molecular signaling pathways activated by IR
  iii. Transcription factors involved in cancer regulation (e.g., MYC, TP53 and associated proteins)
  iv. Cell death pathways and main associated players
    a). Intrinsic vs extrinsic apoptosis (caspases)
    b). *BCL-2* family member proteins (pro- vs anti-apoptotic)

c. Mechanisms of cancer development
  i. Hallmarks of cancer and how they could affect 4/5 Rs of radiobiology
  ii. Common oncogenes (e.g., *HER2/neu*, *Ras*, *Myc*) & tumor suppressors (*Rb, p16, p53, BRCA1/BRCA2, APC, NF1*)
  iii. Telomeres and pathways in cancer to overcome telomere shortening (e.g., TERT promoter mutations and alternative lengthening of telomeres [ALT])
  iv. Signaling abnormalities and association with treatment response
  iv. Cancer as a genetic disease
  v. Multistep nature of carcinogenesis
  vi. Signaling abnormalities in carcinogenesis
  vii. Prognostic and therapeutic significance of tumor characteristics

d. Cancer genetics/genomics
  i. Types of epigenetic regulation (e.g., DNA methylation (DNMTs/TETs), histone modifications (e.g. HDACs/HATs), chromatin remodelers)
  ii. Main epigenetic alterations (e.g., CpG island methylator phenotype [CIMP]) in cancer
    a). *IDH1/2* mutations in glioma and AML
    b). *TET2* mutations in AML
  iii. Epigenetic targets in cancer (DNMTi, HDACi, IDHi, EZH2i)
  iv. Omics approaches in cancer (next-gen sequencing/arrays) and newer methods (ctDNA)
  v. Biomarkers in cancer (e.g., BCR-ABL, EGFR, ALK)
  vi. Molecular profiling of cancer

https://www.theabr.org/radiation-oncology/initial-certification/the-qualifying-exam/studying-for-the-exam/radiation-cancer-biology

ABR Exam Results

Physics Students

Part 1 – Clinical

First-Time Takers Enrolled in a CAMPEP Program

Exam Dates[1]	Percentage Passed	Total Examinees
2015	73	199
2016	71	239
2017	64	219
2019	79	190
2020[2]	69	182
2021	64	94
2022	73	117
2023[3]	75	361

[1]Numbers from the 2018 exam are not available because of an inconsistency in the test administration.

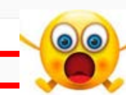
[2]Results include December 2020 and April 2021 administrations.

[3]Results include January 2023 and August 2023 administrations.

Radiation Oncology Residents

Biology

Year	Percentage Passed	Total Examinees
2016	94	192
2017	89	203
2018	74	206
2019	99	211
2020[1]	99	295
2021	97	149
2022	95	203
2023	93	209
2024	100	203



[1]Results include December 2020 and April 2021 administrations.

ARRO Lectures

- About ARRO
- Latest News
- Resident Resources
  - Educational Resources
    - ARRO's Favorite Resources
    - Webinars
    - ARROCase
    - ARRO Book Club
    - Image Challenge
  - Board Certification
  - Career Center
  - Funding Opportunities
- Global Health

Radiation Biology and Physics

On this page are lectures by experts in Radiation and Cancer Biology and Physics to help residents learn these critical subjects and pass the qualifying examinations for board certification. Stay tuned as we develop this series!

Gayle E Woloschak, PhD
Associate Dean for Graduate Student and Postdoctoral Affairs
Professor of Radiation Oncology and Radiology
Pronouns: she, her, hers

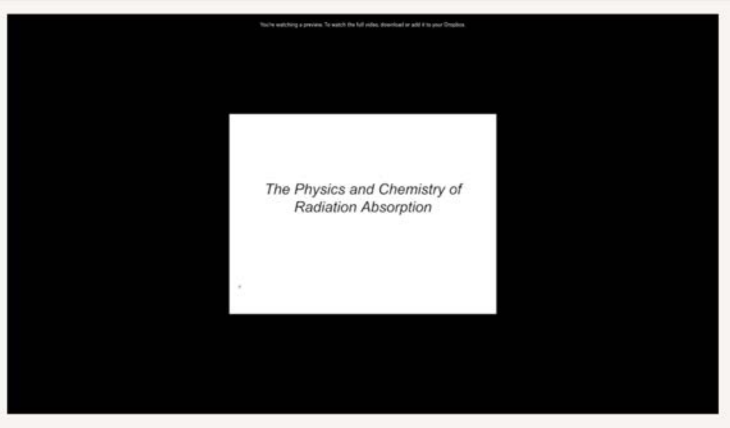
Radiobiology Lectures

2020 Review Videos

- Cancer Biology by Pippa Cosper, MD, PhD
- History of Time-Dose Relationships by Elaine Zeman, PhD

Chicago Radiobiology Course by Gayle Woloschak, PhD (2020-2021)

Lecture Number	Lecture Subject	Year
Lecture 1	The Physics and Chemistry of Radiation Absorption	2020-2021
Lecture 2	DNA Strand Breaks and Chromosomal Aberrations	2020-2021
Lecture 3	Cell Survival Curves	2020-2021
Lecture 4	Radiosensitivity and Cell Age in the Mitotic Cycle	2020-2021
Lecture 5	Repair of Radiation Damage and the Dose-Rate Effect	2020-2021
Lecture 6	The Oxygen Effect and Reoxygenation	2020-2021
Lecture 7	LET and RBE	2019-2020
Lecture 8 (Part 1)	Acute Effects of Total Body Radiation	2020-2021
Lecture 8 (Part 2)	Radiologic Terrorism	2020-2021
Lecture 9	Radioprotectors	2020-2021
Lecture 10	Radiation Carcinogenesis	2020-2021
Lecture 11	Hereditary Effects of Radiation	2020-2021
Lecture 12	Effects of Radiation on Embryo and Fetus	2020-2021
Lecture 13	Radiation Cataractogenesis	2020-2021



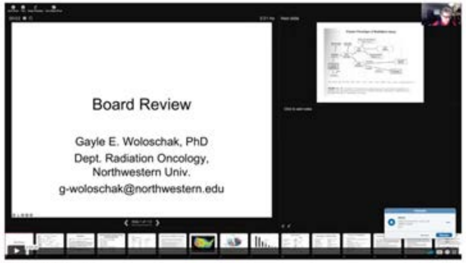
You can watch videos and download mp3

2023 Review Videos

- O2 Effect and Tumor Hypoxia (Part One) by Elaine Zeman, PhD
- O2 Effect and Tumor Hypoxia (Part Two) by Elaine Zeman, PhD

High-Yield Radiobiology Board Review by Gayle Woloschak, PhD

- 2019 - Radiation and Cancer Biology: A High Yield Review
- 2020 - High-yield radiobiology lecture by Gayle Woloschak, PhD
- 2022 - High-yield Radiation Biology Board Review by Gayle Woloschak, PhD



Board Review 2022

https://www.astro.org/Affiliate/ARRO/Resident-Resources/Educational-Resources/Webinars/Radiation-Biology-and-Physics

ASTRO Study Guide

2023 ASTRO
RADIATION AND CANCER BIOLOGY
STUDY GUIDE

Produced by the Radiation and Cancer Biology
Study Guide Task Force

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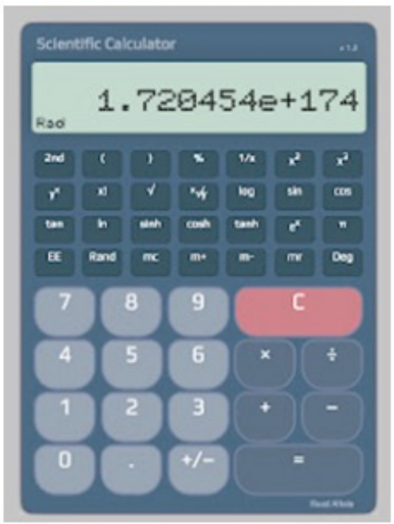
Study guide from last few years on Canvas

Table of Contents

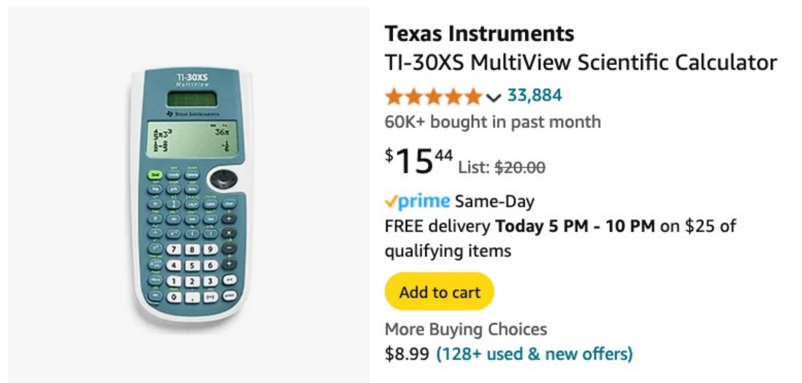
ABR Exam Calculator

For the convenience of our candidates, a calculator is included in the exam interface.



Embedded calculator

For the purpose of the in-class exams, a scientific calculator is required



Using smart phone during exam is NOT allowed!!!

Chapter 1

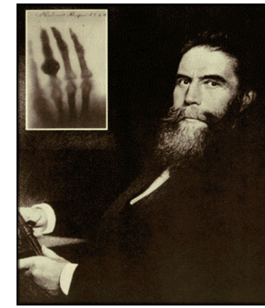
Physics and Chemistry of Radiation Absorption

Outline

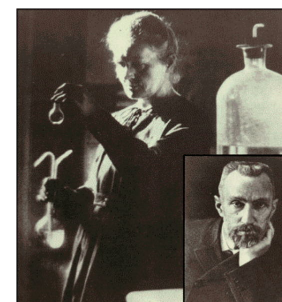
- Brief Historical Overview
- Examples of clinical application of radiation biology
- Types of Ionizing Radiations
  - Electromagnetic Radiations
  - Particulate Radiations
- Absorption of X-rays
- Direct and Indirect Action of Radiation
- Absorption of Neutrons, Protons and Heavy Ions

Milestones in History of Radiation Physics

- ???? – Roentgen discovered X-ray
- 1896 – Becquerel discovered radiation emitted by uranium compounds
- 1898 – Pierre and Marie Curie isolated the radioactive elements polonium and radium



Wilhelm Conrad Roentgen
(1845-1923)



Pierre Curie (1859-1906)
Marie Curie (1867-1934)

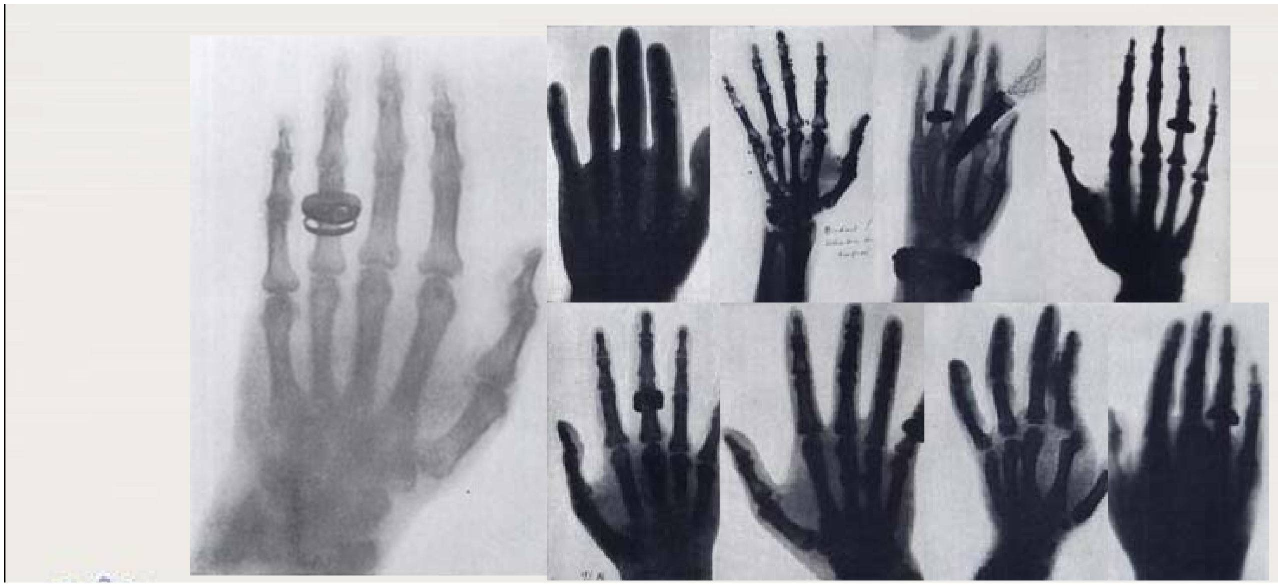
Wilhem Röentgen & First X-rays

Wilhelm Conrad Roentgen
(1845-1923)

Left hand of his wife Anna Bertha Ludwig

First publically taken radiograph (hand of a prominent Swiss professor of anatomy. Jan 1896)

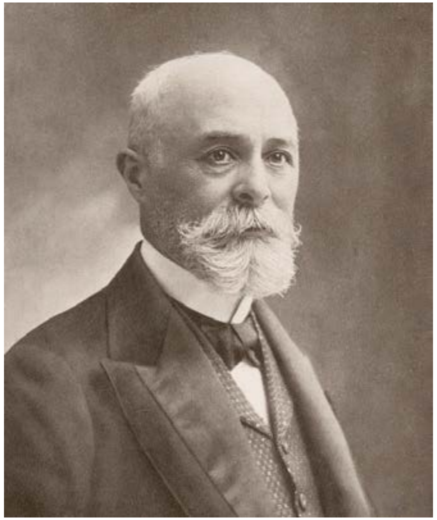
Many Unnecessary Exposures

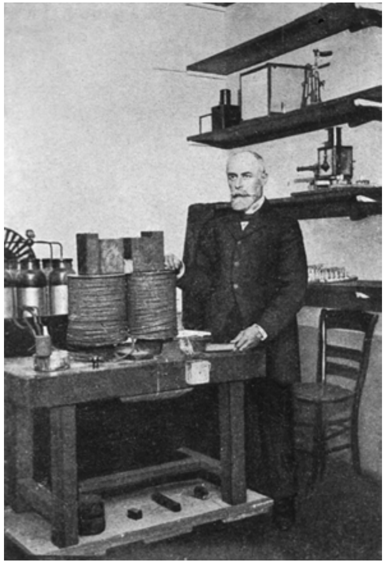


Ola Holmberg, Ph.D.
Head, Radiation Protection of Patients Unit
Radiation Safety and Monitoring Section
Division of Radiation, Transport and Waste Safety
International Atomic Energy Agency
Vienna, Austria

IAEA
International Atomic Energy Agency

Antoine Henri Becquerel (1852-1908)





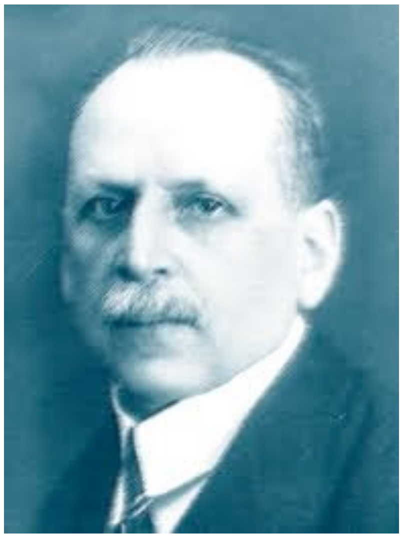
- French physicist
- Discovered radioactivity along with Marie Curie and Pierre Cure
- All three won the 1903 Nobel Prize in Physics
- The SI unit for radioactivity, the Bq, is named after him

First Medical Use of X-ray

- 1896 – X-ray was used to locate a broken part of a knife in a drunken sailor → **Diagnostic Radiology**

- 1896 – Leopold Freund demonstrated the disappearance of a hairy mole following treatment with x-rays → **Therapeutic Radiology**

Leopold Freund (1868-1943)



- Austrian-Jewish radiologist
- Founder of medical radiology and radiotherapy
- The first physician known to have used ionizing radiation for therapeutic purposes
- Successfully treated a 4 yo patient in Vienna suffering from **hairy moles** covering her whole back
- The case was published by the girl's local physician in 1901

Picture taken at age 74

- Skin scarring
- Keratosis

} Skin/soft tissue

- Kyphosis
- Osteoporosis

} Skeletal

What could be another significant late effect?

Early Medical Use of X-rays

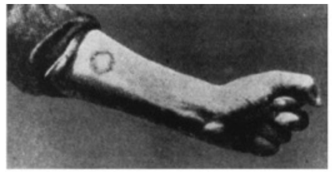
- **1896** – Emil Grubbe, a Chicago electrician and metallurgist, first treated the recurrent breast cancer of a 55-year-old woman
- **1898** – William Pusey reported beneficial effects on hypertrichosis and acne
- **1898** – Leopold Freund pioneered the use of the x-rays in pediatric nevus and lupus vulgaris
- **1901** – Frands Williams published on the X-ray cure of a cancer of the lower lip

Heber Robarts editor could list over 100 different surface and deep-seated conditions treated by 1902

Early Recorded Biologic Effect of Radiation

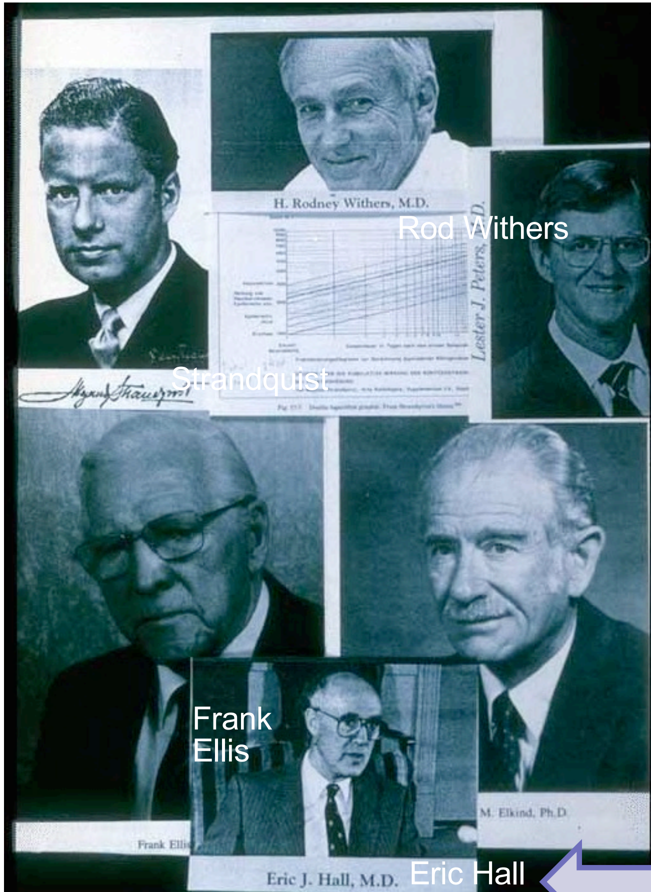
the removal of hair by the roots

- **1896** – Becquerel reported skin erythema caused by radium left in vest pocket
- **1896** – John Daniel described scalp epilation during a diagnostic exposure
- **1901** – Pierre Curie deliberately produced a radium "burn" on his forearm

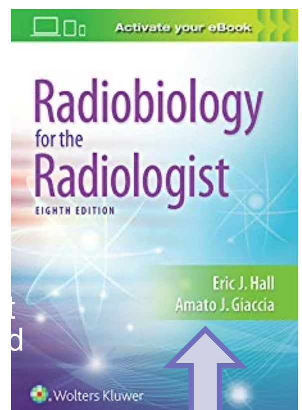


Radiobiology = the study of the action of **ionizing radiations** on **living things**

Contemporary Radiobiologists



Some of the 20th century radiobiologists whose work advanced our understanding of radiation biology and formed the basis of modern radiotherapy



Outline

- Brief Historical Overview
- Examples of clinical application of radiation biology
- Types of Ionizing Radiations
  - Electromagnetic Radiations
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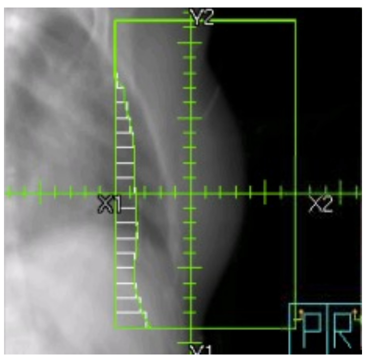
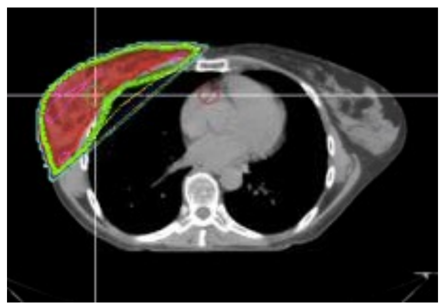
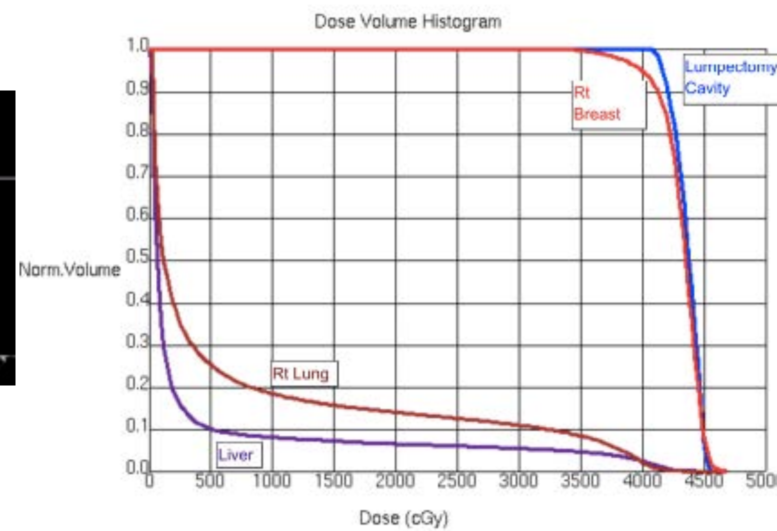
Case 1

- 60 yo female w/ early-stage breast cancer
- Underwent surgery and radiation therapy, completed July 2013



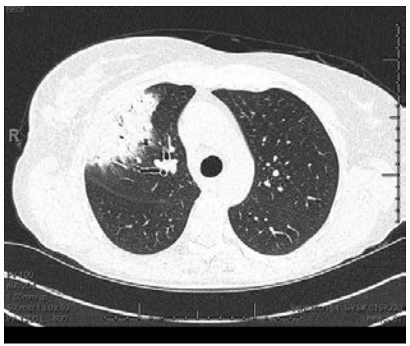


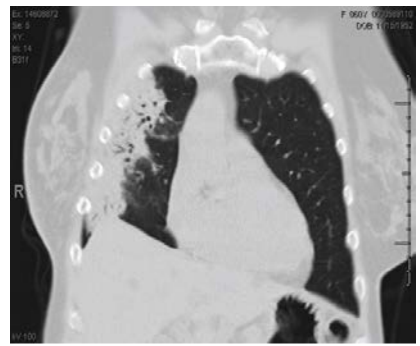


4240 cGy / 16 fx + 1000 cGy / 4 fx boost

Oct 2013 (3 mo after Radiation)

- Dry cough, fever 100.8°F, chest tightness
- Symptoms did not improve with antibiotics





Radiation Pneumonitis

What are the factors predisposing this lady to developing radiation pneumonitis?

What are the underlying mechanism of radiation lung injury?

Are there any predictive assays that may allow us to identify the subset of patients with such predisposition?

Preview

chapter 20 | **Clinical Response of Normal Tissues**

Lungs

The lung is an intermediate- to late-responding tissue. Two waves of damage can be identified: acute pneumonitis at 2 to 6 months after treatment, and fibrosis, which may develop slowly over a period of several months to years. The only symptom of early acute pneumonopathy may be an opacity on a chest x-ray, although it may be accompanied by functional signs, including cough, dyspnea, and respiratory difficulties. Progressive pulmonary fibrosis develops in most patients, including those who previously were asymptomatic, beginning about a year after irradiation.

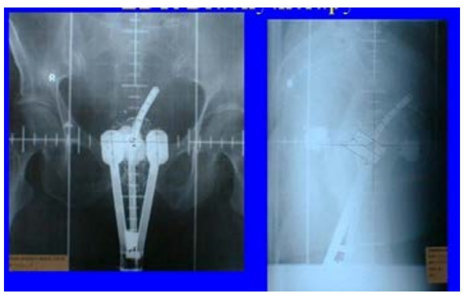
Difficulties in respiratory function increase in severity with time and are generally irreversible. Their severity depends on three factors: volume irradiated, dose, and fraction size. The lung is particularly sensitive to fractionation, with an α/β estimated to be about 3 Gy. The most likely target cells are the pulmonary endothelial cells and the type II pneumocytes (cells of the alveolar wall). Type II cells are associated with the production of surfactant during the first few days after irradiation.

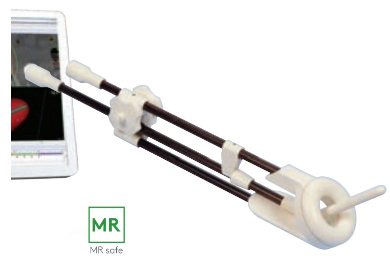
The lung is among the most sensitive of late-responding organs. The FSU in the lung is the pulmonary lobule, consisting of the terminal bronchioli and respiratory parenchyma that it serves. The FSUs are arranged in parallel, with a large number of bronchi and alveoli working together; consequently, volume as well as dose are important. Because of this organization of the FSUs, the lung is only dose limiting if large volumes are irradiated and if the remaining lung is not capable of providing adequate function.

Pulmonary damage also may occur following the use of chemotherapy agents, notably bleomycin, cyclophosphamide, and mustine. Combining radiation with these drugs reduces lung tolerance.

Case 2

- 47 yo F with FIGO IIB cervical cancer treated with definitive chemoradiotherapy with brachytherapy boost





$EQD2 = D \times [(d + \alpha/\beta)/2 + \alpha/\beta]$

D = Total dose
d = dose per fraction
α/β = 3 (late normal tissue)
α/β = 10 (tumor)

EBRT, dose to ICRU 52 point or median dose in case of IMRT	Fractionation to point A (Gy)	EQD2 (Gy) to the tumor (point A dose with α/β = 10 Gy)[a]
25 × 1.8 Gy	4 × 7 Gy	83.9
25 × 1.8 Gy	5 × 6 Gy	84.3
25 × 1.8 Gy	6 × 5 Gy	81.8
25 × 1.8 Gy	5 × 5.5 Gy	79.8

What is α/β ?

How do you calculate BED and EQD2?

Preview

chapter 23 **Time, Dose, and Fractionation in Radiotherapy**

The quantity E/α is the **biologically effective dose (BED)** and is the quantity by which different fractionation regimens are intercompared. In words, the final equation is

$$\text{BED} = (\text{total dose}) \times (\text{relative effectiveness})$$
$$\frac{E}{\alpha} = (nd) \times \left(1 + \frac{d}{\alpha/\beta}\right)$$

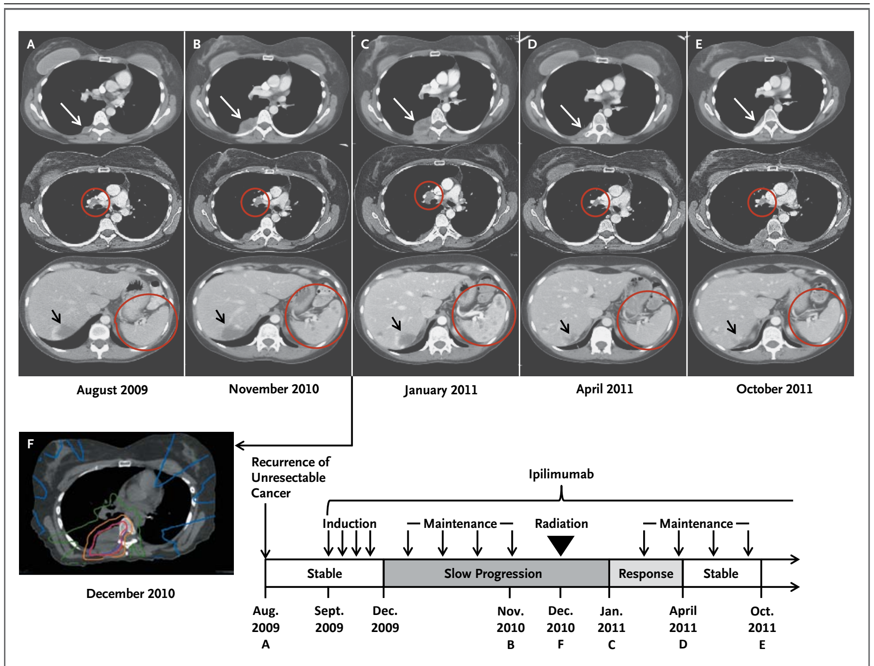
The quantity BED was first suggested by Barendsen but was popularized by Fowler.

Immune Checkpoint Therapy

December 2015

Jimmy Carter announced this week he is free of melanoma.
In addition to surgery and radiation, Mr. Carter was treated with a new immunotherapy drug called ***pembrolizumab.***

Abscopal Effect

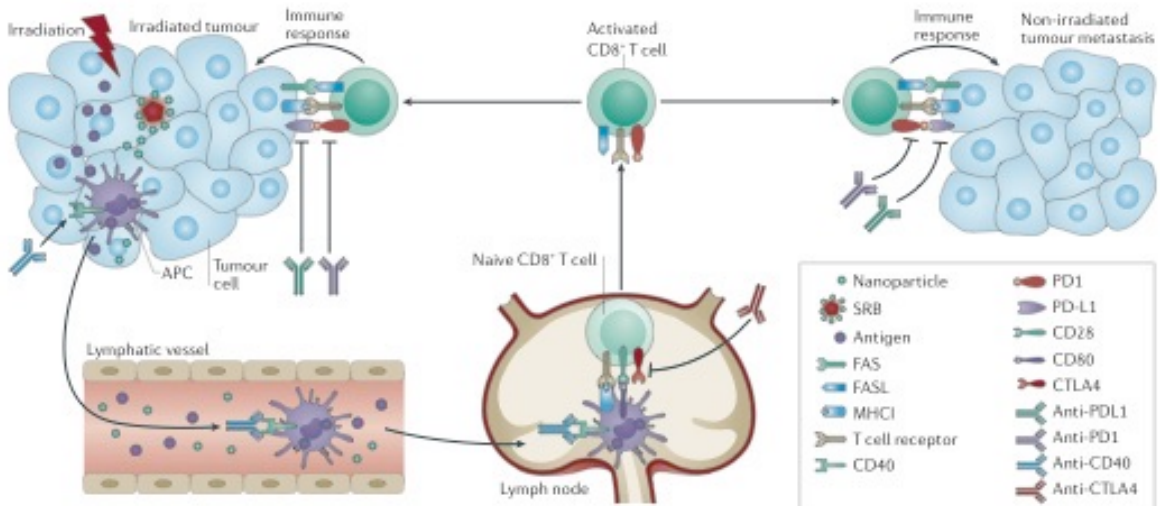


The patient had a response in hilar nodes and spleen after localized radiotherapy to paraspinal mass while receiving ipilimumab

Abscopal effect is a phenomenon in which local radiotherapy is associated with the regression of metastatic cancer at a distance from the irradiated site

Postow 2012; NEJM 366:925-931

Mechanism of the Abscopal Effect



The use of smart radiotherapy biomaterials (SRBs) and nanoparticles provides promising avenues to boost abscopal response rates.

- Radiation generates neoantigens from tumor cells.
- Antigens from damaged tumor cells can be taken up by antigen-presenting cells (APCs), which travel to the lymph node to prime the T cell-mediated abscopal effect.
- Activated T cells directed against tumor-specific antigens then infiltrate the primary tumor and non-irradiated tumor metastases.

Preview

ABR Study Guide

c. Immune therapeutics
   i. Types of immunotherapy treatments in oncology
      a) Monoclonal antibodies (MABs)
      b) Checkpoint inhibitors
      c) Cytokines
      d) Vaccines
      e) Adoptive cell transfer types (chimeric antigen receptors [CARs], tumor infiltrating lymphocytes [TILs], and T cell receptors [TCRs])
   ii. Combination of immune therapies and radiation
      a) Recently published trials (e.g., PACIFIC, KEYNOTE)
      b) Known predictors of response/biomarkers

Dr. Sloan will present most up to date information on these topics.

Types of Immunotherapy Treatments in Oncology

	Immunotherapy	Key Features
Vaccines	Whole tumor	◆ Tumor lysates contain all known and unknown tumor antigens ━ Poorly immunogenic, lots of overlap with normal cells Refs 58 - 66
Vaccines	Peptide	◆ Known specificity for tumor-associated antigen ━ HLA-restricted, small number of responding T cells Refs 67 - 80
Vaccines	Virus	◆ Known specificity for tumor-associated antigen and naturally immunogenic ━ Toxicity (cytokine storm) Refs 81 - 87
Vaccines	Dendritic cell (DC)	◆ Known specificity for tumor-associated antigen and can generate its own immune response ━ Preparation cost and time Refs 88 - 95
Cells	Adoptive cell therapy (ACT)	◆ Bypasses need to generate immune response, highly tumor specific ━ Preparation cost and time, target dependent toxicity (e.g. colitis) Refs 96 - 105
Abs	Checkpoint Inhibitors	◆ Targets immunosuppresive pathways allowing for greater anti-tumor immune response ━ Toxicity (e.g. autoimmune dermatitis, colitis) Refs 110 - 115

(Markman and Shiao 2015)

Cytokines for Therapy

Table 2 | **Cytokines as cancer therapy**

Cytokine	Therapeutic actions	Clinical administration	Phase of clinical trials	References*
IL-2	Enhances NK cell and CD8+ T-cell function; increases vascular permeability	Systemic, local	III	67,68,118,119
IL-3	Enhances tumour antigen presentation	Systemic	II	120
IL-4	Enhances eosinophil function and T-cell activation	Systemic, local	I	121,122
IL-6	Enhances T-cell and B-cell function; inhibition of IL-6 reduces lymphoproliferation	Systemic, local	I	123
IL-7	Enhances T-cell function	Local	I	124
IL-10	Inhibits tumour antigen presentation	Pending		125
IL-12	Enhances T_H1 immunity and cytotoxicity; inhibits angiogenesis	Systemic, local	I–II	126
IL-13	Inhibits cytotoxicity against viral neoplasms	Pending	–	127
IL-15	Enhances cytotoxicity	Pending	–	128
IL-18	Enhances T_H1 immunity and cytotoxicity; inhibits angiogenesis	Pending	–	129
M-CSF	Enhances macrophage function	Systemic	I–II	130
GM-CSF	Enhances tumour antigen presentation	Systemic, local	II–III	79
IFN-α	Enhances tumour antigen presentation and cytotoxicity	Systemic	III	131
IFN-γ	Enhances tumour antigen presentation and cytotoxicity	Systemic, local	III	30
TNF-α	Induces tumour-cell apoptosis; activates endothelium and granulocytes	Systemic	III	132
TRAIL	Induces tumour-cell apoptosis	Pending	–	133
FLT3 ligand	Stimulates dendritic-cell and NK-cell function	Systemic	I–II	134
Lymphotactin	Enhances T-cell recruitment	Local	I	135
TGF-β	Inhibits T-cell effector function	Pending	–	136

*Please note that space limitations preclude a detailed listing of all relevant references. GM-CSF, granulocyte–macrophage colony stimulating factor; IFN, interferon; IL, interleukin; M-CSF, macrophage CSF; TGF-β, transforming growth factor-β; TNF, tumour-necrosis factor; NK, natural killer; T_H1, T helper type-1; TRAIL, TNF-related apoptosis-inducing ligand.

(Dranoff 2004)

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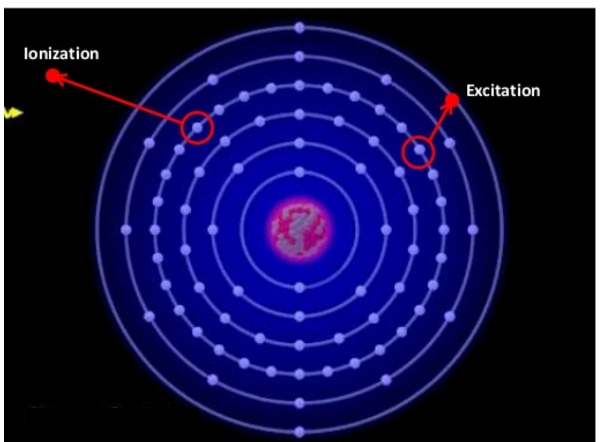
  - Particulate Radiations
- Absorption of X-rays
- Direct and Indirect Action of Radiation
- Absorption of Neutrons, Protons and Heavy Ions

Excitation and Ionization

- Absorption of energy from radiation in biological material may lead to ***excitation*** or to ***ionization***



***Excitation* –** electron from atom or molecule raised to a higher energy level but not ejected

Ionization – ejection of one or more electrons

<u>Ionizing Radiation</u> vs. <u>Non-ionizing Radiation</u>

- Energy of ionizing radiation is deposited **unevenly** in **discrete** packets
- Energy in the form of heat or mechanical energy is absorbed **uniformly** and **evenly**
- The critical difference b/w nonionizing and ionizing radiations is **the size of the <u>individual</u> packets of energy, not the <u>total</u> energy involved**

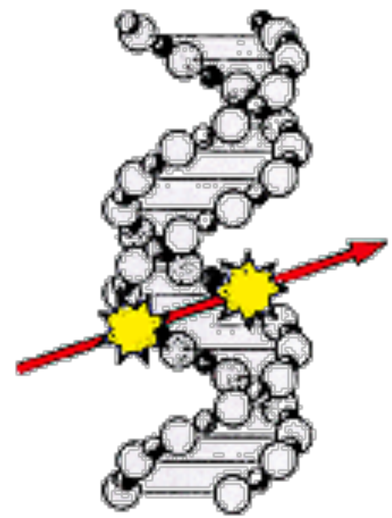
Ionizing Radiation

- An important characteristic of ionizing radiation is the **localized** release of **large amounts** of energy
- The biologic effect of radiation is determined not by the amount of the energy absorbed but **by the photon size, or packet size, of the energy**

Ionizing Radiation

- Avg energy dissipated per ionizing event ≈ **33 eV**
- Typical energy required to break a chemical bond = 2-5 eV

Bond	Bond	Bond-dissociation energy at 298 K		
		(kcal/mol)	(kJ/mol)	(eV)
C–C	C–C bond	83–85	347–356	3.60–3.69
Cl–Cl	Chlorine	58	242	2.51
Br–Br	Bromine	46	192	1.99
I–I	Iodine	36	151	1.57
H–H	Hydrogen	104	436	4.52
O–H	Hydroxyl	110	460	4.77
O=O	Oxygen	119	498	5.15
N≡N	Nitrogen	226	945	9.79



Energy Absorption – Ionizing Radiation

$LD_{50/60}$: Dose at which 50% of the irradiated population will die by day 60

Lethal Dose $_{50/60}$ = **4 Gy**

Total-Body Irradiation

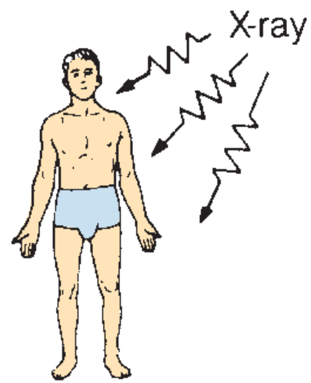
Mass = 70 kg

$LD_{50/60}$ = 4 Gy

Energy absorbed =

$$70 \times 4 = 280 \text{ joules}$$

$$= \frac{280}{4.18} = 67 \text{ calories}$$



1 Gy = 1 J/kg

Energy Absorption – Heat

Drinking Hot Coffee

Excess temperature (°C) = 60° − 37° = 23°

Volume of coffee consumed to equal the energy in the $LD_{50/60}$ $= \frac{67}{23}$

= 3 mL

= 1 sip

Equal to energy absorbed

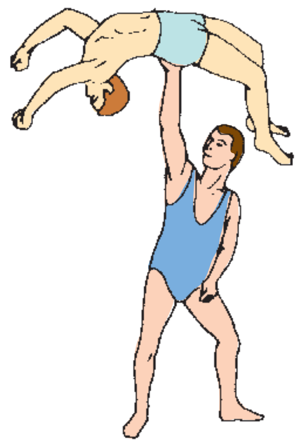
- Drinking one sip of warm coffee or
- A temp rise of 0.002° C or

Energy Absorption – Mechanical Energy

Mechanical Energy: Lifting a Person

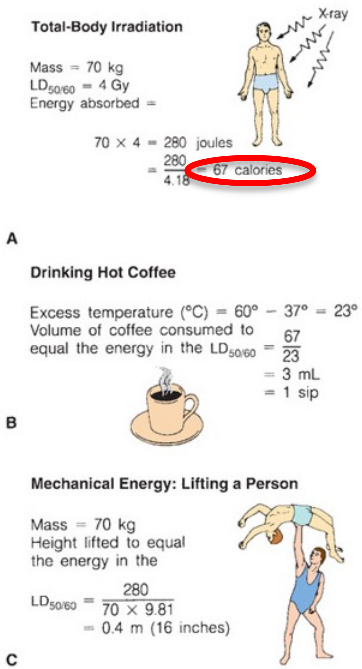
Mass = 70 kg
Height lifted to equal the energy in the

$$LD_{50/60} = \frac{280}{70 \times 9.81} = 0.4 \text{ m (16 inches)}$$



Work done in lifting a person 16 inches from the ground

Absorption of Energy



4Gy = Lethal Dose $_{50/60}$

A temp rise of 0.002° C or
Drinking one sip of warm coffee

Work done in lifting a person 16 inch from the ground

Total Energy
= 67 cal

Energy of ionizing radiation is deposited **unevenly** in **discrete** packets

The biologic effect of radiation is determined not by the amount of the energy absorbed but **by the photon size, or packet size, of the energy**

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  - Particulate Radiations
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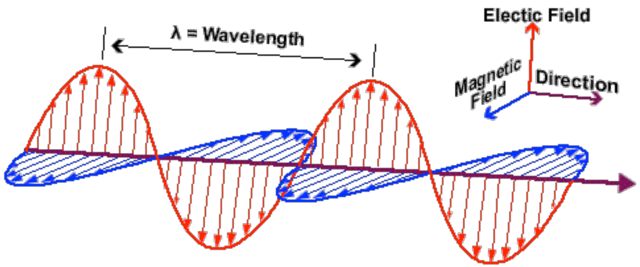
- Direct and Indirect Action of Radiation
- Absorption of Neutrons
- Summary

Electromagnetic Radiation

- X-rays may be thought of as waves of electrical and magnetic energy
- Velocity (c) = 3×10^{10} cm/sec in vacuum
- Wavelength (λ)
- Frequency (ν)



$$\lambda \nu = c$$

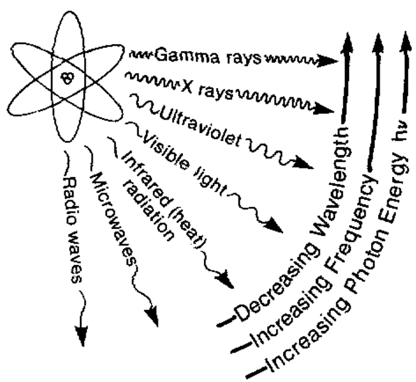
Electromagnetic Radiation

- Alternatively, x-rays may be thought of as streams of **photons**, or **"packets" of energy**

$$E = h\nu = h\,(c/\lambda)$$

$$\lambda\,(\text{Å}) = 12.4/E\,(\text{keV})$$

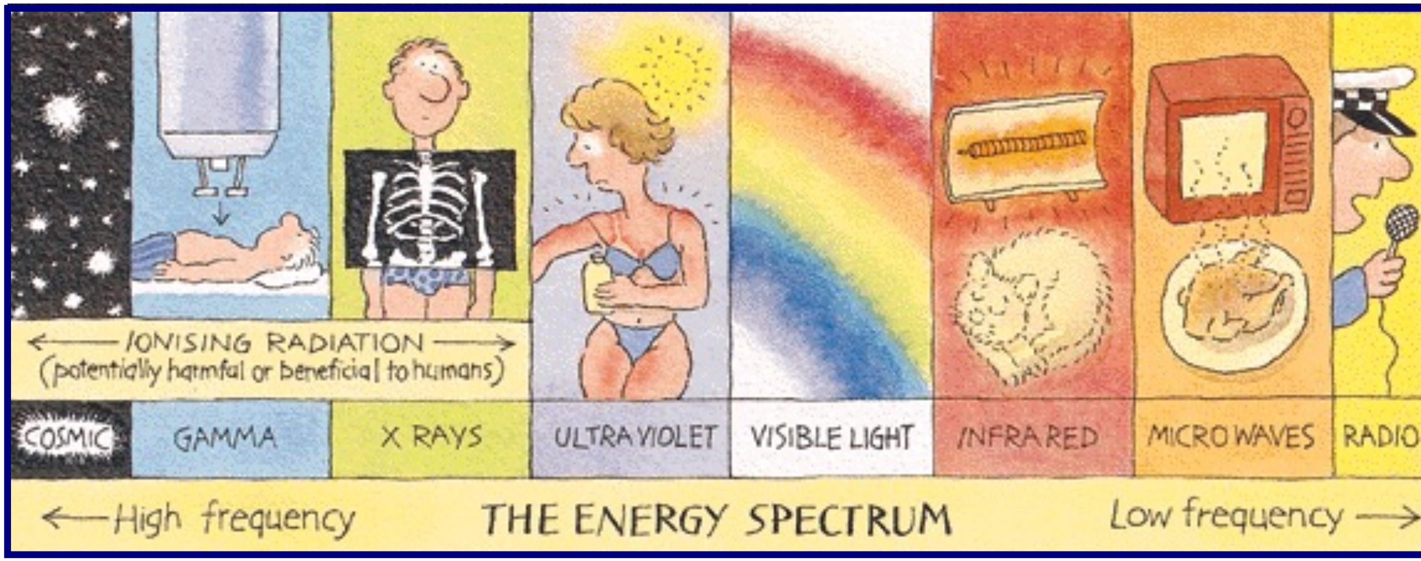
h = Planck's constant
$= 6.626068 \times 10^{-34}\ m^2\ kg\ /\ s$



short $\lambda \rightarrow$ large $\nu \rightarrow$ large E

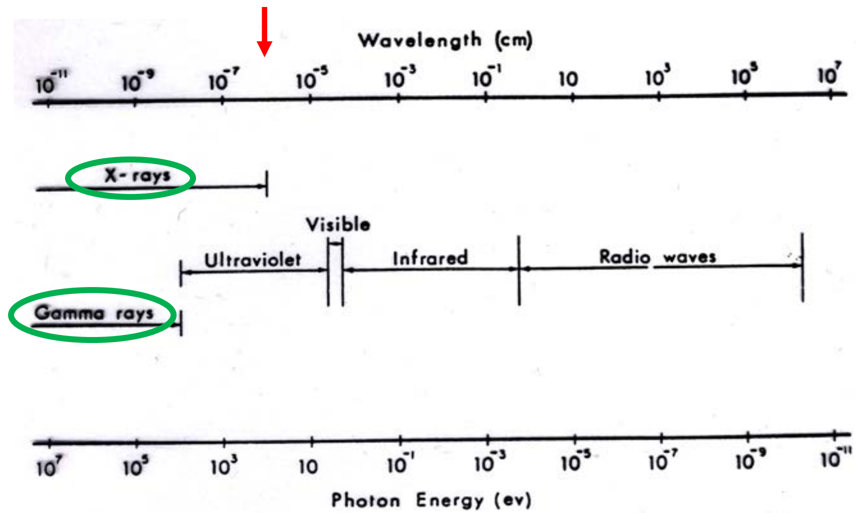
long $\lambda \rightarrow$ small $\nu \rightarrow$ small E

Electromagnetic Spectrum



All have same c, but different λ, and thus different ν

Ionizing Radiation



Electromagnetic radiations are usually considered **ionizing** if they have a photon energy **> 124 eV (or $\lambda < 10^{-6}$ cm)**

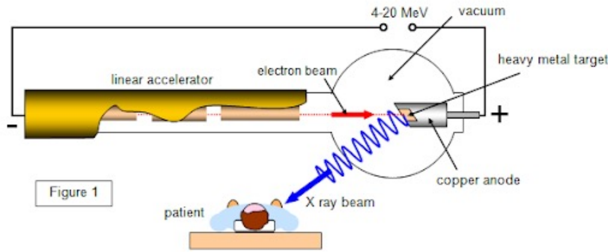
↓

Biological change

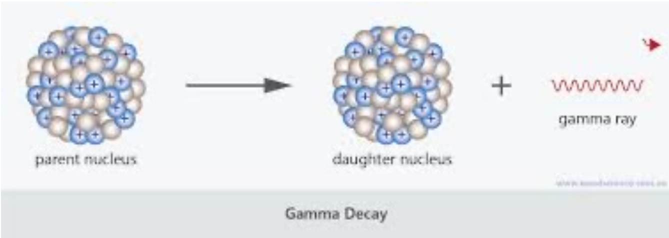
X-ray vs. Gamma-ray

X-rays or γ -rays do not differ in nature or properties but are produced in different ways

- **X-rays** – produced extranuclearly (from orbital electrons)

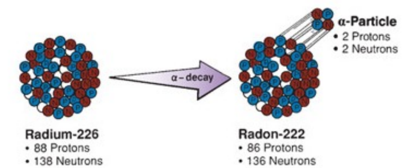


- **γ -rays** – produced intranuclearly (from decay of an unstable nucleus – radioactive element)



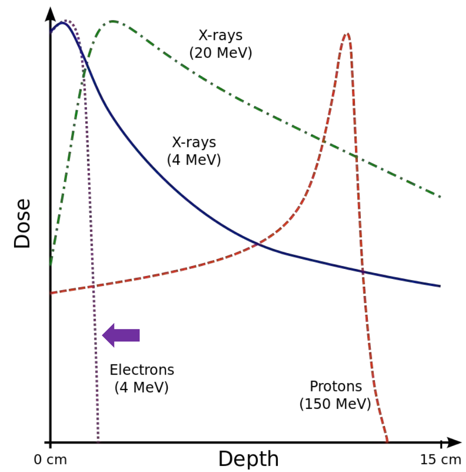
Particulate Radiations

- **e⁻** – small, - charge, accelerated to high energy
- **p⁺** – 2000 x mass of e-, +charge
- **α** – nuclei of He atoms; 2p+/2n; +charge
- **n** – mass = p+, no charge; cannot be accelerated (no charge); by-product of fission
- **Heavy charged particles** – nuclei of elements (C, Ne, Ar,Fe), + charge; can be produced by accelerating ions



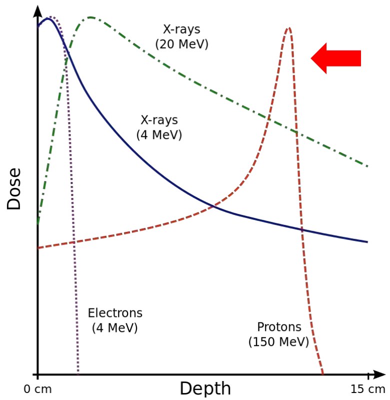
Electron

- Negatively charged particles
- Very light – mass = 9.10938291 $\times$ 10^{-31} kilograms
- Accelerated by betatron or linear accelerator
- Most commonly used in the treatment of superficial tumors



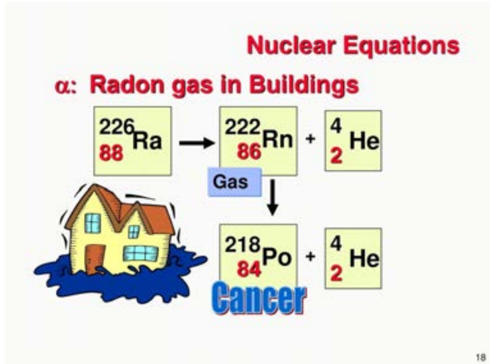
Proton

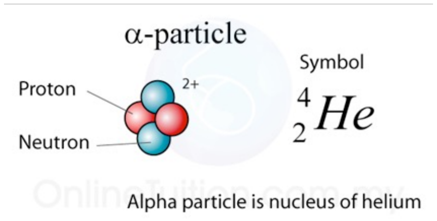
- Positively charged
- Mass = ~ 2000x of electron
- Accelerated by cyclotron
- Increasingly used in clinic – favorable dose distribution (Bragg peak)
- A component of natural background radiation
- Major hazard to astronauts on long-duration space missions



α Particles

- Nuclei of helium atoms
- Consists of 2 protons and 2 neutrons
- Positively charged
- Accelerated by cyclotron
- Used in radioimmunotherapy – short range
- Major source of natural background radiation – radon gas





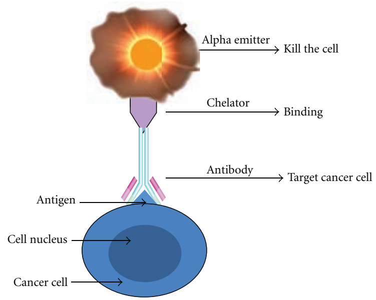
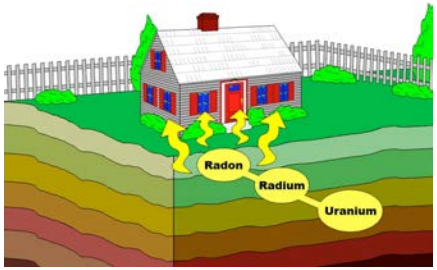


FIGURE 1: Schematic diagram of an AIC targeting a cell.



Neutrons

- Mass similar to proton
- Electrically neutral
- Generated via accelerated proton impinging on berylium targets or as a byproduct of nuclear reaction
- UW Seattle is the only facility in the US that offers neutron therapy

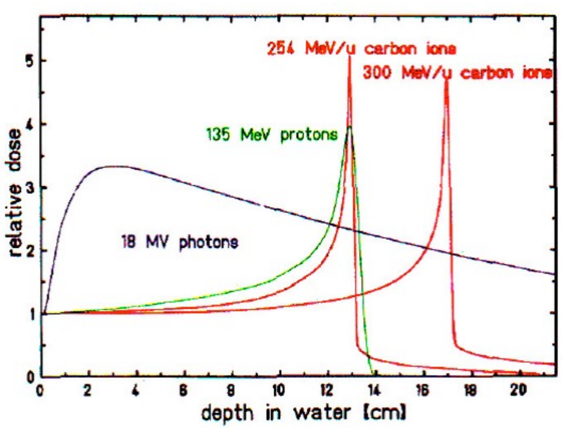
UW Medicine
DEPARTMENT OF RADIATION ONCOLOGY

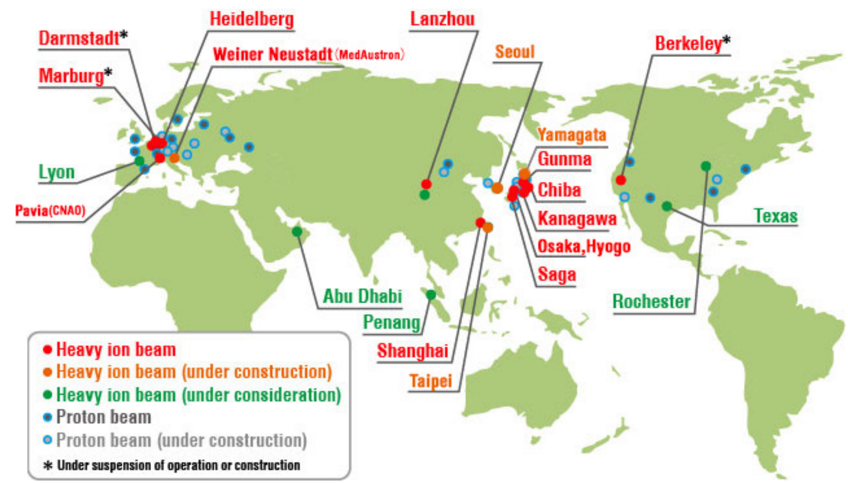
Cancers Treated with Fast Neutron Therapy

- Salivary Gland Tumors
- Pediatric/Childhood Tumors
- Metastatic Cancer
- Head and Neck Cancers
- Brain and Spine Tumors
- Sarcomas

Heavy Charged Particles

- Nuclei of element such as C, Ne, Ar, Fe
- Positively charged
- Accelerated by synchrotron
- A major hazard to astronauts on long missions





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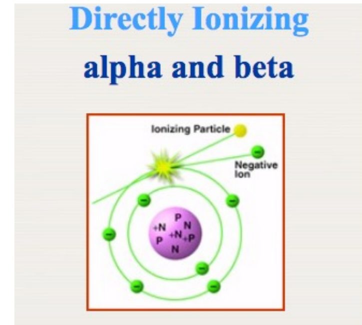
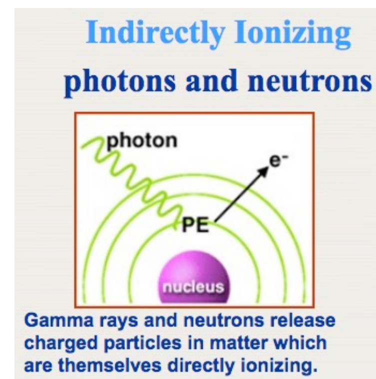
Direct vs. Indirect Ionization

- **Directly Ionizing:**
  - Directly disrupt atomic structure of the absorber through which they pass, thereby produce chemical and biologic changes
  - All charged particles are directly ionizing



- **Indirectly Ionizing:**
  - Do not produce chemical and biologic damage themselves
  - Instead, they give up their energy to produce fast-moving charged particles that in turn are able to produce damage
  - Electromagnetic radiations (x- and γ–rays) are indirectly ionizing



Direct vs. Indirect Radiation

Direct

- Able to directly alter atom
- Charged particles
  - Alpha particles
  - Electrons
  - β particles
  - Heavy charged particles
  - Protons

Indirect

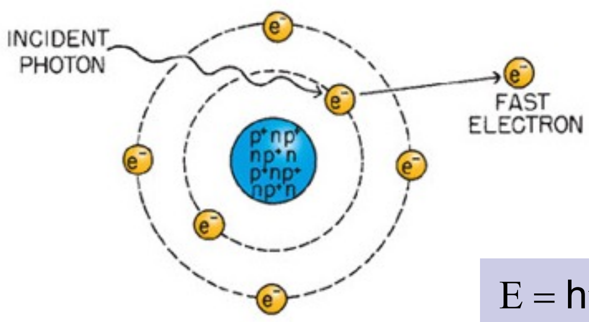
- Uncharged particles
  - Gamma rays
  - X-rays
    - Generates a fast-moving electron when interacts with electron shell
  - Neutrons
    - Sets nuclear particle in motion (proton, alpha particle, spallation products)

Absorption of X-rays

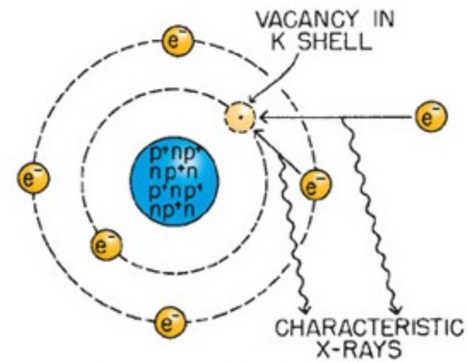
- The way photons are absorbed depends on the energy of the photon and the chemical composition of the absorbing material

- 5 major types of interaction
  - Photoelectric effect
  - Compton effect
  - Pair production
  - Coherent scattering
  - Photodisintegration

Photoelectric Process



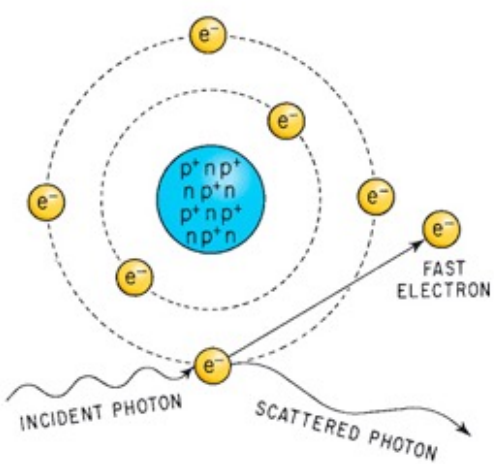
$E = h\nu - E_B$

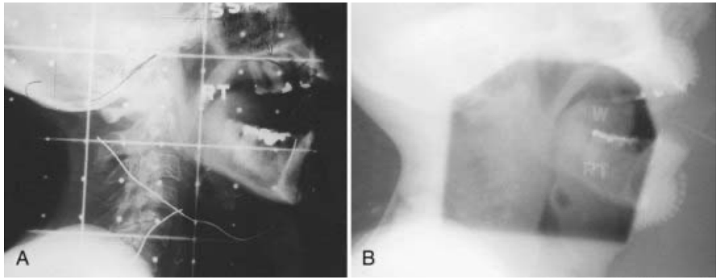


Little biological consequence b/c energy ~ 0.5 kV

- Dominates at energies characteristic of **diagnostic radiology**
- Mass absorption coefficient $\propto \mathbf{Z^3}$

Compton Effect





KV film

MV film

- Compton Process dominates at energies characteristics for radiotherapy
- Independent of Z

Pair Production

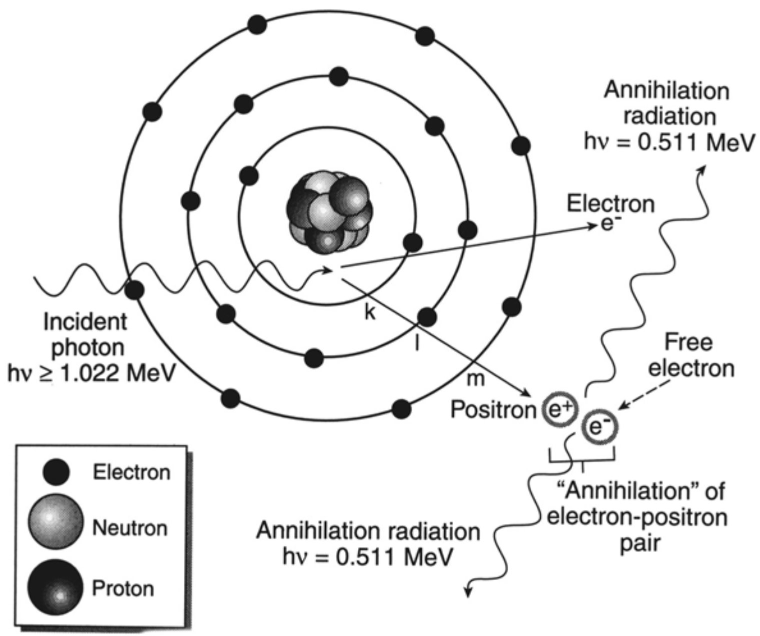


FIGURE 3–16.
Pair production.

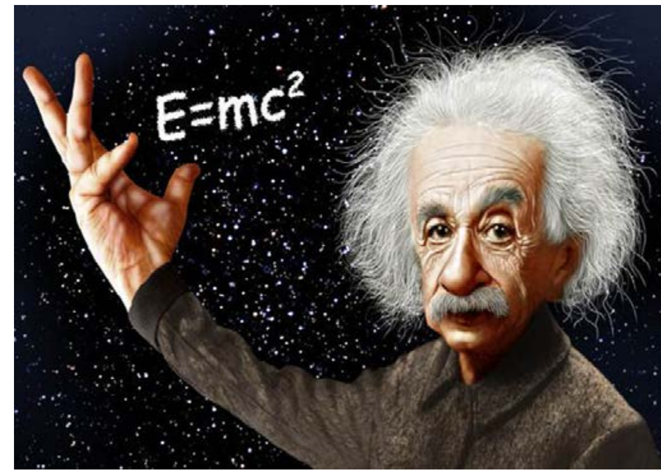


Photo-induced Disintegration

Only important at photon energies > 10 MeV

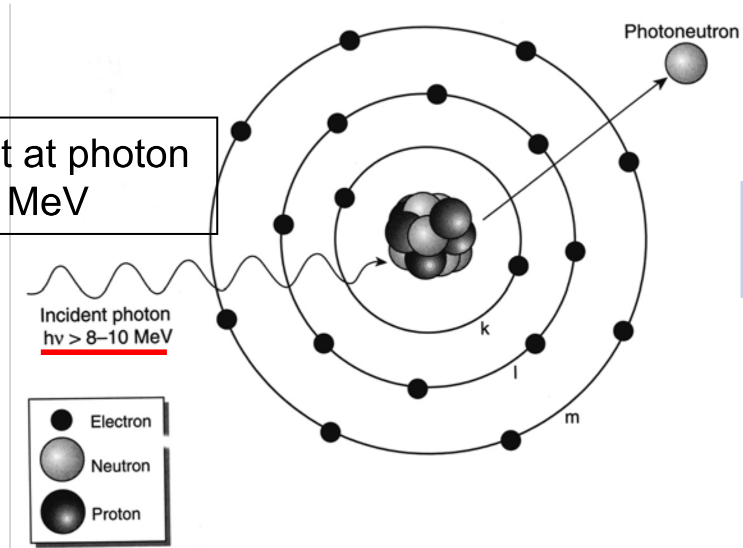


FIGURE 3–17.
Photodisintegration.

Example:
$^{63}Cu + \gamma \rightarrow {}^{62}Cu + n$

Absorption of X-ray

- Although the differences among the various absorption processes are of practical importance in radiology, the consequences for radiobiology is minimal
- Regardless of the absorption process, much of the energy of the absorbed photon is converted to the kinetic energy of a fast electron
- What we are concerned about is the biological effects of radiation

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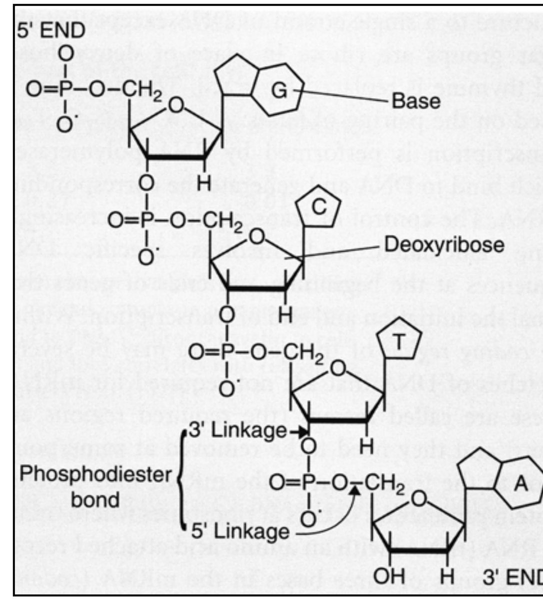
Critical Target of Ionizing Radiation

- The biologic effects of radiation result principally from damage to **DNA**
- Main problem = strand breaks
- Non-rejoined breaks → cell death
- Incorrectly rejoined breaks → mutations
- Damage of bases → mutations

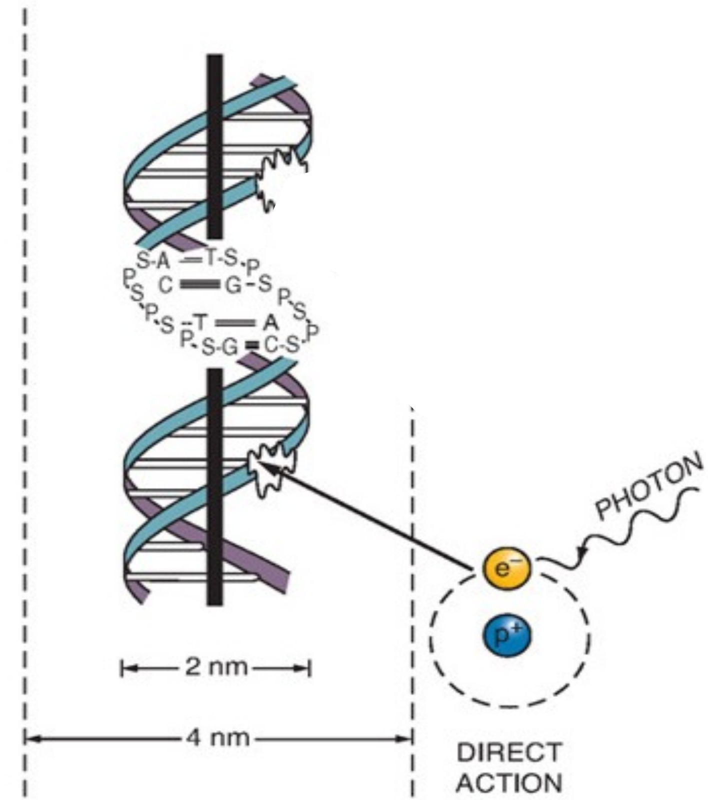


Direct vs. Indirect Action

- **Direct Action**
  - Radiation interacts directly with critical targets in the cell (DNA)
- **Indirect Action**
  - Radiation interacts first with other atoms or molecules in the cell (usually H_2O) to produce free radicals, which in turn diffuse and damage DNA

These terms are defined with respect to the way IR interacts with **DNA**

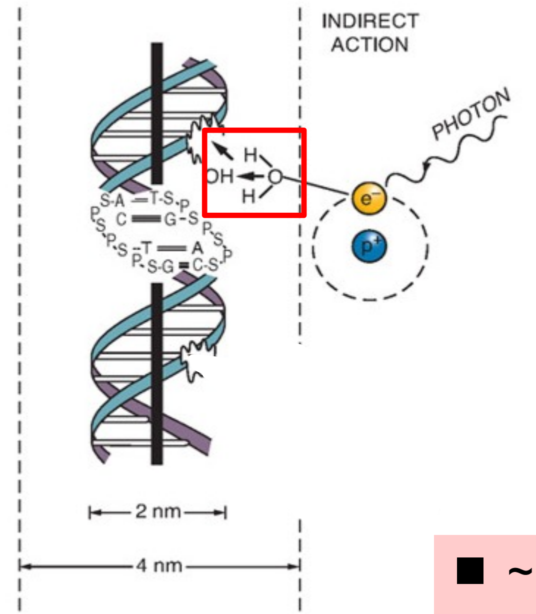
Direct Action



- The atoms of the target (DNA) itself may be ionized, thus initiating the chain of events that leads to a biologic change
- Is the dominant process for radiations with high linear energy transfer (LET, e.g., neutrons or α particles)

We will discuss LET in Chapter 7

Indirect Action



Ion radical

$$H_2O \rightarrow H_2O^+ + e^-$$

$$\Downarrow$$

$$H_2O^+ + H_2O \rightarrow H_3O^+ + OH\cdot$$

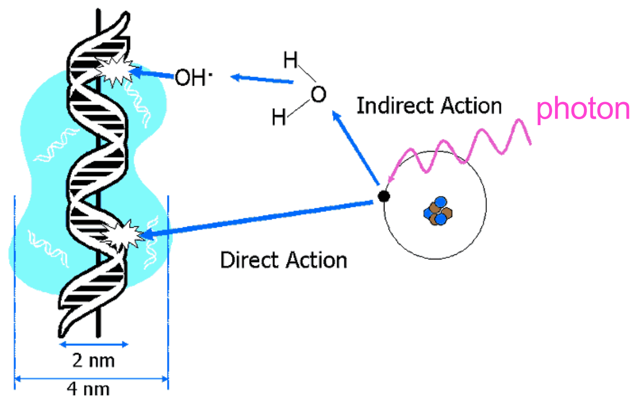
free radical

Free radical – an atom or molecule carrying an unpaired orbital electron in the outer shell

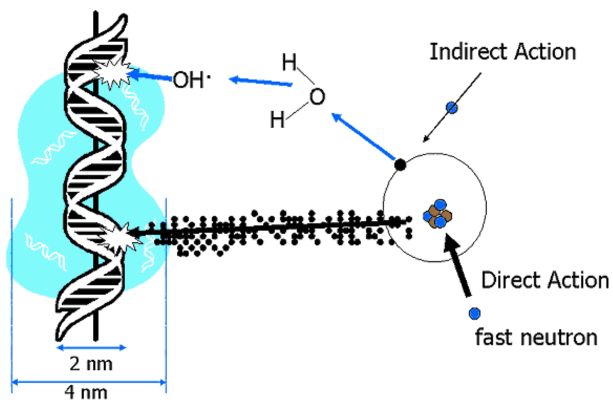
Free radical can diffuse a short distance (2x of the diameter of the DNA double helix)

- ~ 2/3 of the **x-ray** damage to DNA in mammalian cells is caused by OH·
- Can be modified by chemical means (protectors or sensitizers)

Direct vs. Indirect Action



- For **Low LET** radiation, 2/3 damage is **indirect action**
- Critical distance of indirect action is within **2nm** radius from DNA



- For **High LET radiation**, most (all?) damage is **direct action**

Chain of Events Leading to Biologic Effects

X-ray is an **ionizing radiation**

X-ray is **indirectly ionizing**

X-ray interact with DNA mainly via **indirect action**

Will I glow in the dark after radiation therapy?

Incident X-Ray Photon

↓ 10^{-15} sec

Fast Electron (e-)

↓

Ion Radical

↓ 10^{-10} sec

Free Radical OH·

↓ 10^{-9} sec

Chemical Changes

↓ 10^{-5} sec

Breakage of Bonds

↓ Hours-Years

Biological Effects

The physics of radiation is short-lived

The biologic effect may take hours, days, months, years, or generations to express

What Biological Effects?

- Cell killing
- Acute (early) tissue and organ damage
- Late (delayed) tissue and organ damage
- Carcinogenesis
- Genetic (hereditary) effects

Outline

- Brief Historical Overview
- Examples of clinical application of radiation biology
- Types of Ionizing Radiations
  - Electromagnetic Radiations
  - Particulate Radiations
- Absorption of X-rays
- Direct and Indirect Action of Radiation
- Absorption of Neutrons, Protons, and Heavy Ions

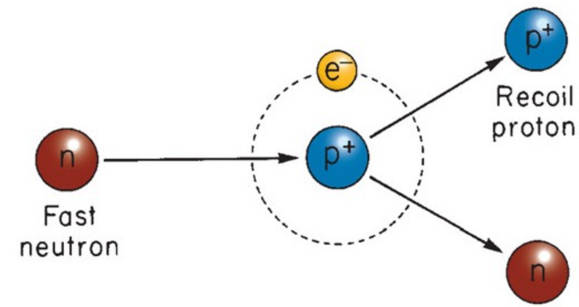
Absorption of Neutrons

- Neutrons are uncharged particles
- Like x- and γ-rays, neutrons are indirectly ionizing
- Unlike x- and γ-rays, which interact with the orbital electrons of atoms, neutrons interact with the nuclei of atoms and set in motion *fast recoil protons*, *α-particles*, and *heavier nuclear fragments*

Elastic Scattering – Proton Recoil Reaction

- Neutron collides with proton (e.g., hydrogen nucleus) and shares its kinetic energy

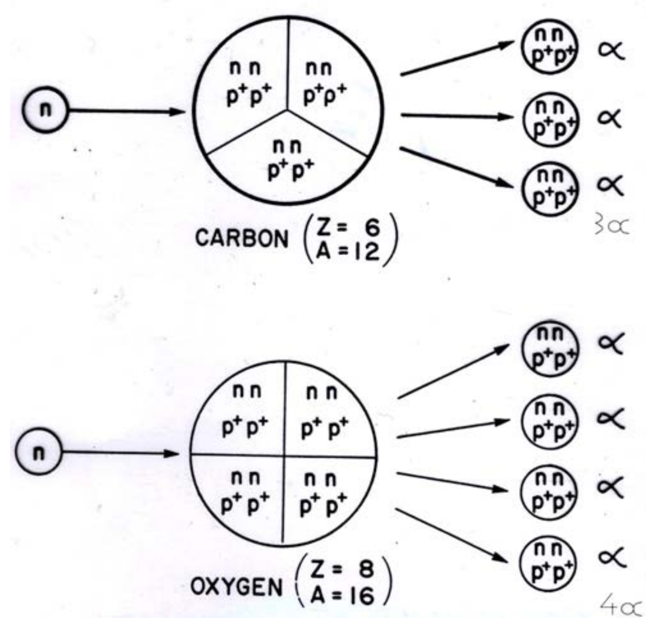
- Dominant process with fast neutrons of energy < 6 MeV



Inelastic Scattering

- Fast neutrons (energy ≥ 6 MeV) interacts with nucleus and causes disintegration

- C → 3 α-particles
- O → 4 α-particles

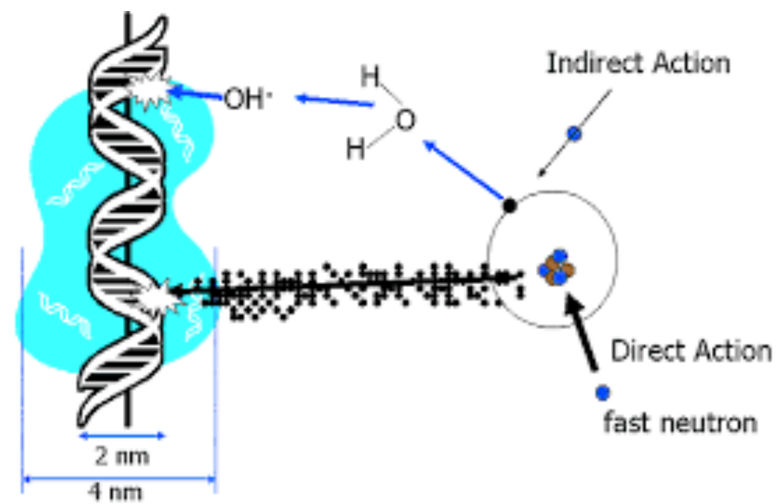


Spallation products

Neutron interact with DNA Predominantly via Direct Action

- Unlike x- or γ-rays, which are sparsely ionizing, neutrons are densely ionizing
- Direct Action dominates
- Chemical sensitizers and protectors are ineffective modifiers

Neutron Interaction with DNA



Absorption of Proton

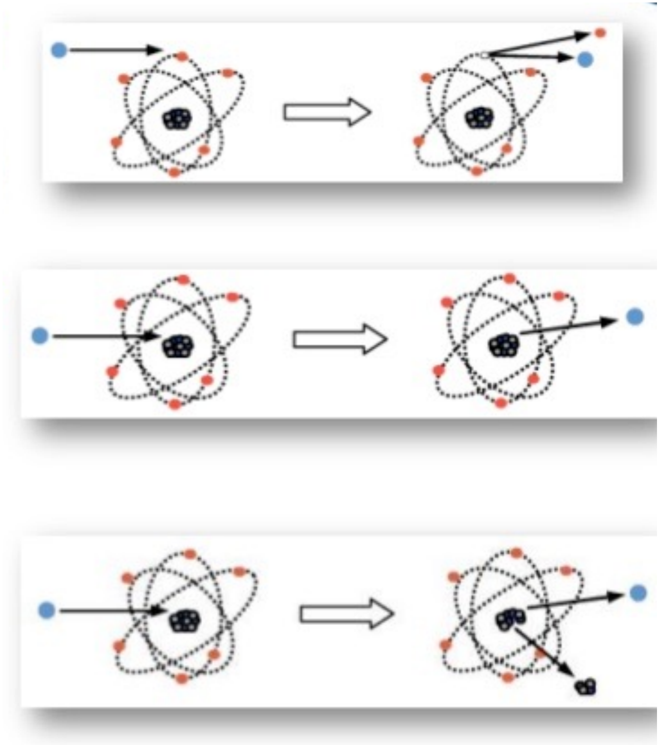
- Coulomb interactions with atomic electrons .

Electronic (ionization ,excitation)

- Coulomb interactions with atomic nuclei .

“multiple Coulomb scattering.”

- Nuclear interactions with atomic nuclei .
  - Elastic nuclear collision
  - Non elastic nuclear collision



http://www.slideshare.net/dinadawi/proton-therapy

Review Questions

Review of Chapter 1 – Question 1

Which of the following ionization processes represents the principal interaction with tissue for X-rays used in radiotherapy?

A. pair production
B. photoelectric effect
C. Compton process
D. photodisintegration
E. coherent scattering

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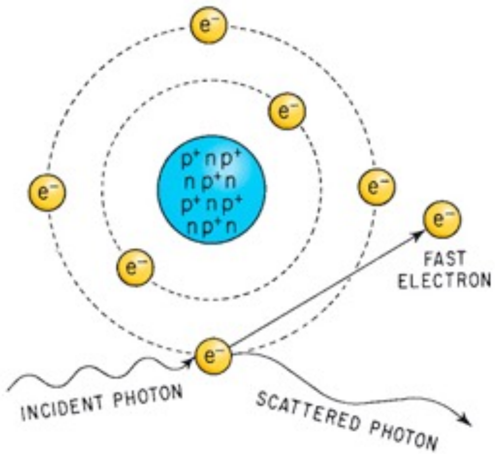

Review of Chapter 1 – Question 2

In terms of radiation-induced damage to mammalian cells, the most important radiolysis products of water are:

A. aqueous solvated electrons
B. hydrogen atoms
C. superoxide radicals
D. hydrogen peroxide
E. hydroxyl radicals

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Review of Chapter 1 – Question 3

How far out from the center of the DNA molecule can the creation of hydroxyl radicals affect the DNA?

A. 0.1 mm
B. 10 nm
C. 2 nm
D. 1 nm

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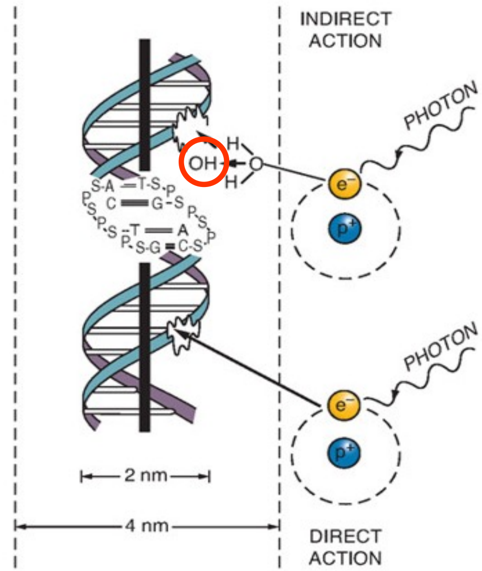


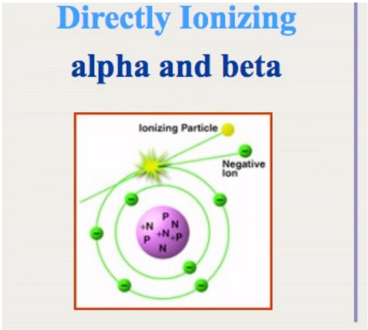
Review of Chapter 1 – Question 4

Which of the following are directly ionizing radiations?

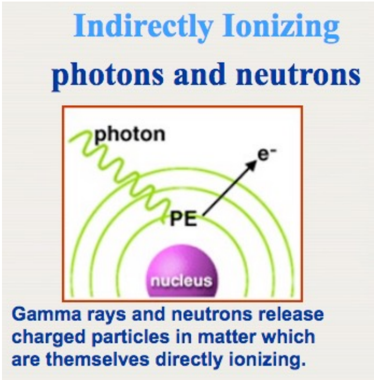
A. alpha particles, neutrons, beta particles, protons
B. x-rays, gamma rays, neutrons
C. neutrons, heavy charged particles, beta particles
D. alpha particles, beta particles, protons, heavy charged particles

Direct vs. Indirect Ionization

- **Directly Ionizing:**
  - Directly disrupt atomic structure of the absorber through which they pass, thereby produce chemical and biologic changes
  - All charged particles are directly ionizing



- **Indirectly Ionizing:**
  - Do not produce chemical and biologic damage themselves
  - Instead, they give up their energy to produce fast-moving charged particles that in turn are able to produce damage
  - Electromagnetic radiations (x- and γ–rays) are indirectly ionizing



Review of Chapter 1 – Question 5

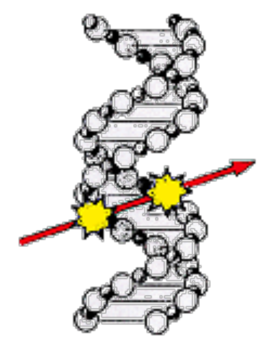
The approximate minimum photon energy required to cause ionization is:

A. 10-25 eV
B. 100-250eV
C. 1-2.5keV
D. 10-25 keV
E. 100-250 keV

Ionizing Radiation

- Avg energy dissipated per ionizing event ≈ **33 eV**
- Typical energy required to break a chemical bond = 2-5 eV

Bond	Bond	Bond-dissociation energy at 298 K		
		(kcal/mol)	(kJ/mol)	(eV)
C–C	C–C bond	83–85	347–356	3.60–3.69
Cl–Cl	Chlorine	58	242	2.51
Br–Br	Bromine	46	192	1.99
I–I	Iodine	36	151	1.57
H–H	Hydrogen	104	436	4.52
O–H	Hydroxyl	110	460	4.77
O=O	Oxygen	119	498	5.15
N≡N	Nitrogen	226	945	9.79



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On average, about 25 eV is required to create an ion pair in water, although the minimum energy needed to eject an electron is only 12.6 eV.