2011
ASTRO
RADIATION/CANCER BIOLOGY
PRACTICE EXAMINATION AND
STUDY GUIDE

Produced by the Radiation/Cancer Biology Practice Examination and Study Guide Subcommittee of the ASTRO Radiation and Cancer Biology Committee

Please address all correspondence to:
Dr. Barry S. Rosenstein
Box 1236
Department of Radiation Oncology
Mount Sinai School of Medicine
One Gustave Levy Place
New York, NY 10029
Tel: (212) 241-9408
Fax: (212) 996-8927
Email: barry.rosenstein@mssm.edu

Editor-in-Chief, Chair of Subcommittee

Members of Subcommittee

Associate Editors

Contributors

Joan Allalunis-Turner, Ph.D.
Cross Cancer Institute

Sally A. Amundson, Ph.D.
Columbia University

Elizabeth K. Balcer-Kubiczek, Ph.D.
University of Maryland School of Medicine

Kevin A. Camphausen, M.D.
National Cancer Institute/NIH

Theodore L. DeWeese, M.D.
Johns Hopkins University School of Medicine

Evan B. Douple, Ph.D.
The National Academies Nuclear and Radiation Studies Board

Adriana Haimovitz-Friedman, Ph.D.
Memorial Sloan-Kettering Cancer Center

Dennis E. Hallahan, M.D.
Vanderbilt University

Martin Hauer-Jensen, M.D., Ph.D.
University of Arkansas for Medical Sciences

Kathryn D. Held, Ph.D.
Harvard Medical School
Massachusetts General Hospital

Richard P. Hill, Ph.D.
Ontario Cancer Institute

Rakesh K. Jain, Ph.D.
Harvard Medical School
Massachusetts General Hospital

David Kirsch, M.D., Ph.D.
Duke University School of Medicine

Amy Kronenberg, Sc.D.
Lawrence Berkeley National Laboratory

William F. Morgan, Ph.D.
University of Maryland

John P. Murnane, Ph.D.
University of California, San Francisco

Peggy L. Olive, Ph.D.
British Columbia Cancer Research Centre

Martin Pruschy, Ph.D.
University Hospital Zurich

Sara Rockwell, Ph.D.
Yale University School of Medicine

Michael E.C. Robbins, Ph.D.
Wake Forest University School of Medicine

Joseph L. Roti Roti, Ph.D.
Washington University School of Medicine

Carolyn I. Sartor, M.D.
University of North Carolina School of Medicine

Joann Sweasy, Ph.D.
Yale University School of Medicine

Marie-Catherine Vozenin-Brotons Ph.D.
Institut Gustave Roussy

Gayle E. Woloschak, Ph.D.
Northwestern University Medical School

Henning Willers, M.D.
Harvard Medical School
Massachusetts General Hospital

Jacqueline Williams, Ph.D.
University of Rochester Medical Center

Elaine M. Zeman, Ph.D.
University of North Carolina School of Medicine

Daniel Zips, Ph.D.
Technical University Dresden

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Preface to the 2011 Edition

In recognition of the critical need to develop new ways to promote education in the biologic basis of radiotherapy, the Radiation and Cancer Biology Committee of ASTRO appointed a subcommittee to develop a dynamic web-based educational tool for radiation oncologists to further their studies of radiation and cancer biology. The ASTRO Radiation/Cancer Biology Practice Examination and Study Guide, referred to as the "RCB Study Guide" for sake of brevity, is the product of these efforts. The RCB Study Guide was created specifically with a goal to stimulate active learning.

The topics included in the ASTRO RCB Study Guide are based upon those listed by the American Board of Radiology (ABR) on their web site for the cognitive exam in radiation and cancer biology. The number of questions in each section reflects the relative weight given by the ABR to that topic. Therefore, the RCB Study Guide should provide guidance both to residents in their preparation for the radiation oncology certification examination as well as to more senior radiation oncologists taking the examination to demonstrate the cognitive expertise in radiation and cancer biology that is required for maintenance of certification.

It is suggested that users of the RCB Study Guide attempt to answer the questions in each section and then review the correct answers and explanations. It is anticipated that this approach will lead to a more complete understanding of each topic. References are included, with a hypertext link to the abstract and article, for topics that are not addressed fully in the major radiation biology textbooks cited in the RCB Study Guide. It should be noted that for the selection of references, an emphasis was placed on recent review articles that provide current and comprehensive information on a particular subject.

Users of the 2011 RCB Study Guide are encouraged to also review the material presented in the 2009 and 2010 versions. This is of importance since a goal associated with creation of the RCB Study Guides is to address all major topics in radiation and cancer biology of relevance to radiation oncologists over a three year period since it is not possible to include material for every pertinent subject in any single year.

Radiation and cancer biology are dynamic fields with new results published daily in the scientific literature. The goal for radiation oncologists is to acquire a solid base of knowledge in radiation and cancer biology during their training and to build upon that foundation during their careers through regular reading of the scientific literature as well as attendance at seminars and scientific conferences. The RCB Study Guides are designed to help radiation oncologists achieve this goal. It is hoped that by helping to provide radiation oncologists with a firm foundation in the biologic principles underlying the treatment of cancer with radiation, they will be able to offer more effective radiotherapy and achieve improved clinical outcomes for their patients.

Finally, I would like to thank all of the Associate Editors and Contributors who wrote and carefully reviewed the questions, explanations and references. Without your assistance, creation of the ASTRO Radiation and Cancer Biology Practice Examination and Study Guides would have not been possible.

Barry S. Rosenstein, Ph.D.
February, 2011

Note on Protein and Gene Nomenclature

The 2011 ASTRO Radiation/Cancer Biology Practice Examination and Study Guide uses the notation system for the name of each gene and protein encoded by that gene that was developed by the HUGO Gene Nomenclature Committee. The details for that system can be found at http://www.gene.ucl.ac.uk/nomenclature/. The guidelines for this system stipulate that gene symbols are italicized and designated by upper-case Latin letters or by a combination of upper-case letters and Arabic numerals. The protein encoded by the gene is given the same symbol as the gene, except that the letters are not italicized. Thus, the symbol for the gene mutated in people with the disease ataxia telangiectasia is *ATM* and the protein encoded by that gene is written as ATM.

It should be noted that although the HUGO is widely used in scientific journals and textbooks, this system is rarely used for some proteins and genes. For these genes/proteins, the common symbol has been used in the exam/study guide, but the HUGO symbol is provided in parentheses the first time that the gene/protein is written in the question. For example, *p53* is used in the exam/study guide rather than the official HUGO symbol for this gene, which is *TP53.* This is noted by indicating *p53 (TP53)* in the question or explanation.

QUESTIONS

I. Interaction of Radiation with Matter

I-1) Which one of the following sequences correctly orders portions of the electromagnetic spectrum in terms of increasing photon energy?

A. radiowaves, infrared, visible light, UV, X-rays
B. UV, X-rays, microwaves, infrared, radiowaves
C. visible light, UV, X-rays, radiowaves, infrared
D. radiowaves, UV, X-rays, visible light, infrared radiation
E. UV, infrared, visible light, X-rays, radiowaves

I-2) 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

I-3) An atom or molecule that has an unpaired electron in its outer shell is referred to as a(n):

A. spallation product
B. heavy ion
C. ion pair
D. recoil proton
E. free radical

I-4) Which of the following statements concerning photons is correct?

A. Exposure to a particular dose of 1 MeV γ-rays compared with mono-energetic 1 MeV X-rays will produce significantly different biological effects.
B. Compton scattering results in the release of characteristic X-rays.
C. Electromagnetic radiations travel at less than the speed of light.
D. The annihilation reaction involves an interaction between a positron and an electron.
E. Higher energy photons have longer wavelengths than lower energy photons.

I-5) Which of the following statements concerning the interaction of radiation with matter is TRUE?

A. Both X- and γ-rays are produced by nuclear disintegration.
B. Auger electrons are a product of pair production.
C. Free radicals have half-lives on the order of seconds.
D. Free radicals carry a net electrical charge.
E. There is complete photon absorption in the photoelectric effect.

I-6) Which one of the following particles has the smallest mass?

A. neutron
B. positron
C. α-particle
D proton
E. carbon ion

I-7) Which of the following statements concerning photons is TRUE?

A. Ideally, photons used for radiotherapy should interact with matter through the photoelectric effect.
B. Photons can be produced by the annihilation reaction, which involves an interaction between a positron and an electron.
C. X-rays travel faster than visible light.
D. The probability of a photoelectric interaction is inversely proportional to the atomic number of the absorber.
E. Compton scattering results in the production of Auger electrons.

II. Molecular Mechanisms of DNA Damage

II-1) The biological effects resulting from exposure to ultraviolet (UV) radiation are due primarily to the formation of:

A. thymine glycols
B. ionizations
C. pyrimidine dimers
D. heat
E. oxidized guanine

II-2) Which type of radiation-induced DNA damage is most important for cell killing caused by exposure to ionizing radiation?

A. base damage
B. DNA double-strand break
C. DNA single-strand break
D. DNA-protein crosslink
E. DNA-DNA inter-strand crosslink

II-3) Which of the following is NOT produced by exposure to ionizing radiation?

A. thymine glycol
B. single-strand break
C. 6-4 photoproduct
D. 8-oxo-guanine
E. DNA-histone crosslink

II-4) The yield of initial DNA double-strand breaks produced in an irradiated mammalian cell will be influenced by all of the following, EXCEPT:

A. radiation dose
B. lack of oxygen during irradiation
C. presence of amifostine during irradiation
D. absence of histone proteins
E. absence of RAD51

II-5) Non-targeted, radiation-induced bystander effects are associated with:

A. production of pyrimidine dimers
B. effects in non-irradiated cells co-cultured with irradiated cells
C. induction of mutations in *BCL2*
D. radiation-induced heat
E. induction of miRNA

III. Molecular Mechanisms of DNA Repair

III-1) Which of the following is NOT a characteristic of DNA-dependent protein kinase (DNA-PK)?

A. Consists of a catalytic subunit and two smaller accessory proteins, Ku70 (XRCC6) and Ku80 (XRCC5).
B. Participates in the repair of DNA double strand breaks primarily through homologous recombination.
C. Loss in mice results in altered radiation sensitivity.
D. Phosphorylates histone H2AX at sites of double strand breaks.
E. Belongs to the phosphatidyl inositol 3-kinase-like protein kinase (PIKK) family.

III-2) Which of the following proteins is NOT directly involved in repairing DNA double strand breaks?

A. Artemis
B. RAD51
C. DNA-PKcs
D. CDK4
E. BRCA1

III-3) SCID mice are often used in cancer research because they:

A. are radioresistant
B. exhibit high levels of non-homologous end joining
C. have efficient immune systems
D. are better able to repair radiation damage
E. are useful hosts for growing human tumor xenografts

III-4) Cells derived from individuals diagnosed with xeroderma pigmentosum are deficient in:

A. nucleotide excision repair
B. methyl-guanine transferase
C. mismatch repair
D. base excision repair
E. homologous recombination

III-5) Homologous recombinational repair of DNA double strand breaks is most likely to occur:

A. in G_0
B. in G_1
C. in early S phase
D. in late S phase
E. throughout the cell cycle

III-6) Which syndrome is caused by a deficiency in the repair-associated protein MRE11?

A. Werner's syndrome
B. ataxia-telangiectasia-like disorder
C. xeroderma pigmentosum
D. Bloom's syndrome
E. Cockayne's syndrome

III-7) All the following statements are true concerning homologous recombinational repair of DNA double strand breaks, EXCEPT:

A. H2AX phosphorylation represents an important step in the formation of repair foci.
B. The BLM protein serves to coat single stranded DNA regions to prevent their degradation.
C. The MRN complex relocates to sites of DNA double strand breaks to process DNA resulting in production of single stranded ends.
D. RAD51 is a recombinase and forms a nucleoprotein filament that facilitates strand invasion for homologous recombination.
E. ATM is activated following irradiation by auto-phosphorylation and conversion from an inactive dimer to an active monomer.

III-8) All of the following statements about non-homologous end joining (NHEJ) are true, EXCEPT:

A. Artemis is primarily responsible for ligating broken DNA ends.
B. DNA ligase IV forms a tight complex with XRCC4.
C. DNA-PKcs associates with Ku70/80 to form the DNA-PK holo-enzyme.
D. The Ku heterodimer has a high affinity for DNA ends and forms a close-fitting asymmetrical ring that threads onto a free end of DNA.
E. NHEJ is an error-prone process.

III-9) Which of the following is NOT a known substrate for ATM?

A. Ku70/80 (XRCC6/XRCC5)
B. BRCA1
C. NBS1
D. p53 (TP53)
E. CHK2 (CHEK2)

III-10) Which of the following statements is TRUE concerning DNA repair processes?

A. Between 10-20% of the population is thought to be heterozygous for the types of mutations that are responsible for causing ataxia telangiectasia (AT).
B. Non-homologous end-joining requires the involvement of a sister chromatid.
C. Mutations in the genes that encode proteins involved in translesion DNA synthesis are typically present in people who develop hereditary non-polyposis colon cancer.
D. The most common types of DNA damage induced by ionizing radiation are repaired through base excision repair.
E. Sublethal damage repair is significant for both x-rays and neutrons.

III-11) Normal tissue complications are most likely to be exhibited following conventional radiotherapy in patients suffering from:

A. ataxia telangiectasia
B. systemic lupus erythematosus
C. Bloom's syndrome
D. xeroderma pigmentosum
E. Fanconi's anemia

III-12) Repair of DNA double-strand breaks can be accomplished by which one of the following pathways?

A. mismatch repair
B. non-homologous end joining
C. base excision repair
D. nucleotide excision repair
E. photoreactivation

III-13) RAD51 and BRCA2 function together:

A. as inhibitors of cyclin dependent kinases.
B. to phosphorylate H2AX and NBS1.
C. to enhance apoptosis by inhibiting p53 (TP53).
D. in the initial steps of homologous recombination.
E. to play a central role in nucleotide excision repair.

IV. Chromosome and Chromatid Damage

IV-1) Radiation-induced anaphase bridges generally result from:

A. dicentric chromosomes
B. ring chromosomes
C. acentric fragment
D. isochromatid breaks
E. a single chromosome break

IV-2) The minimum whole body radiation dose that can be detected through the measurement of dicentric chromosomes in peripheral blood lymphocytes is approximately:

A. 0.0005 Gy
B. 0. 015 Gy
C. 0.25 Gy
D. 3.5 Gy
E. 10 Gy

IV-3) Which one of the following radiation-induced chromosome aberrations is a "single hit" type?

A. terminal deletion
B. acentric ring
C. dicentric
D. anaphase bridge
E. inversion

IV-4) Which of the following types of chromosomal aberrations is **most likely** to cause lethality?

A. insertion
B. dicentric
C. translocation
D. inversion

IV-5) An accidental exposure to a radiation source is reported one month following irradiation of a person not wearing a dosimeter. Which of the following assays would represent the best method to estimate the radiation dose received by this person?

A. alkaline elution
B. staining with a monoclonal antibody to γ-H2AX
C. karyotyping peripheral blood lymphocytes
D. pulsed-field gel electrophoresis
E. neutral comet assay

IV-6) Which of the following statements is FALSE concerning chromosome aberrations in irradiated cells?

A. The yield of dicentric chromosomes in X-irradiated cells follows a linear function of dose.
B. Spectral karyotyping (SKY) may be useful for the detection of translocations.
C. Acentric fragments and micronuclei often result from asymmetrical exchanges.
D. Ring chromosomes can be detected through staining and karyotyping.
E. It is possible to detect symmetrical exchanges using fluorescence **in situ** hybridization (FISH).

IV-7) Which of the following statements concerning chromosome aberrations is FALSE?

A. Ring chromosomes are induced as a linear function of dose for high LET radiation.
B. The induction of radiation-induced terminal deletions is a linear function of dose.
C. An anaphase bridge is a chromatid aberration.
D. For a given dose of X-rays, the yield of dicentrics decreases with decreasing dose rate.
E. Symmetrical translocations are unstable chromosome aberrations.

V. Mechanisms of Cell Death

V-1) Which of the following would NOT be a useful assay for the detection of cells undergoing apoptosis?

A. TUNEL
B. DNA ladder formation
C. Annexin V labeling
D. DAPI
E. staining with pimonidazole

V-2) Which of the following methods would represent the best way to assess the ability of radiation to decrease the survival of actively dividing cells following irradiation?

A. clonogenic assay
B. division delay
C. apoptosis levels at 24 hours
D. giant cell formation
E. detection of necrotic cells

V-3) The primary reason for cell death in most solid tumors following ionizing irradiation treatment is due to:

A. activation of apoptosis by the DNA damage response
B. DNA damage induced senescence
C. mitotic catastrophe following incorrect segregation of genetic material
D. oxidative damage to cellular proteins
E. generation of ceramide through the action of sphingomyelinase

V-4) Following radiotherapy-relevant doses of ionizing radiation, apoptosis:

A. is the main mechanism of cell death for most cell types
B. is manifested primarily in cells of myeloid and lymphoid lineage and in some epithelial cell types
C. takes place when p53 blocks BAK and BAX
D. generally only happens during mitosis
E. occurs only in tumor cells, not in normal tissue cells

V-5) Which of the following would be the **least** likely to contribute to reduced colony-forming ability of irradiated cells?

A. presence of chromosomal inversions
B. senescence
C. autophagy
D. apoptosis
E. necrosis

V-6) Which of the following statements concerning cells undergoing radiation-induced apoptosis is TRUE?

A. Loss of plasma membrane integrity is one of the first steps in the apoptotic process.
B. Caspases become active, move to the nucleus and degrade DNA.
C. Cells susceptible to undergoing apoptosis tend to be radioresistant.
D. Annexin V is able to bind to phosphatidyl serine on the outer membrane.
E. Apoptotic cells usually appear in clusters in irradiated tissues.

V-7) Which of the following statements regarding radiation-induced cell death is TRUE?

A. The majority of cells undergoing radiation-induced cell death do so following mitotic catastrophe
B. The cells that will undergo mitotic catastrophe can be identified immediately post-irradiation by their characteristic morphological features.
C. Apoptosis occurs exclusively through a p53-dependent pathway.
D. Cells that undergo necrosis can be identified by blebbing of their cell membrane, shrinking of the cytoplasm and development of specific DNA fragmentation patterns.
E. At sublethal doses, most cells undergo permanent growth arrest.

V-8) Cells undergoing apoptosis following irradiation:

A. elicit a strong inflammatory response
B. display enhanced expression of the gene encoding MSH2
C. exhibit nuclear fragmentation
D. rapidly swell and burst
E. only initiate this process upon entry into mitosis

V-9) Which of the following statements concerning apoptosis is TRUE?

A. Caspase 8 is an important downstream effector once apoptosis is initiated.
B. p53 activation down-regulates apoptosis.
C. The extrinsic apoptosis mechanism involves stimulation of TNFR family members.
D. BAD is an anti-apoptotic protein.
E. A distinguishing feature of the extrinsic mechanism is the release of mitochondrial cytochrome c.

V-10) Bcl-xL (BCL2L1) inhibition of apoptosis takes place at the:

A. mitochondrion
B. ribosome
C. cell membrane
D. nucleus
E. lysosome

V-11) Which of the following statements is TRUE concerning the irradiation of a series of cell lines derived from breast carcinomas with an X-ray dose of 4 Gy?

A. Most cells will die within several hours.
B. Annexin V staining will be detectable in the majority of cells within minutes.
C. A majority of cells will undergo apoptosis before completing mitosis.
D. Cells derived from tumors with a mutant p53 (TP53) are radioresistant.
E. Many cells will continue to divide for several days.

VI. Cell and Tissue Survival Assays

VI-1) Which one of the following is NOT a fundamental assumption underlying the use of the jejunal crypt cell assay to measure cell survival *in vivo*?

A. All crypts contain approximately the same number of stem cells.
B. Surviving stem cells (and their progeny) in the irradiated volume do not migrate between crypts during regeneration.
C. Stem cells from outside the irradiated volume do not migrate into the area and contribute to the regeneration of the crypts.
D. Stem cells can be identified morphologically and distinguished from differentiated cells.
E. Stem cells in all crypts proliferate within 3 days after irradiation.

VI-2) Till and McCulloch's studies of the radiation response of murine hematological colony forming units (CFU's) represent the first:

A. demonstration of the presence of rare, pluripotent stem cells in a normal tissue
B. clonogenic assay of mammalian cell survival after irradiation
C. attempt at bone marrow transplantation
D. demonstration that pre-irradiation of a bone marrow recipient could enhance the "take rate" of donated marrow
E. demonstration that bone marrow transplantation can rescue lethally-irradiated recipients

VII. Models of Cell Survival

VII-1) A set of data defining the survival of cells irradiated with graded doses of X-rays is well-fitted by the mathematical expression for a single-hit survival curve having an SF_2 of 0.37. The best estimate for the α parameter that describes this survival response is:

A. 0.1 Gy^{-1}
B. 0.01 Gy^{-1}
C. 0.05 Gy^{-1}
D. 0.5 Gy^{-1}
E. 2.0 Gy^{-1}

VII-2) According to classical target theory, D_0 is a measure of the:

A. amount of sublethal damage a cell can accumulate before lethality occurs
B. total number of targets that must be inactivated to kill a cell
C. dose required to produce an average of one lethal lesion per irradiated cell
D. width of the shoulder region of the cell survival curve
E. total number of hits required per target to kill a cell

VII-3) The D_0 for most mammalian cells irradiated with X-rays *in vitro* under well-aerated conditions falls in the range of:

A. 0.1 - 0.2 Gy
B. 0.2 - 1 Gy
C. 1 - 2 Gy
D. 2 - 4 Gy
E. 4 - 8 Gy

VII-4) For a particular cell line characterized by a D_0 of 1 Gy and n equal to 1, what would be the approximate percentage of cells killed by a dose of 3 Gy?

A. 5
B. 10
C. 37
D. 50
E. 95

VII-5) A multifraction protocol for cells exposed to x-rays produces an effective survival curve that is:

A. linear-quadratic
B. bell-shaped
C. linear
D. parabolic
E. exponential

VII-6) For a cell line whose single-dose survival curve is characterized by an n of 10, increasing fraction size causes the effective D_0 to:

A. remain the same
B. increase
C. decrease
D. decrease over a low dose range, but increase at high doses
E. increase over a low dose range, but decrease at high doses

VII-7) Following an X-ray dose of 8 Gy, a clonogenic assay revealed that 20 colonies arose from an initial cell population of 2,000 cells. When 200 unirradiated cells were assayed for clonogenic survival, 40 colonies grew. What is the percent survival following the 8 Gy dose?

A. 0.1
B. 0.5
C. 1
D. 5
E. 10

VII-8) What would be the estimated surviving fraction of V79 Chinese hamster cells irradiated with an X-ray dose of 5 Gy delivered acutely? (Assume α=0.2 Gy^{-1} and β=0.05 Gy^{-2})

A. 0.01
B. 0.10
C. 0.37
D. 0.50
E. 0.90

VII-9) Referring back to the previous question, what would the approximate surviving fraction be if the 5 Gy dose had been delivered over a 10 hour period?

A. 0.01
B. 0.10
C. 0.37
D. 0.50
E. 0.90

VII-10) What is the approximate surviving fraction following 5 doses of 0.5 Gy of carbon ions, assuming that the surviving fraction following one dose is 0.4?

A. 0.01
B. 0.10
C. 0.37
D. 0.50
E. 0.90

VII-11) Which of the following is the most plausible explanation for the decreased clonogenic survival observed among the progeny of cells that survived a prior irradiation?

A. increased expression of genes which encode repair enzymes
B. genomic instability
C. increased synthesis of glutathione
D. adaptive response
E. decreased expression of caspase 8

VII-12) The X-ray survival curve for a particular cell line is characterized by α = 0.4 Gy^{-1} and β = 0.2 Gy^{-2}. What is the dose at which the amount of single-hit cell killing equals the amount of multi-hit cell killing?

A. 0.08 Gy
B. 0.16 Gy
C. 0.4 Gy
D. 0.6 Gy
E. 2 Gy

VIII. Linear Energy Transfer

VIII-1) Which of the following types of ionizing radiation has the highest LET?

A. 2.5 MeV alpha particles
B. 75 MeV/nucleon argon ions
C. 1 GeV/nucleon carbon ion
D. 18 MeV/nucleon carbon ions
E. 150 MeV protons

VIII-2) The carbon ion RBE for hypoxic cells compared with that for aerated cells is:

A. equal
B. lower
C. greater
D. dependent upon the endpoint being measured
E. the same as the OER

VIII-3) Which of the following statements concerning LET is FALSE?

A. The highest RBE occurs for radiations with LET values of approximately 100 keV/μm.
B. High LET radiations yield survival curves with low D_0 values.
C. The OER increases with increasing LET.
D. High LET radiations often produce exponential survival curves.
E. LET is an average energy (in keV) transferred from a charged particle traversing a distance of 1 μm in the medium.

VIII-4) What is the effect on both RBE and the α/β ratio as the LET for the type of radiation increases up to 100 keV/μm?

A. both remain the same
B. both increase
C. both decrease
D. the RBE decreases while the α/β increases
E. the RBE increases while the α/β decreases

IX. Modifiers of Cell Survival: Oxygen Effect

IX-1) For a given biological system, the D_{37} in the presence of O_2 was determined to be 2 Gy for a particulate radiation of energy A and 1 Gy for the same particle with energy B. Under hypoxic conditions, the D_{37} was 6 Gy for A and 1.5 Gy for B. Which of the following statements best describes the relationship between the two radiations?

A. Radiation A has a higher LET than type B.
B. The OER for radiation A is 2.
C. If a given dose of radiation B was delivered at a low dose rate, the amount of cell killing would not differ markedly from that produced at a high dose rate.
D. Radiation B likely has a higher energy than radiation A.

IX-2) In irradiated cells, oxygen:

A. acts as a radical scavenger by converting free radicals to non-reactive species
B. acts as a radioprotector
C. reacts with hydrogen radicals to form water, thus reducing the number of free radicals formed
D. modifies the level and spectrum of free radical damage produced in DNA
E. is unlikely to play a role in the indirect effect of radiation

IX-3) Which one of the following statements regarding radiation and hypoxia is TRUE?

A. Irradiation under hypoxic conditions yields more DNA strand breaks than under aerated conditions.
B. Irradiation under aerated conditions leads to less overall cellular damage than irradiation under hypoxic conditions.
C. The presence of oxygen reduces radiation toxicity.
D. Oxygen must be present either during or within microseconds following irradiation to act as a radiosensitizer.
E. The effect of oxygen on radiation-induced damage varies most between 2% and 5% oxygen.

IX-4) For large, single doses of low LET radiation, the OER is typically in the range of:

A. 0-1
B. 1-2
C. 2-3.5
D. 3.5-5
E. 5-10

IX-5) The oxygen enhancement ratio is:

A. equal to the survival of cells irradiated under hypoxic conditions divided by the survival under aerobic conditions for a fixed radiation dose.
B. greater at low radiation doses than at high radiation doses.
C. the same regardless of radiation quality (LET).
D. equal to the dose of radiation under hypoxic conditions divided by the dose of radiation under aerobic conditions that results in the same biological effect.

X. Modifiers of Cell Survival: Repair

X-1) The mechanism of the radiation bystander effect is thought to involve all of the following, EXCEPT:

A. communication through gap junctions
B. presence of reactive oxygen species
C. aberrant signaling in cancer cells
D. extracellular signaling molecules
E. involvement of specific cytokines

X-2) An X-ray dose of 10 Gy delivered at 1 Gy/min has a greater biologic effect than the same dose delivered at 1 Gy/day because:

A. fewer free radicals are produced
B. apoptosis predominates as the major form of cell death when radiation is delivered at a high dose rate
C. the normal ATM-mediated inhibition of cell cycle progression is inhibited at the higher dose rate
D. cell proliferation may occur during irradiation at the high dose rate
E. there is less repair of the sublethal damage during the course of irradiation at a high dose rate

X-3) What would be the expected effect of a drug that inhibits repair of X-ray-induced chromosome breaks? It would:

A. decrease the yield of terminal deletions
B. increase the dose rate effect
C. stimulate the repair of sublethal damage
D. enhance repair of potentially lethal damage
E. sensitize cells to low dose rate irradiation

X-4) Generally, the sparing effect of dose fractionation increases with increasing time between fractions. Under certain irradiation conditions however, an increase in the interval between fractions results in **decreased** cell survival. This occurs because of:

A. reassortment
B. repopulation
C. repair
D. reoxygenation
E. adaptive response

X-5) Which of the following statements is TRUE concerning SLDR and PLDR?

A. As the dose rate is reduced and exposure time increased for an X-ray treatment, the biological effectiveness of a given dose of radiation increases.
B. PLDR is best demonstrated with a split dose experiment.
C. There is an inverse correlation between the α/β ratio of an acute dose X-ray survival curve and the amount of SLDR in a fractionated irradiation.
D. The magnitude of PLDR and SLDR is greater following exposure to high LET compared to low LET radiation.
E. PLDR plays an important role in the decreased survival seen with fractionated irradiation to the normal lung as compared to lung cancer cells.

X-6) Sublethal damage recovery is best demonstrated by:

A. determining the TCD_{50}
B. a cell synchronization experiment
C. a split dose experiment
D. a delayed plating experiment
E. the paired survival curve technique

X-7) The dose rate range over which SLDR most contributes to the dose rate effect for X-rays is:

A. 0.001 - 0.01 Gy/min
B. 0.01 - 1 Gy/min
C. 1 - 5 Gy/min
D. 5 - 10 Gy/min
E. 10 - 20 Gy/min

XI. Solid Tumor Assay Systems

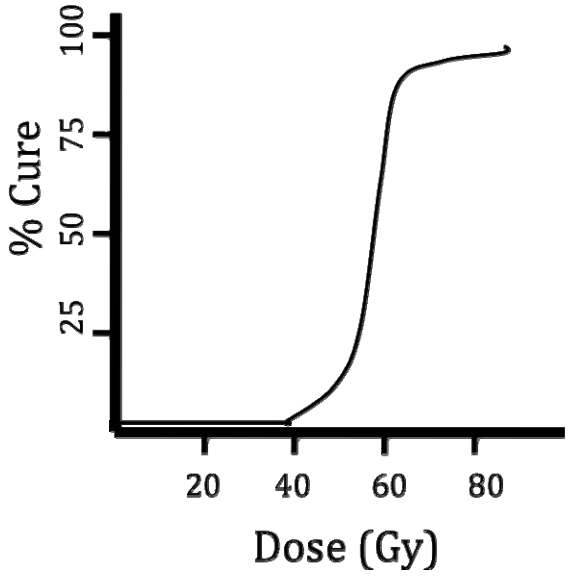
XI-1) Tumor-bearing mice are randomized into a control group and groups treated with localized irradiation of the tumor alone, an anticancer drug alone, or radiation in combination with the drug. Which of the following represents the most rigorous, reliable and informative approach to comparing the effectiveness of the different treatments?

A. Killing the mice at a predetermined time after treatment, removing and weighing the tumors, and calculating the ratio of the volumes of the treated and control tumors.
B. Measuring three diameters of the tumors with calipers at a predetermined time after treatment, calculating the volume and computing the ratio of the volumes of the treated and control tumors.
C. Measuring the tumors 3x per week until the treated tumors return to their pre-irradiation volume and calculating the mean time needed for each group to reach that volume.
D. Measuring the tumors 3x per week until the control tumors reach 4 times the volume at the time of treatment, and comparing the mean volume of the tumors in each treatment group at that time.
E. Measuring the tumors 3x per week until each tumor reaches 4 times the volume at the time of treatment and calculating the mean time needed for the tumors in each group to reach that volume.

XI-2) For a group of tumors identical in size and homogeneous with respect to cellular radiosensitivity, what would be the general shape of the curve in a linear-linear graph defining the increase in tumor control probability with increasing radiation dose?

A. step function from 0 – 100% at the dose that kills all of the cells
B. linear increase from 0 – 100% over a narrow range of doses
C. logarithmic increase from 0 – 100% over a wide range of doses
D. sigmoidal increase from 0 – 100% over a narrow range of doses
E. exponential increase from 0 – 100% over a narrow range of doses

XI-3) The following graph shows data for the percent of tumors controlled by different doses of radiation therapy. Based upon the data provided in this graph, which of the following statements is correct?



A. TCD_{50} is 70 Gy
B. $NTCP_{50}$ is 60 Gy
C. The additional dose required to increase the probability of tumor control from 50 to 60% is larger than the dose required to increase the probability of tumor control from 90 to 100%
D. The impact of a radiosenisitizer upon tumor control will be most readily detected for experimental protocols that result in a 50% rate of tumor cure.

XII. Tumor Microenvironment

XII-1) Which of the following statements concerning the tumor microenvironment is true?

A. Hypoxia is found primarily at the core of large tumors.
B. Cellular oxygenation status in solid tumors is expected to remain relatively constant over a 24 hr period.
C. Tumors of a similar size have similar hypoxic fractions.
D. Acute changes in blood flow contribute to tumor hypoxia.
E. Hypoxic tumors are resistant to irradiation due to expression of HIF1.

XII-2) Tumor hypoxia has been specifically associated with all of the following, EXCEPT:

A. reduced radiosensitivity
B. large tumors
C. increased genomic instability
D. poor patient prognosis
E. increased metastasis

XII-3) In a respiring tissue, the maximum diffusion distance of oxygen from a capillary is:

A. 1-2 μm
B. 100-200 μm
C. 1-2 mm
D. independent of cellular respiration rate
E. independent of hemoglobin concentration

XII-4) Which of the following statements concerning tumor hypoxia is FALSE?

A. Chronically hypoxic cells are generally more radiation resistant than acutely hypoxic cells.
B. For a tumor containing only 1% radiobiological hypoxic fraction, essentially all hypoxic cells would be eliminated by the end of a typical course of radiotherapy, even in the absence of any reoxygenation.
C. Hypoxic regions in tumors may be detected using pimonidazole.
D. Regions of acute hypoxia may develop in tumors due to the temporary closing/blockage of a blood vessel.
E. Reoxygenation during fractionation in radiotherapy reduces the influence of hypoxic cells on tumor response.

XII-5) HIF-1 activity is increased primarily during hypoxia as a consequence of:

A. increased transcription of HIF-1α
B. reduced stability of HIF-1β
C. increased turnover of HIF-1 α
D. reduced hydroxylation of HIF-1α
E. increased activity of VHL

XII-6) With regard to the radiobiological influence of oxygen, which of the following statements is FALSE?

A. Reoxygenation of human tumors during fractionated radiation therapy reduces the impact of both chronically and acutely hypoxic cells on overall response.
B. Metabolically-active hypoxic cells in human tumors can be identified through preferential binding of administered nitroimidazole compounds.
C. Hypoxia induces pro-angiogenic factors such as VEGF.
D. HIF-1α is stabilized under hypoxic conditions and dimerized with constitutive HIF-1β.
E. The oxygen enhancement ratio (OER) for X-rays is higher for doses < 2 Gy than for doses > 10 Gy.

XII-7) Which of the following markers and imaging approaches would be **least** useful for measuring tumor hypoxia non-invasively?

A. [^{18}F]-fluorodeoxyglucose (FDG) – PET
B. [^{18}F]-fluoromisonidazole (FMISO) – PET
C. [^{123}I] radioiodinated azomycin arabinosides - SPECT
D. [^{64}Cu]-Cu-ATSM - PET

XII-8) A non-invasive method for the detection of hypoxic regions in tumors and/or measuring oxygen concentration in tumors would allow the:

A. identification of patients to receive alternative therapy.
B. histology of the tumor to be determined.
C. volume of the tumor to be calculated.
D. radiation sensitivity of the tumor to be determined.
E. repair capacity of the tumor to be estimated.

XII-9) The expression of which of the following genes is regulated by the stabilization of HIF-1α in the absence of oxygen in tissues?

A. polε
B. ATR
C. PDGFR
D. VEGF
E. RAS

XII-10) All of the following have been shown to be affected by HIF1α during hypoxia, EXCEPT:

A. glycolysis
B. angiogenesis
C. epo production
D. p53 activation
E. pH regulation

XII-11) Which of the following statements concerning hypoxia is TRUE?

A. Hypoxic cell radiosensitizers produce a greater increase in the therapeutic index when used with conventional fractionated radiotherapy than for treatment with one or a few large radiation doses.
B. A biphasic survival curve would result from low LET irradiation of a mixed population of both aerated and hypoxic cells.
C. The OER is defined as the dose to produce a given effect in aerated cells divided by the dose to produce the same effect in hypoxic cells.
D. The diffusion distance of oxygen in air is typically less than 100 μm.
E. For low LET radiation, the maximum OER is typically observed only when the tissue oxygen concentration reaches about 20%.

XII-12) Which of the following would best be used to estimate the proportion of radiation resistant viable hypoxic cells in an experimental tumor model?

A. Comparison of radiation response with and without breathing of hyperbaric oxygen.
B. Paired survival curve analysis in vitro following irradiation in vivo under standard conditions and conditions where blood flow to the tumor has been stopped.
C. Extrapolation of the initial exponential portion of the cell survival curve for cells comprising the tumor.
D. Comparison of radiation responses with and without misonidazole administration.

XIII. Cell and Tissue Kinetics

XIII-1) Which of the following statements is FALSE concerning the cell cycle?

A. Irradiation of cells causes a delay in progression from G_1 into S phase of the cell cycle.
B. Cells in M phase typically have X-ray survival curves with low α/β ratios.
C. Cells are most resistant in late S phase of the cell cycle.
D. G_1 is the cell cycle phase most variable in duration.
E. The G_0 phase of resting cells is within G_1.

XIII-2) The diameter of a tumor was found to double in 18 days. Assuming that all of the cells in the tumor are proliferating and no cells are lost, the tumor cell doubling time is closest to:

A. 1 day
B. 3 days
C. 6 days
D. 12 days
E. 18 days

XIII-3) CDK1/cyclin B plays an important role in the transition of cells from:

A. G_0 into G_1
B. G_1 into S
C. S into G_2
D. G_2 into M
E. M into G_1

XIII-4) Which of the following statements is TRUE concerning the cell cycle kinetics of human tumors?

A. The growth fraction of a tumor represents the proportion of cells capable of transplanting the tumor.
B. Cell loss is often the major factor that determines the tumor volume doubling time.
C. The growth rate generally increases with increasing tumor size.
D. Volume doubling times are shorter than the value that would be predicted from the cell cycle time of individual cells.
E. The volume doubling time is largely determined by the cell cycle time.

XIII-5) A tumor is characterized by a cell cycle time of 10 days, a growth fraction of 0.5 and a cell loss factor of 1.0. Assuming these kinetic parameters remain constant over a one month period, how much would the tumor volume have increased during that time?

A. increase 2-fold
B. increase 3-fold
C. increase 4-fold
D. increase 5-fold
E. remain the same

XIII-6) The T_{pot} for a tumor can be calculated from the cell cycle time of the cells comprising the tumor, the tumor's growth fraction and with the assumption that the cell loss factor is:

A. 0
B. 1.0
C. 0.2
D. 0.6
E. nearly 1.0 when the tumor is small, but decreasing exponentially as the tumor grows

XIII-7) The T_{pot} for most head and neck tumors is in the range of:

A. 1-2 days
B. 2-6 days
C. 6-24 days
D. 24-100 days
E. greater than 100 days

XIII-8) If the T_S, LI and λ (the correction factor for the non-linear distribution of cells through the cell cycle) were determined for a tumor to be 10 hours, 0.2 and 0.7, respectively, then the T_{pot} is:

A. 2 hours
B. 10 hours
C. 18 hours
D. 25 hours
E. 35 hours

XIII-9) Two patients are diagnosed on the same day with tumors of approximately the same size. However, the T_{pot} for patient A's tumor was determined to be 5 days while the T_{pot} for patient B's tumor was calculated as 20 days. Assuming that there was no cell loss taking place and the tumor's growth fractions did not change, if treatment had been initiated 20 days earlier, the ratio of the number of cells in the tumors of patient A to patient B would have been approximately:

A. 16:1
B. 8:1
C. 1:1
D. 1:8
E. 1:20

XIII-10) The most likely explanation for why a tumor, composed of cells with short cell cycle times, would have a long volume doubling time is a:

A. high cell loss factor
B. large percentage of cells entering G_0 following mitosis
C. low growth fraction
D. large hypoxic fraction
E. abnormally long S phase

XIII-11) The volume doubling time (in days) for a tumor with a cell loss factor of 90% and a T_{pot} of 20 days would be estimated as:

A. 5
B. 20
C. 50
D. 100
E. 200

XIII-12) Which of the following proteins does NOT participate in the p53 pathways involved in cell cycle regulation?

A. SMC1
B. CAK
C. p21 (CDKN1A)
D. GADD45A
E. 14-3-3-σ

XIV. Molecular Signaling

XIV-1) Mutations in growth factor receptors are common alterations in cancer that may:

A. signal cells to enter senescence
B. directly inhibit protein translation
C. cause formation of γ-H2AX foci in cell nuclei
D. result in constitutive kinase activity that signals cells to proliferate
E. stimulate ubiquitination of caspase 3 to induce apoptosis

XIV-2) In cancer treatment, there has been clinical interest in targeting the RAS oncogene product using:

A. HDAC inhibitors
B. cyclin-dependent kinases
C. farnesyl transferase inhibitors
D. I-κB
E. Iressa

XIV-3) The transcriptional activity of the tumor suppressor p53 has been shown to be regulated by all of the following, EXCEPT:

A. phosphorylation of p53 (TP53) by ATM
B. changes in the subcellular localization of p53
C. changes in the ubiquitination of MDM2
D. $p19^{ARF}$-induced changes in acetylation of p53
E. binding of FAS ligand (FASLG/CD95-L) to FAS (CD95/APO-1)

XIV-4) RAS functions as a:

A. GTPase
B. protein kinase
C. phosphatidyl inositol kinase
D. phosphatase
E. transcription factor

XIV-5) Which one of the following is NOT a part of the RAS pathway that stimulates cell proliferation following irradiation?

A. RAF1
B. MEK
C. MAPK (ERK)
D. FADD
E. RHO

XIV-6) Epigenetic modification of DNA-associated histones can occur through all of the following mechanisms, EXCEPT:

A. phosphorylation
B. acetylation
C. glycosylation
D. methylation
E. ubiquitination

XIV-7) Which of the following is the most likely consequence of EGFR activation?

A. increased proliferation
B. apoptosis
C. cell cycle arrest
D. stabilization of microtubules
E. endocytosis

XV. Cancer

XV-1) Which of the following statements concerning telomerase is TRUE? Telomerase:

A. is activated when telomeres decrease below a critical size
B. plays a central role in base excision repair
C. is present at high levels in senescent cells relative to normal cells
D. adds DNA sequence repeats onto the ends of chromosomes
E. activation in tumor cells represents a promising cancer treatment strategy

XV-2) Which of the following statements regarding p53 (TP53) is FALSE? p53:

A. is targeted by MDM2 for degradation
B. mutation in lymphoma cells usually renders these cells radiosensitive
C. is a substrate for the ATM protein kinase
D. serves as a transcription factor and upregulates p21 (CDKN1A)
E. upregulates the pro-apoptotic factors BAX and PUMA

XV-3) Which of the following statements concerning retinoblastoma and the RB (RB1) protein is TRUE?

A. The RB protein suppresses cell proliferation by binding to the E2F transcription factor, thereby inhibiting gene expression.
B. Cell cycle dependent kinases add hydroxyl groups to the RB gene product causing it to release E2F.
C. A mutant *RB* gene is inherited from one parent in the sporadic form of retinoblastoma.
D. The RB protein product is phosphorylated by CDK1.
E. In the familial form of retinoblastoma, patients are only at elevated risk for retinoblastoma, and not other cancers.

XV-4) The importance of DNA repair in preventing carcinogenesis is demonstrated by all of the following clinical/experimental findings, EXCEPT:

A. People suffering from hereditary non-polyposis colon cancer often exhibit mutations in DNA mismatch repair genes.
B. Mutations in caretaker genes may play an important role in cancer progression.
C. Xeroderma pigmentosum patients show an elevated incidence of skin cancers.
D. Virtually all tumor cell lines analyzed have been found to have one or more DNA repair deficiencies.
E. Alteration of a mutator gene may be an early step in carcinogenesis.

XV-5) Oncogenes:

A. can be activated by epigenetic silencing
B. are inherited in familial cancers
C. are induced by gene loss
D. can be activated by point mutation
E. are important barriers to prevent tumor formation

XV-6) $p16^{INK4A}$ (CDKN2A):

A. is an oncogene
B. is a CDK inhibitor
C. is rarely found mutated in tumors
D. over-expression is associated with metastatic potential
E. is inactivated in hypoxic cells

XV-7) Which of the following disorders associated with chromosomal instability does NOT predispose to cancer?

A. Cockayne's syndrome
B. Bloom's syndrome
C. Fanconi's anemia
D. Nijmegen breakage syndrome
E. Ataxia telangectasia

XV-8) Following irradiation, which of the following events involving ATM occurs? ATM:

A. activation is inhibited by the MRN complex.
B. is phosphorylated and undergoes dimerization resulting in its activation.
C. causes phosphorylation of MDM2, stimulating its inhibitory action against p53.
D. phosphorylates CHEK2 and inhibits CDC25C activity.
E. dephosphorylates γH2AX.

XV-9) All of the following are phosphatidyl inositol 3-kinase like kinases, EXCEPT:

A. ATM
B. BRCA1
C. ATR
D. RAD3
E. DNA-PK (PRKDC)

XV-10) Which of the following statements is FALSE concerning NFκB? NFκB:

A. inhibits non-homologous end-joining of DNA double strand breaks.
B. typically inhibits apoptosis.
C. is a transcription factor.
D. activation is associated with tumor progression.
E. can be activated following irradiation.

XV-11) Which of the following statements concerning tumor suppressor genes is FALSE?

A. Loss of heterozygosity is a mechanism for the inactivation of tumor suppressor genes.
B. The products of tumor suppressor genes generally accelerate cell growth.
C. One or more tumor suppressor genes are typically mutated or absent in human cancers.
D. The most commonly altered tumor suppressor gene is *p53* (*TP53*).
E. The first tumor suppressor gene discovered was RB (RB1).

XV-12) Which one of the following is a tumor suppressor gene?

A. NEU
B. RET
C. BRAF
D. RAS
E. PTEN

XV-13) Which of the following is NOT a phenotypic characteristic of a person diagnosed with ataxia telangiectasia?

A. neurodegeneration
B. abnormalities in ocular blood vessels
C. immune system defects
D. sensitivity to UV induced cancers
E. radiosensitivity

XV-14) Which statement regarding oncogenes and tumor suppressor genes is TRUE?

A. A gain of function mutation of an oncogene would be recessive on a cellular level.
B. A gain of function mutation in a tumor suppressor gene would stimulate malignant progression of a tumor.
C. Cancer susceptibility due to inheritance of a mutated tumor suppressor gene behaves in a dominant fashion.
D. A loss of function mutation in a tumor suppressor gene would be dominant on a cellular level.
E. A loss of function mutation in an oncogene would be dominant in a pedigree in regard to cancer susceptibility.

XV-15) Which of the following statements is FALSE?

A. BRCA1 is deleted in the majority of breast cancers.
B. An increased incidence of CLL has not been found in irradiated populations.
C. A translocation between chromosome 9 and 22 is often present in CML.
D. DCC is a tumor suppressor gene that has been found altered in colon cancer.
E. A mutated mismatch repair gene is often found in people with hereditary non-polyposis colon cancer (HNPCC).

XV-16) Which of the following statements is FALSE?

A. RAS stimulates the MAPK pathway.
B. CDK1/cyclin B constitute the mitosis promoting factor (MPF).
C. The first oncogene discovered was in a retrovirus (Rous sarcoma virus).
D. p21 (CDKN1A) levels decrease in irradiated cells.
E. ATM acts upstream of p53.

XV-17) Which of the following processes is NOT a typical mechanism for the activation of a proto-oncogene to an oncogene?

A. loss of heterozygosity
B. point mutation
C. retroviral insertion
D. chromosomal rearrangement
E. gene amplification

XV-18) Defects in mismatch repair proteins have been associated with which one of the following tumors?

A. Hereditary non-polyposis colorectal cancer
B. Neurofibromatosis
C. Ovarian carcinoma of the serous type
D. Glioblastoma
E. Retinoblastoma

XV-19) Overexpression of BCL2 promotes tumorigenesis because BCL2 over-expressing cells:

A. exhibit diminished levels of apoptosis
B. proliferate more rapidly than their normal counterparts
C. have increased angiogenesis
D. are more likely to be hypoxic
E. have a decreased ability to repair DNA double strand breaks

XVI. Total Body Irradiation

XVI-1) Which of the following statements concerning whole body effects of radiation is TRUE?

A. The time to death from the hematopoietic syndrome is 1-2 months.
B. The time to death from the cerebrovascular syndrome is 2-4 weeks.
C. The time to death from the gastrointestinal syndrome is 2-4 months.
D. The threshold dose for the gastrointestinal syndrome is 1 Gy.
E. The threshold dose for the hematopoietic syndrome is 10 Gy.

XVI-2) The main cause of death from the hematopoietic syndrome is:

A. hypotension arising from microvascular destruction
B. hemolytic anemia
C. infection and hemorrhage resulting from loss of white cells and platelets
D. loss of erythrocytes resulting in organ ischemia
E. dehydration due to extravasation of fibrin from blood vessels

XVI-3) Which of the following statements is TRUE concerning a female worker at a radioactive waste reprocessing facility who accidentally receives an estimated 3 Gy acute whole body γ-ray dose?

A. Antibiotic treatment should not be initiated until signs of infection.
B. Tissue typing should be done for a possible bone marrow transplant.
C. Within one week she will become dehydrated, suffer infections, develop bloody diarrhea and likely die.
D. She should be sent home and advised to schedule an appointment with a physician about 6 months later, as this represents the minimum latency period prior to the manifestation of radiation injury.
E. She should be monitored carefully to watch for symptoms of infection

XVI-4) Which of the following would probably NOT be noted in an individual who received an acute, whole body dose of 5 Gy of X-rays and received no medical care?

A. infection
B. nausea
C. bleeding
D. death within 1 week following irradiation
E. epilation

XVI-5) A detectable change in blood count would be expected following a minimum whole body dose of approximately:

A. 0.001 Gy
B. 0.01 Gy
C. 0.1 Gy
D. 1 Gy
E. 10 Gy

XVI-6) Within 4 days of an accidental whole body radiation exposure at a nuclear power plant, 8 workers develop severe diarrhea. Assuming that 3 of the workers are female and 5 male, what is their likely prognosis?

A. All will live, but will likely develop radiation-induced cancers.
B. Approximately 50% will survive.
C. All will live, but with an increased risk of cataracts.
D. They will all die in less than a month following the irradiation.
E. The men will be sterilized, but the women will remain fertile.

XVI-7) Which of the following radiation-induced effects could be a cause of death one year after total body irradiation of a patient being prepared for a bone marrow transplant?

A. hematopoietic syndrome
B. gastrointestinal syndrome
C. cerebrovascular syndrome
D. brain necrosis
E. lung fibrosis

XVI-8) Immunosuppression observed within 24 hours following exposure to a whole body dose of 5 Gy X-rays would be due primarily to:

A. death of hematopoietic progenitor cells
B. apoptosis of peripheral blood lymphocytes
C. a loss of circulating granulocytes
D. decreased activity of NK cells
E. inactivation of circulating antibodies

XVI-9) Which of the following statements concerning the human LD_{50} is TRUE?

A. The $LD_{50/60}$ associated with an acute whole body irradiation is approximately 3.5 Gy for people who do not receive appropriate medical care following irradiation.
B. Even with optimal medical care, the $LD_{50/60}$ cannot be increased.
C. The most common cause of death in people who receive a dose close to the $LD_{50/60}$ is severe anemia.
D. A person who received a whole body dose close to the $LD_{50/60}$ would exhibit severe diarrhea within 24 hours.
E. The $LD_{50/60}$ is the dose that leads to death within 50 days of 60% of the population.

XVI-10) Total body irradiation in preparation for a bone marrow transplant is delivered at a low dose rate in order to reduce injury to the:

A. parotid glands
B. lung
C. skin
D. oral mucosa
E. lymphocytes

XVI-11) Which of the following is the correct temporal sequence for the appearance of the stated radiation effect on peripheral blood components?

A. lymphocytopenia, granulocytopenia, thrombocytopenia, anemia
B. anemia, lymphocytopenia, granulocytopenia, thrombocytopenia
C. granulocytopenia, thromobocytopenia, anemia, lymphocytopenia
D. lymphocytopenia, anemia, granulocytopenia, thrombocytopenia
E. lymphocytopenia, thrombocytopenia, granulocytopenia, anemia

XVII. Clinically Relevant Normal Tissue Responses to Radiation

XVII-1) Which of the following statements concerning radiation cataractogenesis is TRUE?

A. The lens of the eye is capable of eliminating cells damaged by radiation, which has the net effect of decreasing the incidence of cataracts.
B. There is a shorter latency period for the development of cataracts following a large radiation dose than a small one.
C. The neutron RBE for cataract formation following irradiation with a series of small doses is approximately 3.0.
D. For an acute exposure, the threshold dose for the induction of an X-ray-induced cataract is 15 Gy.
E. As is true for most radiation-induced injuries, there are no pathognomonic characteristics specific for a radiation-induced cataract.

XVII-2) Which of the following statements concerning the radiation-induced effects of fractionated total body irradiation in children being prepared for a bone marrow transplant is FALSE?

A. Approximately half of the children develop severe restrictive pulmonary disease.
B. The majority will develop cataracts.
C. Thyroid cancer is the main second malignancy observed.
D. The younger the child at the time of irradiation, the greater the risk for the development of osteochondroma.
E. Manifestations of hypogonadism are common in both boys and girls.

XVII-3) Which of the following statements is TRUE concerning irradiation of the testes?

A. Spermatids and spermatozoa are relatively radiosensitive, whereas spermatogonia tend to be radioresistant.
B. A substantial drop in testosterone levels can be detected following a scattered X-ray dose of 0.1 Gy to the testes of an adult man.
C. If sterility in the male is not observed within one month following irradiation, it is unlikely to occur at a later time.
D. Dose fractionation increases the risk for sterility in the male.
E. Full recovery of a normal sperm count following radiation-induced azoospermia caused by exposure to a dose of 6 Gy of X-rays generally occurs within 6 months.

XVII-4) Concerning irradiation of the small and large intestine, which of the following statements is FALSE?

A. Chronic radiation injury is attributable primarily to fibrosis and vascular insufficiency (chronic ischemia).
B. The most common portions of the intestinal tract that display radiation damage include the cecum, terminal ileum, rectum and distal sigmoid.
C. Acute radiation injury is most prominent in the mucosa, whereas late effects tend to manifest themselves in the submucosa.
D. Compared to other hierarchical tissues, the gastrointestinal mucosa is a slowly renewing system.
E. Killing of the stem cells in the gut crypts and the resulting failure to replace mature cells causes the gastrointestinal syndrome following acute radiation exposure.

XVII-5) Which of the following statements concerning complications arising from pelvic irradiation is FALSE?

A. Diarrhea is the most common manifestation of radiation injury to the bowel.
B. Diarrhea usually does not appear until at least 6 months following the completion of radiotherapy.
C. Late bowel reactions include mucosal atrophy, stenosis, ulceration, obstruction, adhesions and perforation.
D. Bowel stenosis can develop in the absence of severe mucosal atrophy or ulceration.
E. Adhesions following irradiation contribute to late bowel injury and usually develop 2-7 months after irradiation.

XVII-6) Which of the following statements concerning irradiation of the spinal cord is FALSE?

A. Early radiation myelopathy differs from transient demyelination in that it is less severe.
B. One of the main manifestations of transient demyelination is Lhermitte's sign.
C. White matter necrosis starts as focal demyelination that develops into focal necrosis.
D. The clinical syndrome resulting from white matter necrosis is "early myelopathy", which has a latency period of 3-6 months following irradiation.
E. Late vascular injury causes a chronic, progressive myelopathy that develops gradually and progresses slowly over several years after a latency period of 3-6 months.

XVII-7) Which of the following statements concerning late radiation effects in the brain is FALSE?

A. The classical late radiation effect in the brain is localized necrosis generally limited to the involved white matter, with focal coagulative necrosis and demyelination as dominant features.
B. Symptoms of late radiation effects include motor, sensory and/or speech/receptive deficits, seizures and symptoms of increased intracranial pressure.
C. The "somnolence syndrome" is observed 1-6 months post-irradiation.
D. During the 3-6 month period following completion of RT, a general neurologic deterioration may occur that results from transient, diffuse demyelination.
E. Arterial cerebrovasculopathy is commonly observed.

XVII-8) Which of the following statements is TRUE concerning the response of the kidney to radiation? The kidney:

A. is considered a relatively radiosensitive organ because of the marked sensitivity of cells that comprise the nephron
B. exhibits little sparing with increasing dose fractionation
C. has a relatively low tolerance dose because of the limited number of clonogens within each functional subunit
D. displays substantial re-treatment tolerance
E. manifests symptoms of radiation nephropathy generally within 3 months following the completion of radiotherapy

XVII-9) Concerning radiation induced liver disease (RILD), all of the following statements are true, EXCEPT:

A. RILD is a clinical syndrome of hepatomegaly in the absence of jaundice, ascites and elevated liver enzymes.
B. RILD is rarely observed earlier than six months following the completion of radiotherapy.
C. Suprahepatic vein obstruction and veno-occlusive liver disease are seen in RILD.
D. Pathologic changes in RILD include marked venous congestion in the central portion of each lobule – with sparing of the larger veins – and atrophy of hepatocytes adjacent to the congested veins.
E. Killing of vascular endothelial cells appears to be of greater importance than hepatocyte lethality in the pathologic changes observed in RILD.

XVII-10) Which of the following effects is typically observed within a week following irradiation of the small intestine?

A. hypertrophic villi
B. lymphocyte infiltration
C. atrophic villi
D. mucosal atrophy
E. bowel stenosis

XVII-11) The best way to spare the parotid gland is to:

A. use hyperfractionated radiotherapy
B. decrease the target volume
C. increase the overall treatment time
D. use hypofractionated radiotherapy
E. accelerate treatment

XVII-12) Of the following, the organ/tissue least able to tolerate re-irradiation is the:

A. spinal cord
B. oral mucosa
C. kidney
D. lung
E. liver

XVII-13) A drug used to treat fibrosis and osteoradionecrosis is:

A. amifostine
B. tirapazamine
C. nicotinamide
D. pentoxifylline
E. misonidazole

XVII-14) The lacrimal gland is comparable to which of the following organs/glands in terms of its radioresponse?

A. parotid
B. heart
C. liver
D. sebaceous
E. skin

XVII-15) Which of the following has the highest radiation tolerance dose ($TD_{5/5}$) for whole organ irradiation?

A. kidney
B. ureter
C. colon
D. stomach
E. liver

XVII-16) Which of the following series of skin reactions match the acute single dose and time to elicit the reaction?

A. temporary erythema - 1 Gy - 7 days
B. permanent epilation - 7 Gy - 3 months
C. moist desquamation - 3 Gy - 4 weeks
D. dry desquamation - 14 Gy - 1 week
E. temporary epilation - 3 Gy - 3 weeks

XVII-17) Renal irradiation can lead to the development of radiation nephropathy, which is characterized by proteinuria, anemia, hypertension and a chronic, progressive decrease in renal function. The decline in kidney function characteristic of radiation nephropathy can be:

A. treated with anti-hypertensive agents such as beta blockers.
B. prevented using anti-inflammatory agents.
C. reversed using calcium channel blockers.
D. mitigated using drugs that block the renin-angiotensin system.
E. accelerated at lower radiation doses.

XVII-18) Which of the following is NOT a delayed effect following head and neck radiation therapy?

A. dysphagia
B. mucositis
C. persistent xerostomia
D. telangiectasia
E. ulcer

XVII-19) Which of the following statements is TRUE concerning radiation effects on lymphoid tissues?

A. T cells are generally more radiosensitive than B cells.
B. Filter function in lymph nodes is unaffected by radiation.
C. Altered immunity is an important factor in gastrointestinal syndrome following whole body irradiation.
D. Morphologically, the spleen shows few late effects.
E. The thymus appears almost fully functional following irradiation, with doses in the range typically used in radiotherapy, for cancers in which this organ is in the radiation field.

XVIII. Mechanisms of Normal Tissue Radiation Responses

XVIII-1) The tolerance dose for xerostomia resulting from treatment of a head and neck tumor with 3 Gy fractions compared to 2 Gy fractions would be expected to:

A. increase substantially
B. increase slightly
C. decrease substantially
D. remain about the same
E. either increase or decrease depending upon the particular patient

XVIII-2) Assuming that the target cells do not have a pro-apoptotic tendency, the time to the expression of radiation damage in early-responding tissues typically correlates best with the:

A. radiosensitivity of the cells
B. lifespan of the mature functional cells of the tissue
C. ability of the cells to perform homologous recombinational repair of DNA damage
D. lifespan of the stem cells comprising that tissue
E. type of radiation used to irradiate the organ

XVIII-3) Which of the following statements is FALSE concerning cytokines?

A. bFGF (FGF2) enhances radiation-induced apoptosis of endothelial cells.
B. High levels of TGFβ1 (TGFB1) have been reported to be associated with an increased risk of pulmonary fibrosis following radiotherapy.
C. IL-1 is a bone marrow radioprotector.
D. VEGF transcription is stimulated by hypoxia as a result of hypoxia inducible factor (HIF-1) binding to a hypoxia responsive element (HRE) within the VEGF promoter.
E. A paracrine response involves production of cytokines in which the target cells are located in the vicinity of the expressing cell.

XVIII-4) All of the following growth factors appear to play a role in radiation-induced lung fibrosis, EXCEPT:

A. TGFβ (TGFB1)
B. IGF
C. bFGF (FGF2)
D. CTGF
E. PDGF

XVIII-5) As the dose to an organ increases, the latency period prior to the development of a late complication generally:

A. increases
B. decreases
C. remains the same
D. increases, but only for an accelerated protocol
E. decreases, but only for a hyperfractionated protocol

XVIII-6) The shape of the dose response curve for the induction of late effects is best described as:

A. Gompertzian
B. linear
C. threshold
D. sigmoidal
E. linear-quadratic

XVIII-7) Which of the following statements regarding the development of radiation-induced lung damage is TRUE?

A. The volume of lung irradiated has relatively little effect on the tolerance dose.
B. Radiation-induced pneumonitis is delineated by the treatment field.
C. The majority of patients who develop radiation pneumonitis go on to develop pulmonary fibrosis.
D. The $TD_{5/5}$ for whole lung irradiation with a single dose is approximately 17.5 Gy.
E. Fractionation has little or no effect on lung tolerance.

XVIII-8) In normal tissues, the radiation tolerance dose is hypothesized to depend on the ability of tissue clonogens to maintain an adequate number of mature functioning cells. The relationship between organ function and clonogenic cell survival is dependent on the structural organization of functional subunits (FSUs) within the particular tissue. Which of the following statements concerning FSUs is TRUE? FSUs:

A. contain a relatively set number of clonogens.
B. cannot be repopulated from a single surviving clonogen.
C. are defined as units with clear anatomical demarcation.
D. are usually dependent on one another in a functional sense.
E. cannot be repopulated from an adjacent FSU.

XVIII-9) With the increasingly sophisticated refinements in radiation therapy techniques, more attention is now being paid to normal tissue dose and volume factors as they relate to the probability of treatment-associated late effects. Which of the following statements concerning the volume dependence of late complications is FALSE?

A. The parameter that best predicts for lung complications after radiotherapy is the V_{20}/V_{30}.
B. Length irradiated is a critical factor in determining the tolerance dose for the esophagus.
C. The percent volume of rectal wall that receives 40-50 Gy positively correlates with the likelihood of rectal bleeding.
D. The V_{eff} for the liver is 0.94.
E. Small volume irradiation of the brain can lead to focal radiation necrosis.

XVIII-10) Which of the following statements about TGFβ (TGFB1) is FALSE? TGFβ:

A. is a chemo-attractant for granulocytes
B. is a suppressor of T lymphocytes
C. increases proliferation of fibroblasts and smooth muscle cells
D. increases proliferation of epithelial cells
E. requires activation to be biologically active

XVIII-11) Which of the following statements concerning the tolerance of normal tissues to re-irradiation is TRUE?

A. Evidence from animal studies suggests that the spinal cord can be re-irradiated to at least partial tolerance provided at least 6 months have passed since an initial course of treatment.
B. Soft tissue or bone necrosis has not been observed in patients receiving re-irradiation of recurrent or new primary head and neck tumors.
C. Mouse lungs appear incapable of tolerating a second course of fractionated radiation, regardless of the total dose given during the initial course of radiotherapy.
D. Rapidly dividing mucosal tissues cannot be re-irradiated, even several years after completion of the initial treatment.
E. Animal experiments show that the kidney can be re-irradiated to 80-90% of a full tolerance dose as long as 3 months have elapsed since the initial treatment.

XVIII-12) The TD_5 as a function of length of spinal cord irradiated:

A. decreases as a linear function of increasing cord length.
B. initially decreases with increasing cord length, and then remains relatively constant for higher total doses.
C. increases steeply for lengths greater than approximately 10 cm.
D. decreases with decreasing cord length.
E. increases with cord length before reaching a plateau.

XVIII-13) Radiation-induced epilation occurs before dermatitis because:

A. basal cells in the epidermis have shorter cell cycle times than the germinal matrix of the hair bulb
B. cells in the germinal matrix of the hair bulb have shorter cell cycle times than the basal cells of the epidermis
C. of the exquisite sensitivity of sebaceous glands
D. of vascular endothelial cell death in the connective tissue at the distal end of the hair follicle
E. of keratin synthesis inhibition in the hair follicle

XVIII-14) All of the following organs can tolerate 70 Gy (delivered in 2 Gy fractions) to 5% of their volume, except the:

A. spinal cord
B. kidney
C. lung
D. liver
E. heart

XIX. Therapeutic Ratio

XIX-1) A tumor contains 10^6 clonogenic cells. Its effective dose response curve has been determined for dose fractions of 2 Gy/day, and is characterized by no shoulder and a D_0 of 2.5 Gy. What is the total dose required to give a 37% chance of tumor cure, assuming sufficient time between fractions to allow full repair of sublethal damage and no cell proliferation between doses?

A. 5 Gy
B. 14 Gy
C. 21 Gy
D. 28 Gy
E. 35 Gy

XIX-2) Based on the same parameters as provided in the previous question, what additional dose must be added to still achieve a 37% chance of tumor cure, if the clonogens in the tumor went through three cell divisions during treatment (assuming that there is no cell loss)?

A. 1 Gy
B. 2 Gy
C. 5 Gy
D. 10 Gy
E. 20 Gy

XIX-3) Suppose a chemotherapeutic agent that killed tumor cells, independently of radiation, was also employed during the aforementioned course of treatment. It is known from previous data that this drug regimen results in a surviving fraction of 10^{-4} for the tumor under treatment. Now what is the total radiation dose required to produce a 37% chance of tumor cure (still assuming that the cells go through three cell divisions)?

A. 12 Gy
B. 17 Gy
C. 24 Gy
D. 36 Gy
E. 48 Gy

XIX-4) Tumors A and B have identical single dose TCD_{50} values. However, the cell survival dose response curve for tumor A is characterized by an α/β ratio of 2 Gy, while the curve for tumor B has an α/β ratio of 30 Gy. If these tumors are both treated with a fractionated protocol using daily dose fractions of approximately 2 Gy in the same overall treatment time, the total dose to yield a TCD_{50} for tumor A compared with tumor B will be:

A. lower
B. greater
C. equal
D. less for a lower probability of tumor control and greater for a higher probability of control
E. impossible to determine from the information provided

XIX-5) The cells comprising a patient's tumor are characterized by an SF_2 of 0.3 and a doubling time of 3 days. Due to an unexpectedly severe skin reaction, the patient is put on a 3 week break during treatment to allow some healing to occur. How much extra dose would be required to achieve the same probability of tumor control if the treatment had not been interrupted? (Assume that treatment is given as daily, 2 Gy fractions, the multifraction survival curve for the cells comprising this tumor is exponential, and that radiation-induced cell cycle perturbations are negligible.)

A. 2 Gy
B. 4 Gy
C. 6 Gy
D. 8 Gy
E. 10 Gy

XIX-6) Assuming that the D_{10} for a tumor cell population is 4 Gy and the extrapolation number n equals 1, the single dose to achieve a TCD_{90} for a tumor containing 100 million clonogenic cells is closest to:

A. 18 Gy
B. 24 Gy
C. 28 Gy
D. 36 Gy
E. 44 Gy

XIX-7) What is the typical shape of a tumor growth curve?

A. Gompertzian
B. exponential
C. parabolic
D. linear
E. linear-quadratic

XIX-8) For conventional fractionation, the tolerance dose for a particular normal tissue complication is found to be 30 Gy. If a patient is treated with a drug that has a dose reduction factor of 1.3, then the new tolerance dose for this tissue should be roughly:

A. 23 Gy
B. 30 Gy
C. 33 Gy
D. 36 Gy
E. 39 Gy

XIX-9) The TCD_{90} for a series of 0.1 cm diameter tumors receiving fractionated radiotherapy in 1.8 Gy daily fractions was determined to be 56 Gy. Assuming that the tumors each contained 10^6 clonogenic cells, what dose would be necessary to maintain the 90% control rate if the tumors were allowed to continue growing until they reached a 1 cm diameter? (Assume that the growth fraction remained constant during the course of treatment.)

A. 48 Gy
B. 56 Gy
C. 64 Gy
D. 71 Gy
E. 80 Gy

XX. Time, Dose, Fractionation

XX-1) Which of the following statements concerning the α/β ratio for tumors and normal tissues is TRUE?

A. The α/β ratio is generally low for early responding tissues and high for late responding tissues.
B. The α/β ratio corresponds to the dose at which the survival curve begins to bend and deviate from its initial slope.
C. *In vivo*, α/β ratios for normal tissues and tumors are derived from an analysis of isoeffect data derived from multi-fraction experiments.
D. The α/β ratio tends to be low for cells with a pro-apoptotic tendency.
E. The α/β ratio represents the surviving fraction at which the linear and quadratic contributions to cell killing are equal.

XX-2) A treatment schedule consisting of 25 daily fractions of 1.8 Gy was found to be biologically equivalent to a schedule consisting of 17 daily fractions of 2.5 Gy with respect to complication probability in a critical normal tissue. The α/β ratio for this tissue is closest to:

A. 1 Gy
B. 3 Gy
C. 6 Gy
D. 10 Gy
E. 20 Gy

XX-3) A hyperfractionated protocol is being proposed in an effort to reduce the incidence of late effects following radiotherapy for head and neck cancer. Compared to standard fractionation, it is likely that this alternate schedule will result in a(n):

A. comparable probability of tumor control
B. increased probability of tumor control
C. decreased probability of tumor control
D. increased probability of early effects
E. decreased probability of early effects

XX-4) The slopes of isoeffect curves for late responding tissues compared to early responding tissues and tumors are typically (assume data are plotted on a log-log scale):

A. variable, depending upon the specific tissue
B. comparable
C. shallower
D. steeper
E. flat

XX-5) Two isoeffect curves, one corresponding to a given level of tumor control and the other for a given probability of a late complication in a critical normal tissue, are found to intersect. If the curves were plotted as total dose on the Y-axis and dose per fraction on the X-axis, the most important application of this information would be to predict the:

A. tumor control probability
B. optimal range of fraction sizes to use for treatment
C. optimal overall treatment time
D. outcomes when split course treatment is used
E. normal tissue complication probability

XX-6) If the dose-limiting, normal tissue toxicity of interest is characterized by an α/β ratio of 6 Gy, and the corresponding tumor possesses an α/β ratio of 2 Gy, it is most likely that a patient being treated for this type of cancer would benefit from:

A. split course treatment
B. accelerated treatment
C. hypofractionation
D. hyperfractionation
E. low dose rate brachytherapy

XX-7) Tumor cell repopulation during treatment causes the BED value to:

A. increase
B. decrease
C. no effect
D. increase, but only if T_{pot} is greater than 5 days
E. increase, but only if the α/β ratio for the tumor is large

XX-8) Accelerated fractionation is used to:

A. counteract the inherent radioresistance of some tumor cells.
B. overwhelm DNA repair processes in tumor cells.
C. overcome the radioresistance of hypoxic tumor cells.
D. increase the potential for repopulation by cells in normal tissues.
E. reduce the potential for tumor cell repopulation.

XX-9) A treatment prescription of 72 Gy delivered in 2 Gy fractions is changed to deliver 3 Gy fractions, with the total dose adjusted accordingly so that the new prescription would be isoeffective with respect to late complications in a normal tissue characterized by an α/β ratio of 2 Gy. If the α/β ratio for the tumor is 10 Gy, what is the approximate change in biologically effective dose to the tumor, assuming no change in overall treatment time?

A. +14%
B. +7%
C. 0
D. -7%
E. -14%

XXI. Brachytherapy

XXI-1) Which of the following isotopes is most commonly used for HDR brachytherapy?

A. Ir-192
B. Pd-103
C. I-125
D. Co-60
E. Y-90

XXI-2) Accelerated partial breast irradiation can be performed using either interstitial multicatheter brachytherapy or intracavitary balloon brachytherapy. Which of the following is NOT a potential advantage associated with these treatments?

A. Because smaller normal tissue volumes are irradiated in a more conformal manner, toxic side effects may be reduced.
B. Ease of implantation of the catheters or balloons makes these techniques highly desirable.
C. The overall treatment times for partial breast irradiation are much shorter than for more conventional, external beam radiotherapy of the whole breast.
D. A higher dose per fraction can be used because of the limited volume of normal tissue irradiated.
E. High dose rate after-loading systems such as these reduce the radiation exposure of medical personnel.

XXI-3) Iodine-131 tositumomab (Bexxar) is:

A. a radiolabeled small molecule tyrosine kinase inhibitor used to treat lung cancer
B. used to treat thyroid cancer
C. of limited clinical utility because of its high toxicity to the GI tract
D. a radiolabeled antibody against the CD20 antigen over-expressed in non-Hodgkin's lymphoma cells
E. highly effective at cell killing because of the high LET α-particle emissions from the I-131

XXI-4) A primary advantage of HDR brachytherapy for the treatment of prostate cancer is that:

A. the OER is expected to be lower for HDR than for LDR brachytherapy.
B. the probability of late normal tissue damage decreases with increasing fraction size.
C. tumor response should be improved by using larger fraction sizes because of the lower α/β ratio associated with prostate cancer compared with that for the surrounding normal tissues.
D. radiation safety issues are generally of less concern for the radioisotopes used for HDR brachytherapy than for those used for LDR brachytherapy.

XXII. Radiobiological Aspects of Alternative Dose Delivery Systems

XXII-1) The use of one or a few large radiation doses is generally contraindicated for radiotherapy because of an increased likelihood of late normal tissue complications compared to more conventional fractionation. However, special procedures such as stereotactic radiosurgery and intraoperative radiotherapy employ large doses, apparently without an increase in late effects. The **best** explanation for this finding is that:

A. these special procedures have not been in use long enough for all of the anticipated late complications to manifest themselves
B. normal tissue radioprotectors are usually administered along with the high dose treatments
C. radioresistance caused by tissue hypoxia is more pronounced when large doses are used rather than small doses
D. extra care is taken in these procedures to produce the most conformal treatment plan possible, so as to minimize the amount of late-responding normal tissue irradiated
E. DNA repair systems in tumor cells are more easily saturated following one or a few large doses than in the surrounding normal tissue cells incidentally irradiated

XXII-2) For which of the following types of radiation is the description provided FALSE?

A. carbon ions – have both depth-dose and biological advantages for radiotherapy
B. electrons – useful for the treatment of deep-seated tumors
C. protons – dose distribution advantages, but with an RBE approximately equal to 1.0.
D. photons – most common type of radiation used for radiotherapy
E. neutrons – relatively poor dose distributions, but with greater biologic effectiveness

XXII-3) Which statement comparing carbon ion with proton beam radiotherapy is FALSE? Both carbon ions and protons:

A. provide the type of precision radiotherapy needed to treat certain tumors located near critical structures
B. display a lower OER compared with X-rays
C. exhibit a Bragg peak.
D. represent particulate forms of radiation

XXII-4) Protons used for cancer radiotherapy:

A. show the greatest potential in the treatment of tumors with high hypoxic fractions and/or poor reoxygenation rates.
B. are typically in the 1 - 10 MeV range.
C. exhibit LET values <10 keV/μm.
D. exhibit an RBE of approximately 5.

XXIII. Chemotherapeutic Agents and Radiation Therapy

XXIII-1) Irinotecan:

A. acts directly on RNA polymerase
B. is activated intracellularly to camptothecin
C. is a proteasome inhibitor
D. acts by stabilizing the topoisomerase I cleavable complex
E. is a derivative of cyclophosphamide

XXIII-2) The epidermal growth factor receptor (EGFR) is a target of which of the following agents?

A. bevacizumab
B. cetuximab
C. celecoxib
D. sirolimus
E. bortezomib

XXIII-3) Herceptin (trastuzumab) is a:

A. mTOR/FRAP inhibitor
B. FLT-3 inhibitor
C. siRNA that targets ATM
D. inhibitor of RAS
E. anti-HER2 antibody

XXIII-4) Iressa (gefitinib) is a(n):

A. monoclonal antibody against VEGF
B. analog of nitrogen mustard
C. COX-2 inhibitor
D. EGFR inhibitor
E. anti-HER2 antibody

XXIII-5) Cyclooxygenase (COX)-2:

A. tends to be down-regulated in tumors.
B. is constitutively produced by most normal tissues.
C. inhibits prostaglandin synthesis.
D. mediates synthesis of eicosanoids from arachidonic acid.
E. is specifically inhibited by erlotinib.

XXIII-6) Which of the following agents acts in a cell cycle specific fashion?

A. cisplatin
B. ifosfamide
C. 5-FU
D. BCNU
E. epirubicin

XXIII-7) Which of the following drugs is an anti-metabolite?

A. melphalan
B. gemcitabine
C. etoposide
D. taxol
E. mitomycin C

XXIII-8) Which of the following pairs of chemotherapeutic agents and their mechanism of action is FALSE?

A. chlorambucil – DNA alkylator
B. gleevec – tyrosine kinase inhibitor
C. etoposide – topoisomerase II poison
D. doxyrubicin – DNA intercalator
E. methotrexate – thymidylate synthase inhibitor

XXIII-9) Which of the following agents has a mechanism of action similar to that of paclitaxel (Taxol)?

A. methotrexate
B. camptothecin
C. carboplatin
D. dactinomycin
E. vincristine

XXIII-10) Cisplatin causes cell lethality due to:

A. microtubule depolymerization
B. formation of DNA-protein crosslinks
C. inhibition of ribonucleotide reductase
D. the formation of cyclobutyl bonds between adjacent bases
E. production of DNA crosslinks

XXIII-11) Bortezomib (Velcade) inhibits the activity of:

A. tyrosine kinases
B. KIT
C. mTOR (FRAP1)
D. proteasomes
E. VEGF

XXIII-12) Avastin (bevacizumab) is a monoclonal antibody that targets:

A. ERBB3
B. DNA-PK
C. VEGF
D. sphingomyelinase
E. caspase 3

XXIV. Radiosensitizers, Radioprotectors and Bioreductive Drugs

XXIV-1) Treatment with an antiangiogenic agent may cause a tumor to exhibit increased sensitivity to a subsequent radiation dose. It has been hypothesized that this reflects the fact that:

A. most antiangiogenic agents are also chemical radiosensitizers
B. vascular damage decreases tumor perfusion and results in longer retention of the toxic, radiation-induced free radicals
C. vascular damage increases hypoxia, which increases expression of HIF-1 in tumor cells, which in turn increases cellular radiosensitivity
D. some antiangiogenic agents transiently “normalize” tumor vasculature, resulting in increased oxygenation of the tumor and increased radiosensitivity
E. transient normalization of the tumor vasculature can occur after treatment with some antiangiogenic agents, resulting in a more uniform radiation dose delivery.

XXIV-2) Which of the following statements is TRUE concerning the DAHANCA trial testing the effectiveness of nimorazole with radiotherapy for the treatment of supraglottic and pharyngeal tumors?

A. Nimorazole radiosensitizes through depletion of natural sulfhydryl compounds present in the cell.
B. No significant improvement was noted with respect to either loco-regional tumor control or disease-free survival.
C. Nimorazole has greater radiosensitizing efficiency than other compounds in its chemical class.
D. The toxicity produced by nimorazole was relatively mild.
E. Due to the negative results, the authors of this trial concluded that nimorazole has no role in the treatment of head and neck cancers.

XXIV-3) A new biological response modifier will be of value in combination with radiotherapy only if it:

A. acts synergistically with radiation on the cellular level
B. selectively modulates the radiation response of proliferating cells
C. selectively modulates the radiation response of the vasculature
D. has minimal cytotoxicity to cells in normal tissues
E. produces a therapeutic gain

XXIV-4) Overgaard has published a meta-analysis of clinical trials in which agents such as oxygen and hypoxic cell radiosensitizers were used to address the problem of radioresistant hypoxic cells. He concluded that the overall effect of these hypoxia-directed interventions on tumor control and patient survival was that:

A. tumor control remained the same, but survival improved
B. tumor control improved, but survival remained the same
C. tumor control decreased, but survival improved
D. neither tumor control nor survival were affected
E. there was an improvement in both tumor control and survival

XXIV-5) One of the mechanisms by which gemcitabine is thought to act as a radiosensitizer is through an effect on:

A.RAD50
B. ribonucleotide reductase
C. ATM
D. DNA pol α (POLA1)
E. DNA topoisomerase II alpha (TOP2A)

XXIV-6) Which one of the following treatment modifications would NOT be expected to alter the radiation response of normal tissues to fractionated radiotherapy?

A. changing the fraction size
B. step down in field size
C. scheduling a gap
D. co-administration of nimorazole
E. administration of amifostine

XXV. Hyperthermia

XXV-1) Which of the following statements concerning methods to produce local tumor heating is FALSE?

A. Microwaves produce uniform temperature distributions at shallow depths, but treatment of more deeply-seated tumors leads to hotspots on the body surface that can limit treatment.
B. The presence of bone or air cavities during ultrasound heating compromises thermal dosimetry.
C. Uniform temperature distributions may be achieved in soft tissues through use of ultrasound for heating.
D. For readily accessible tumors, the use of implanted microwave or radio-frequency sources results in good temperature distributions.
E. Radiofrequency ablation combined with radiotherapy produces radiosensitization.

XXV-2) The optimal time to deliver heat (relative to radiation) in order to achieve the greatest radiosensitization is:

A. two hours prior to RT
B. one hour prior to RT
C. during RT
D. one hour after RT
E. two hours after RT

XXV-3) Which of the following statements concerning hyperthermia is TRUE?

A. There is little or no age response through the cell cycle for hyperthermia.
B. Hyperthermia is thought to enhance the effect of radiation primarily by creating additional DNA damage.
C. Once thermotolerance develops, it becomes a permanent, heritable phenotype in the heated cells.
D. Step-up heating may be useful clinically because it inhibits the development of thermotolerance.
E. The thermal enhancement ratio is the dose of radiation to produce a given effect in cells or tissues irradiated at normal physiologic temperature, divided by the dose of radiation for cells or tissues irradiated at elevated temperature to produce the same effect.

XXV-4) Which of the following statements concerning hyperthermia is TRUE?

A. G_2 cells are the most resistant with respect to both heat and X-rays.
B. Cells maintained in a low pH microenvironment tend to be more sensitive to heat than cells maintained at physiologic pH.
C. Acutely hypoxic tumor cells are more sensitive to hyperthermia than chronically hypoxic ones.
D. In laboratory rodents, hyperthermia tends to increase blood flow in tumors, but decrease blood flow in most normal tissues.
E. The amount of killing produced in a population of cells heated at 43ºC for 10 minutes will be greater than for cells heated at 46ºC for 5 minutes.

XXVI. Radiation Carcinogenesis

XXVI-1) Thymic irradiation during infancy has been shown to increase the incidence of:

A. breast cancer
B. leukemia
C. thyroid cancer
D. bone tumors
E. head and neck cancers

XXVI-2) Which of the following organs has the highest tissue weighting factor (W_T)?

A. breast
B. bladder
C. brain
D. gonads
E. kidney

XXVI-3) What is the most common type of cancer identified in children who were in the vicinity of the Chernobyl nuclear power plant when it exploded in 1986?

A. osteosarcoma
B. leukemia
C. thyroid cancer
D. glioma
E. mesothelioma

XXVI-4) In the Childhood Cancer Survivor Study, the incidence of which of the following cancers was NOT elevated in irradiated children compared to those who did not receive radiotherapy as part of their cancer treatment?

A. skin cancer
B. sarcoma
C. meningioma
D. pancreatic
E. thyroid cancer

XXVI-5) Which of the following statements is FALSE concerning radiation carcinogenesis?

A. The use of prenatal X-rays during the 1950's and 1960's increased the risk for the development of childhood cancer among children who received these diagnostic examinations while *in utero*.
B. For radiation protection purposes, it is assumed that the shape of the dose response curve for radiation-induced solid tumors is linear with no threshold.
C. Evidence for radiation-induced leukemia comes from epidemiological studies of children irradiated *in utero* and from the Japanese A-bomb survivors.
D. A radiation oncologist with a lifetime dose equivalent of 250 mSv has about a 10% chance of developing a fatal radiation-induced cancer.

XXVI-6) Approximately how many excess, fatal cancers would be induced by the use of CT scanning if 10 million people receiving this type of radiologic examination got an average effective dose equivalent of 10 mSv?

A. 25
B. 150
C. 800
D. 5,000
E. 20,000

XXVI-7) Which of the following radiation-induced malignancies has the shortest median latent period?

A. colorectal cancer
B. leukemia
C. bone sarcoma
D. breast cancer
E. lung cancer

XXVI-8) The EPA estimates that the fraction of the total number of U.S. lung cancer deaths annually caused by indoor radon is approximately:

A. zero for non-smokers
B. 0-0.1%
C. 1-2%
D. 10-20%
E. 40-60%

XXVI-9) Which one of the following conditions treated with radiation is associated with an increased incidence of leukemia?

A. breast cancer
B. ankylosing spondylitis
C. cervical cancer
D. brain tumors
E. enlarged thymus

XXVII. Heritable Effects of Radiation

XXVII-1) The probability of a hereditary disorder in the first generation born to parents exposed to radiation is estimated to be approximately:

A. 0.02/mSv
B. 0.2/mSv
C. 0.002/Sv
D. 0.02/Sv
E. 0.2/Sv

XXVII-2) The genetically significant dose (GSD) resulting from diagnostic radiology procedures performed in the U.S. annually has been estimated to be:

A. 0.3 μSv
B. 0.3 mSv
C. 0.3 cSv
D. 0.3 Sv
E. 3 Sv

XXVII-3) A 22-year-old man completed a course of radiation therapy for Hodgkin's lymphoma one year ago. For the previous 6 months, he and his wife tried unsuccessfully to conceive a child. He expressed concern to his radiation oncologist that the radiation exposure (gonadal dose of 0.83 Gy) may have left him sterile. How should the radiation oncologist respond?

A. The radiation dose likely caused permanent sterility.
B. The dose of radiation should have had no effect on the patient's sperm count and probably isn't the cause of the couple's fertility problems.
C. The patient should not even be attempting to conceive a child due to a significantly increased risk for radiation-induced mutations in the offspring of irradiated individuals.
D. Hormonal dysfunction caused by the radiation, and not lowered sperm count *per se*, probably accounted for the couple's fertility problems.
E. This dose should interfere with fertility for no more than about a year, so the patient should keep trying to conceive a child.

XXVIII. Radiation Effects in the Developing Embryo and Fetus

XXVIII-1) Midway through the course of a standard external beam treatment for breast cancer, the patient discovered she was pregnant and near the end of her first trimester. Which of the following statements about this situation is TRUE?

A. The woman should be advised to discontinue treatment until she gives birth.
B. The fetus is quite resistant to radiation during this gestational stage, so there is no need to discuss options with the patient.
C. The scattered dose already delivered to the fetus is sufficiently high that a miscarriage or stillbirth is probable.
D. The fetus will be at an increased risk for the development of a radiation-induced cancer later in life, even if the scattered dose is relatively small.
E. The fetus probably received less than 0.01 cGy, so no remedial action is necessary.

XXVIII-2) The thyroid of a developing fetus will incorporate radioactive iodine:

A. at no point during gestation
B. at any point during gestation
C. from about the 10th week of gestation onward
D. only during the first trimester of gestation
E. only during the third trimester of gestation

XXVIII-3) A young woman is concerned about ovarian irradiation secondary to a screening mammogram she had received with respect to possible deleterious effects on her future offspring. The radiologist should inform her that:

A. transient changes in hormonal balance will likely result from the ovarian dose received during mammography, but these should not affect future offspring
B. mature ova are highly radiosensitive and those present at the time of irradiation were probably killed, so future offspring cannot be affected
C. her ovaries received no scattered dose from screening mammography
D. her ovaries received the equivalent of a genetic doubling dose for mutations
E. effects on possible future offspring cannot be excluded but are highly unlikely

XXVIII-4) Temporary growth inhibition would most likely be observed for a developing mouse irradiated during which stage of gestation?

A. preimplantation
B. organogenesis
C. early fetal period
D. mid fetal period
E. late fetal period

XXVIII-5) Many types of congenital abnormalities, and of varying severity, have been noted in laboratory animals irradiated during the organogenesis period of gestation. This wide spectrum of effects is due primarily to:

A. the sex of the irradiated fetus.
B. which organs were actively developing at the time of irradiation.
C. the type of ionizing radiation to which the fetus was exposed.
D. innate differences in radiosensitivity of the different cell types.
E. maternal age at conception.

XXVIII-6) What dose to an embryo or fetus during the 10 day to 25 week period of gestation is considered the threshold above which a physician should discuss with a pregnant patient the risk of radiation-induced birth defects, and possible actions to be taken?

A. 0.001 Gy
B. 0.01 Gy
C. 0.1 Gy
D. 1.0 Gy
E. 10 Gy

XXIX. Radiation Protection

XXIX-1) Which of the following statements is FALSE concerning exposure to radiation?

A. The largest contributor to background radiation exposure in the United States is radon.
B. The average annual dose equivalent resulting from the combined exposure to cosmic, terrestrial, and internal background radiation is roughly 1 mSv.
C. The effective dose equals the equivalent dose only under conditions where the whole body is irradiated.
D. Radiation exposure from medical diagnostic tests constitutes about 2% of the average total radiation dose residents of the United States receive each year.
E. Background radiation exposure increases with increasing altitude at which an individual resides.

XXIX-2) The ratio of the human genetic doubling dose to the average annual genetically significant dose (GSD) resulting from diagnostic X-ray procedures performed in the U.S. is closest to:

A. 1
B. 20
C. 3,000
D. 100,000
E. 600,000

XXIX-3) It is important for radiologists to use medical X-rays judiciously and avoid ordering unnecessary tests for all of the following reasons, EXCEPT:

A. Radiation-induced cancers caused by diagnostic X-ray procedures are thought to account for at least 1% of all cancer deaths each year.
B. There is no dose of radiation that can be considered “safe”.
C. According to Medicare regulations, an order for a diagnostic X-ray examination may be based not only upon medical need, but also for the purpose of limiting legal liability.
D. The use of X-rays for medical diagnosis has been increasing.
E. Diagnostic X-rays are the greatest source of man-made background radiation exposure in the human population.

XXIX-4) The maximum permissible dose per year for a member of the general population includes dose contributions received from:

A. storage of radioactive waste material
B. radioactive elements in the earth's crust
C. a course of radiotherapy
D. exposure to radon
E. mammography

XXIX-5) Which one of the following effects that may be caused by irradiation, represents a deterministic effect?

A. breast cancer
B. phenylketonuria
C. mental retardation
D. leukemia
E. galactosemia

XXIX-6) The term stochastic is used to describe an effect of radiation in which the:

A. severity of the effect depends on the dose above a threshold.
B. severity of the effect depends on the dose without a threshold.
C. probability of occurrence is a function of dose, with no threshold.
D. probability of occurrence is a function of dose above a threshold.
E. dependency is on age at exposure.

XXX. Molecular Techniques Used in Radiation and Cancer Biology

XXX-1) Which of the following statements concerning molecular techniques is FALSE?

A. Fluorescence *in situ* hybridization (FISH) can be used to identify the chromosome location of a gene of interest.
B. A restriction fragment length polymorphism (RFLP) may result if the copy number of a particular DNA fragment varies.
C. An exonuclease produces a cut in the middle of a DNA strand.
D. A Western blot can be used to detect and characterize a particular protein.
E. A restriction endonuclease typically cuts DNA at a specific sequence.

XXX-2) Which one of the following reagents is NOT used for a reporter gene assay?

A. chloramphenicol acetyltransferase (CAT)
B. firefly luciferase
C. RNA polymerase
D. β-galactosidase
E. green fluorescent protein (GFP)

XXX-3) An antibody would be used to screen which type of library?

A. genomic
B. expression
C. cDNA
D. intronic
E. endonuclease

XXX-4) The sequence of temperatures (in °C) used in a round of PCR to amplify a particular DNA fragment would most likely be:

A. 95, 72, 57
B. 57, 95, 72
C. 72, 57, 95
D. 95, 57, 72
E. 72, 95, 57

XXX-5) Which of the following assays would NOT be used for the detection of single nucleotide polymorphisms (SNPs)?

A. TaqMan assay
B. subtractive hybridization
C. single-stranded conformation polymorphism (SSCP)
D. invader assay
E. molecular beacons

XXX-6) Which of the following statements is TRUE concerning the structure of eukaryotic genes?

A. An exon can generally be identified by its lack of stop codons.
B. Introns represent only a small percentage of the total genome.
C. Most human genes do not contain intronic regions.
D. Introns represent the coding sequences of genes.
E. The RNA transcribed from a DNA template is translated directly on the ribosomes.

XXX-7) A DNA ligase:

A. performs the resynthesis step of nucleotide excision repair.
B. is responsible for the initial step in non-homologous end joining of DNA double strand breaks.
C. recognizes a particular type of DNA damage and produces single strand breaks on either side of the damaged nucleotide.
D. recognizes and removes a damaged base from DNA.
E. rejoins simple strand breaks.

XXX-8) Which technique would best be used to investigate gene expression?

A. Western blot
B. EMSA
C. Southern blot
D. DNase I footprinting
E. Northern blot

XXX-9) The best method to locate a gene on a chromosome is:

A. promoter bashing
B. ELISA
C. two-hybrid screen
D. FISH
E. RFLP

XXX-10) Which of the following statements is TRUE?

A. A mature mRNA contains the information present only in the DNA introns.
B. Sequencing of a cDNA can be used to predict the amino acid sequence of the protein encoded by the gene.
C. A functional complementation assay involves hybridization of a probe to its complementary sequence in genomic DNA.
D. A cDNA library is created using whole genomic DNA.
E. A unique oligonucleotide probe for a particular gene can be ”backwards engineered” from the amino acid sequence of the protein encoded by that gene.

ANSWERS, EXPLANATIONS AND REFERENCES

GENERAL REFERENCES

Please note: Unless specific references are indicated along with the answer and explanation to a question, the material addressed in each question can be found in one or more of the following textbooks:

The major textbook used in radiation biology is:

Hall EJ and Giaccia AJ, Eds. *Radiobiology for the Radiologist*, 6th Ed. Lippincott Williams & Wilkins, Philadelphia, 2006.

Additional useful textbooks include:

Joiner M and van der Kogel A, Ed. *Basic Clinical Radiobiology*, 4th Ed. Arnold, London, 2009.

Lehnert S, *Biomolecular Action of Ionizing Radiation*. Taylor and Francis, London, 2007.

Dale R and Jones B, Ed. *Radiobiological Modelling in Radiation Oncology*. The British Institute of Radiology, 2007.

Tannock IF, Hill RP, Bristow RG*, et al.*, Eds. *The Basic Science of Oncology*, 4th Ed. McGraw-Hill, Medical Pub. Division, New York, 2005.

Mettler FA and Upton AC, Eds., *Medical Effects of Ionizing Radiation*, 3rd Ed. W.B. Saunders, Philadelphia, 2008.

Chapters on radiation and cancer biology in the major radiation oncology textbooks:

Haffty B and Wilson L, Eds., *Handbook of Radiation Oncology: Basic Principles and Clinical Protocols.* Jones and Bartlett Publishers, Sudbury MA, 2009.

Halperin EC, Perez CA, Brady LW*, et al.*, Eds., *Principles and Practice of Radiation Oncology*, 5th Ed. Lippincott Williams & Wilkins, Philadelphia, 2007.

Gunderson LL and Tepper JE, Eds., *Clinical Radiation Oncology*, *Second Edition* Churchill Livingstone, New York, 2007.

Hoppe R, Phillips TL and Roach M, Eds., *Leibel and Phillips Textbook of Radiation Oncology*, 3rd Ed. W.B. Saunders, Philadelphia, 2010.

The following represent overviews of radiation and cancer biology that are recommended:

Rosenstein BS. Chapter 2. The Biologic Basis of Radiotherapy: in *Handbook of Radiation Oncology: Basic Principles and Clinical Protocols.* Haffty B and Wilson L, Eds. Jones and Bartlett Publishers, Sudbury MA, 2009.

Rosenstein BS. Chapter 3. Molecular Radiobiology: in *Handbook of Radiation Oncology: Basic Principles and Clinical Protocols.* Haffty B and Wilson L, Eds. Jones and Bartlett Publishers, Sudbury MA, 2009.

McBride WH and Withers R. Chapter 2. Biological Basis of Radiation Therapy. pp. 76 108, in *Principles and Practice of Radiation Oncology*, 5th Ed. Halperin EC, Perez CA, Brady LW*, et al.*, Eds., Lippincott Williams & Wilkins, Philadelphia, 2007.

Baumann M, Cordes N, Hasse M and Zips D. Chapter 3. Molecular Cancer and Radiation Biology. pp. 109-125, in *Principles and Practice of Radiation Oncology*, 5th Ed. Halperin EC, Perez CA, Brady LW*, et al.*, Eds., Lippincott Williams & Wilkins, Philadelphia, 2007.

Jain RK and Kozak KR, Chapter 4. Molecular Pathophysiology of Tumors, pp.126-141, in *Principles and Practice of Radiation Oncology*, 5th Ed. Halperin EC, Perez CA, Brady LW*, et al.*, Eds., Lippincott Williams & Wilkins, Philadelphia, 2007.

Zeman EM, Chapter 1. Biologic Basis of Radiation Oncology, pp. 1-46, in *Clinical Radiation Oncology*, *Second Edition*. Gunderson LL and Tepper JE, Eds. Churchill Livingstone, New York, 2007. *(Third Edition due in 2010)*

Willers H, Held KD. Introduction to clinical radiation biology. Hematol Oncol Clin North Am 20:1-24, 2006. PubMed link

Bernier J, Hall EJ and Giaccia A. Radiation Oncology: A Century of Achievements. Nat Rev Cancer 4: 737-747, 2004. PubMed link

Constine LS, Milano MT, Friedman D, et al. Late Effects of Cancer Treatment on Normal Tissues pp. 320-355, in *Principles and Practice of Radiation Oncology*, 5th Ed. Halperin EC, Perez CA, Brady LW*, et al.*, Eds., Lippincott Williams & Wilkins, Philadelphia, 2007.

Dewey W and Bedford J. Chapter 1. Radiobiologic Principles, pp. 3-30 in *Textbook of Radiation Oncology*, 2nd Ed. Leibel SA and Phillips TL, Eds. W.B. Saunders, Philadelphia, 2004.

Kufe DW, Holland JF and Frei E, Eds., BC Decker. Cancer Biology in *Cancer Medicine, 6th ed.* Hamilton, Ont., Section 1. 2003.

Note: Those whose primary language is Spanish may find a new Spanish language Radiation Oncology textbook to be of value:

N Urdaneta, A Vera, R E Peschel, and L H Wilson,. *Radiotheripa Oncologia, Enfoque Multidisciplinario.* This textbook includes chapters reviewing different aspects of different areas of clinical radiation oncology. Editorial Disinlimed, Columbia, 2009.

The articles in Volume 20, Issue 4, October 2010 of Seminars in Radiation Oncology Issue 4 on Harnessing DNA Repair to Improve Radiotherapy Outcome are of interest:

Bristow RG. Introduction: DNA Repair and Radiotherapy Targeting: An Overview, Seminars in Radiation Oncology 20:215-216, 2010. PubMed link

John Thoms, Robert G. Bristow. DNA Repair Targeting and Radiotherapy: A Focus on the Therapeutic Ratio, Seminars in Radiation Oncology, 20:217-222, 2010. PubMed link

Ali Sak, Martin Stuschke. Use of [gamma]H2AX and Other Biomarkers of Double-Strand Breaks During Radiotherapy, Seminars in Radiation Oncology, 20:223-231, 2010. PubMed link

Matthew B. Parliament, David Murray. Single Nucleotide Polymorphisms of DNA Repair Genes as Predictors of Radioresponse, Seminars in Radiation Oncology, 20:232-240, 2010. PubMed link

Vens C, Begg AC. Targeting Base Excision Repair as a Sensitization Strategy in Radiotherapy, Seminars in Radiation Oncology, 20:241-249, 2010. PubMed link

Mukherjee B, Choy H, Nirodi C, Burma S. Targeting Nonhomologous End-Joining Through Epidermal Growth Factor Receptor Inhibition: Rationale and Strategies for Radiosensitization, Seminars in Radiation Oncology, 20:250-257, 2010. PubMed link

Udayakumar T, Shareef MM, Diaz DA, Ahmed MM, Pollack A. The E2F1/Rb and p53/MDM2 Pathways in DNA Repair and Apoptosis: Understanding the Crosstalk to Develop Novel Strategies for Prostate Cancer Radiotherapy, Seminars in Radiation Oncology, 20:258-266, 2010. PubMed link

Barker CA, Powell SN. Enhancing Radiotherapy Through a Greater Understanding of Homologous Recombination, Seminars in Radiation Oncology, 20:267-273.e3, 2010. PubMed link

Chalmers AJ, Lakshman M, Chan N, Bristow RG. Poly(ADP-Ribose) Polymerase Inhibition as a Model for Synthetic Lethality in Developing Radiation Oncology Targets, Seminars in Radiation Oncology, 20:274-281, 2010. PubMed link

Klein TJ, Glazer PM. The Tumor Microenvironment and DNA Repair, Seminars in Radiation Oncology, 20:282-287, 2010. PubMed link

The articles in Volume 18, Issue 4, October 2008 of Seminars in Radiation Oncology Hypofractionation are of interest:

Timmerman, RD. An Overview of Hypofractionation and Introduction to This Issue of Seminars in Radiation Oncology, Seminars in Radiation Oncology, 18:215-222, 2008. PubMed link

Kavanagh, B. Clinical Experience Shows That Catastrophic Late Effects Associated With Ablative Fractionation Can Be Avoided by Technological Innovation, Seminars in Radiation Oncology, 18:223-228, 2008. PubMed link

Dolinsky, C, Glatstein E. Some Cases of Severe Normal Tissue Toxicity Can Be Anticipated With Ablated Fractionated Radiation With Appropriate Long-term Follow-up, Seminars in Radiation Oncology, 18:229-233, 2008. PubMed link

Brenner, DJ. The Linear-Quadratic Model Is an Appropriate Methodology for Determining Isoeffective Doses at Large Doses Per Fraction, Seminars in Radiation Oncology, 18:234-239, 2008. PubMed link

Kirkpatrick JP, Meyer JJ, Marks LB. The Linear-Quadratic Model Is Inappropriate to Model High Dose per Fraction Effects in Radiosurgery, Seminars in Radiation Oncology, 18:240-243, 2008. PubMed link

Story M, Kodym R, Saha D. Exploring the Possibility of Unique Molecular, Biological, and Tissue Effects With Hypofractionated Radiotherapy, Seminars in Radiation Oncology, 18:244-248, 2008. PubMed link

Ritter M. Rationale, Conduct, and Outcome Using Hypofractionated Radiotherapy in Prostate Cancer, Seminars in Radiation Oncology, 18:249-256, 2008. PubMed link

Whelan TJ, Kim DH, Sussman J. Clinical Experience Using Hypofractionated Radiation Schedules in Breast Cancer, Seminars in Radiation Oncology, 18:257-264, 2008. PubMed link

Nedzi LA. The Implementation of Ablative Hypofractionated Radiotherapy for Stereotactic Treatments in the Brain and Body: Observations on Efficacy and Toxicity in Clinical Practice, Seminars in Radiation Oncology, 18:265-272, 2008. PubMed link

The articles in the special issue of The International Journal of Radiation Oncology, Biology, Physics, volume 76, issue 3, March 2010 devoted to QUANTEC are of interest:

Jeraj R, Cao Y, Ten Haken RK, Hahn C, Marks L. Imaging for Assessment of Radiation-Induced Normal Tissue Effects, The International Journal of Radiation Oncology, Biology, Physics, 76:S140-S144, 2010. PubMed Link

Rancati T, Schwarz M, Allen AM, Feng F, Popovtzer A, Mittal B, Eisbruch A. Radiation Dose–Volume Effects in the Larynx and Pharynx, The International Journal of Radiation Oncology, Biology, Physics, 76:S64-S69, 2010. PubMed link

Jaffray DA, Lindsay PE, Brock KK, Deasy JO, Tomé WA. Accurate Accumulation of Dose for Improved Understanding of Radiation Effects in Normal Tissue, The International Journal of Radiation Oncology, Biology, Physics, 76:S135-S139, 2010. PubMed link

Marks LB, Yorke ED, Jackson A, Ten Haken RK, Constine LS, Eisbruch A, Bentzen SM, Nam J, Deasy JO. Use of Normal Tissue Complication Probability Models in the Clinic. The International Journal of Radiation Oncology, Biology, Physics, 76:S10-S19, 2010. PubMed link

Mayo , Yorke E, Merchant TE. Radiation Associated Brainstem Injury, The International Journal of Radiation Oncology, Biology, Physics, 76:S36-S41, 2010. PubMed link

Marks LB, Bentzen SM, Deasy JO, Kong FM, Bradley JD, Vogelius IS, El Naqa I, Hubbs JL, Lebesque JV, Timmerman RD, Martel MK, Jackson A. Radiation Dose–Volume Effects in the Lung, The International Journal of Radiation Oncology, Biology, Physics, 76:S70-S76, 2010. PubMed link

Bhandare N, Jackson A, Eisbruch A, Pan CC, Flickinger JC, Antonelli P, Mendenhall WM.Radiation Therapy and Hearing Loss, The International Journal of Radiation Oncology, Biology, Physics, 76:S50-S57, 2010. PubMed link

Bentzen SM, Constine LS, Deasy JO, Eisbruch A, Jackson A, Marks LB, Ten Haken RK, Yorke ED. Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC): An Introduction to the Scientific Issues, The International Journal of Radiation Oncology, Biology, Physics, 76:S3-S9, 2010. PubMed link

Roach M, Nam J, Gagliardi G, El Naqa I, Deasy JO, Marks LB. Radiation Dose–Volume Effects and the Penile Bulb, The International Journal of Radiation Oncology, Biology, Physics, 76:S130-S134, 2010. PubMed link

Gagliardi G, Constine LS, Moiseenko V, Correa C, Pierce LJ, Allen AM, Marks LB. Radiation Dose–Volume Effects in the Heart, The International Journal of Radiation Oncology, Biology, Physics, 76:S77-S85, 2010. PubMed link

Jackson A, Marks LB, Bentzen SM, Eisbruch A, Yorke ED, Ten Haken RK, Constine LS, Deasy JO. The Lessons of QUANTEC: Recommendations for Reporting and Gathering Data on Dose–Volume Dependencies of Treatment Outcome, The International Journal of Radiation Oncology, Biology, Physics, 76:S155-S160, 2010. PubMed link

Pan CC, Kavanagh BD, Dawson LA, Li XA, Das SK, Miften M, Ten Haken RK. Radiation-Associated Liver Injury. The International Journal of Radiation Oncology, Biology, Physics, 76:S94-S100, 2010. PubMed link

Werner-Wasik M, Yorke E, Deasy JO, Nam J, Marks LB. Radiation Dose-Volume Effects in the Esophagus, The International Journal of Radiation Oncology, Biology, Physics, 76:S86-S93, 2010. PubMed link

Deasy JO, Bentzen SM, Jackson A, Ten Haken RK, Yorke ED, Constine LS, Sharma A, Marks LB. Improving Normal Tissue Complication Probability Models: The Need to Adopt a "Data-Pooling" Culture, The International Journal of Radiation Oncology, Biology, Physics, 76:S151-S154, 2010. PubMed link

Kirkpatrick JP, van der Kogel AJ, Schultheiss TE. Radiation Dose–Volume Effects in the Spinal Cord, The International Journal of Radiation Oncology, Biology, Physics, 76:S42-S49, 2010. PubMed link

Mayo C, Martel MK, Marks LB, Flickinger J, Nam J, Kirkpatrick J. Radiation Dose–Volume Effects of Optic Nerves and Chiasm, The International Journal of Radiation Oncology, Biology, Physics, 76:S28-S35, 2010. PubMed link

Michalski JM, Gay H, Jackson A, Tucker SL, Deasy JO. Radiation Dose–Volume Effects in Radiation-Induced Rectal Injury, The International Journal of Radiation Oncology, Biology, Physics, 76:S123-S129, 2010. PubMed link

Deasy JO, Moiseenko V, Marks LB, Chao KS, Nam J, Eisbruch A. Radiotherapy Dose–Volume Effects on Salivary Gland Function, The International Journal of Radiation Oncology, Biology, Physics, 76:S58-S63, 2010. PubMed link

Viswanathan AN, Yorke ED, Marks LB, Eifel PJ, Shipley WU. Radiation Dose–Volume Effects of the Urinary Bladder, The International Journal of Radiation Oncology, Biology, Physics, 76:S116-S122, 2010. PubMed link

Bentzen SM, Parliament M, Deasy JO, Dicker A, Curran WJ, Williams JP, Rosenstein BS.Biomarkers and Surrogate Endpoints for Normal-Tissue Effects of Radiation Therapy: The Importance of Dose–Volume Effects, The International Journal of Radiation Oncology, Biology, Physics, 76:S145-S150, 2010. PubMed link

Kavanagh BD, Pan CC, Dawson LA, Das SK, Li XA, Ten Haken RK, Miften M.Radiation Dose–Volume Effects in the Stomach and Small Bowel, The International Journal of Radiation Oncology, Biology, Physics, 76:S101-S107, 2010. PubMed link

Dawson LA, Kavanagh BD, Paulino AC, Das SK, Miften M, Li XA, Pan C, Ten Haken RK, Schultheiss TE.Radiation-Associated Kidney Injury, The International Journal of Radiation Oncology, Biology, Physics, 76:S108-S115, 2010. PubMed link

Lawrence YR, Li XA, el Naqa I, Hahn CA, Marks LB, Merchant TE, Dicker AP. Radiation Dose–Volume Effects in the Brain. The International Journal of Radiation Oncology, Biology, Physics, 76:S20-S27, 2010. PubMed link

Marks LB, Ten Haken RK, Martel MK. Guest Editor's Introduction to QUANTEC: A Users Guide, The International Journal of Radiation Oncology, Biology, Physics, 76:S1-S2, 2010. PubMed link

I. Interaction of Radiation with Matter

I-1) A Portions of the electromagnetic spectrum show the following order with increasing photon energy: radio waves, microwaves, infrared radiation, visible light, UV and X-rays. This corresponds to decreasing wavelength and increasing frequency. Through the process of ionization, only X-ray and γ-ray photons have sufficient energy to disrupt atomic structure and break chemical bonds.

I-2) C For photons in the energy range used typically in radiotherapy, the Compton process is predominant. In the Compton process, a high-energy photon interacts with an atom to cause ejection of an outer shell electron (referred to as a recoil electron) and a scattered photon. The energy of the incident photon is distributed between the scattered photon and the kinetic energy of the recoil electron. The Compton interaction may occur when photon energies range from 150 keV to 3 MeV although it also occurs to some extent at lower energies of 100-150 keV. Pair production occurs when a photon of greater than 1.02 MeV interacts with a nucleus to form an electron-positron pair. This amount of energy is just sufficient to provide the rest mass of the electron and positron, 0.51 MeV each. Excess of energy above 1.02 MeV will be possessed by these two particles, which produce ionizations as they travel in the material. As the positron comes to rest, it interacts with an electron in an annihilation reaction and is replaced by two photons, each having an energy of 0.51 MeV and moving in opposite directions. Pair production becomes an important form of interaction above about 10 MeV. The photoelectric effect is predominant for photons that have energies less than approximately 100-150 keV, typical of X-rays used in diagnostic radiology. In the photoelectric process, a photon interacts with an inner orbital electron and is completely absorbed. The electron is ejected from the atom becoming a free photoelectron. The kinetic energy of the ejected electron is equal to the energy of the incident photon minus the binding energy of the electron that has been ejected. The vacancy left in the shell by the ejected electron is filled in by the transition of an electron from an outer shell and is accompanied by the emission of a characteristic X-ray, whose energy represents the difference in the energy levels of the shells involved in the electron transition. When the excess energy derived from the transition of the electron from the higher to the lower energy state is transferred to an orbital electron that is ejected, this is referred to as an Auger electron. Photodisintegration occurs at photon energies much higher than those used in either diagnostic radiology or radiation therapy. In this process, a high-energy photon interacts with the nucleus of an atom resulting in the emission of one or more nucleons. An electron is not ejected through coherent scattering and no energy is transferred in this type of interaction, only the direction of the incident photon is altered.

I-3) E A free radical is an atom or molecule with an unpaired electron, making it highly reactive with other atoms and molecules. Spallation products are the result of nuclear fragmentation; for example, when high energy particles, such as neutrons, strike a target nucleus. Nuclear reaction products include nuclear fragments called spallation products in addition to nucleons (protons and neutrons) and alpha particles. Conventionally, ionized atoms with an atomic number less than or equal to 10 are called light ions, whereas those with an atomic number greater than 10 are termed heavy ions. In the case of water radiolysis produced from an X-ray interaction, an electron is produced in addition to a positively charged water ion radical. This is referred to as an ion pair. For neutrons with energies less than 6 MeV, the main type of interaction is elastic scattering, which in soft tissue involves interaction of the neutron with a hydrogen nucleus causing the formation of a recoil proton that goes on to cause ionizations.

I-4) D The positron formed through pair production combines with an electron on a separate atom to form two photons, each with energy of 0.511 MeV and moving in exactly opposite directions. This process is termed the annihilation reaction. 1 MeV γ-rays and mono-energetic 1 MeV X-rays are identical as they are both photons with an energy of 1 MeV and will therefore have the same relative biological effectiveness (RBE). The photoelectric effect results in the production of characteristic X-rays. All forms of electromagnetic radiation travel at 3×10^8 m/sec, the speed of light. The probability of a photoelectric interaction is proportional to the atomic number, Z^3. The wavelength is inversely proportional to photon energy.

I-5) E There is complete absorption of the incident photon during the photoelectric process. Although γ-rays, which represent energy released from the nucleus of an atom, are produced during nuclear disintegration, X-rays are produced from physical processes that occur outside of the nucleus. Auger electrons may be produced through the photoelectric effect, not pair production. Free radicals have half-lives on the order of micro- to milliseconds. Free radicals do not necessarily possess charge. An atom with an unpaired electron that is charged is referred to as an ion radical.

I-6) B A positron has a mass approximately 1,840 times smaller than either a neutron or proton. An α-particle is the nucleus of a helium atom and therefore consists of 2 protons and 2 neutrons. A carbon ion is the nucleus of a carbon atom and therefore consists of 6 protons and 6 neutrons.

I-7) B The annihilation reaction involves an interaction between a positron and an electron to produce two photons, each with energy of 0.511 MeV and moving in exactly opposite directions. Photon energies in the range that would result in the photoelectric effect are suboptimal for radiotherapy since there would be undesirable, preferential absorption by bone, which contains a disproportionate amount of higher atomic number elements (such as calcium and phosphorus) than soft tissues. This is because, unlike the Compton process, the probability of a photoelectric interaction is proportional to the third power of the atomic number of the absorber. In addition, the relatively low photon energies associated with the photoelectric effect result in poor penetration through tissue and therefore result in large doses to skin and superficial tissues. All forms of the electromagnetic radiation spectrum (i.e. radio waves, infrared radiation, visible light, ultraviolet light, X-rays, etc.) travel at 3×10^8 m/sec in a vacuum. The different types of electromagnetic radiation are categorized not by their speed, but by their frequency or wavelength. The Auger effect is seen as the result of the movement of an electron from an atom's outer shell to a vacant more tightly bound, inner orbital. An Auger electron may be produced through the photoelectric effect because the excess energy that results when an electron moves to a lower energy state during replacement of the ejected photoelectron may cause ejection of a second electron, which is referred to as an Auger electron.

II. Molecular Mechanisms of DNA Damage

II-1) C Ultraviolet radiation is non-ionizing but its wavelengths are preferentially absorbed by bases of DNA and by aromatic amino acids of proteins. The major types of DNA damage produced in cells by exposure to UV radiation include cyclobutane pyrimidine dimers and pyrimidine (6-4) pyrimidone photoproducts. In both cases, two pyrimidines, located next to each other, react to form a dimer following excitation of atoms in DNA. DNA-protein crosslinks are also important lesions in cells exposed to UV radiation. Crosslinks are particularly disruptive, as they occur mostly in the area of the chromosome that is undergoing replication. Thymol glycol [5,6-dihydroxy-5,6-dihydrothymine] and oxidized guanine [8-oxo-7,8-dihydroguanine (8-oxo-G)] are DNA base lesions present in clustered DNA damage induced in cells by ionizing radiation. Heat is a form of energy associated with the motion of atoms and molecules.

II-2) B The type of radiation-induced DNA damage most implicated in cell killing is the double-strand break.

II-3) C 6-4 photoproducts are produced by UV and not ionizing radiation.

II-4) E The absence of RAD51, which is a recombinase that plays a role in homologous recombinational repair, may affect the reparability of DNA double-strand breaks, but not their initial yield. The number of double-strand breaks produced increases with radiation dose. A lack of oxygen will decrease the number of initial breaks because the free radicals formed through interactions with oxygen that may result in the formation of DNA double-strand breaks will not be created if oxygen is at a diminished level. In tissues, amifostine is converted to a compound that is a radical scavenger whose presence would decrease the number of breaks induced by a particular dose of radiation. Nuclear proteins play a critical role in protecting DNA from radiation damage. Thus removal of histones greatly enhances the sensitivity of mammalian cells to radiation damage.

II-5) B Non-targeted, radiation-induced bystander effects are effects that appear in unirradiated cells in the presence of irradiated cells. Pyrimidine dimers are produced in DNA by UV. There is no evidence that the product of the antiapoptotic gene, BCL2, is involved in bystander responses. The average heat input from the absorption of ionizing radiation is very small. For example, the temperature rise in the tissues irradiated with 5 Gy is only about $0.001^{o}C$.

III. Molecular Mechanisms of DNA Repair

III-1) B DNA-PK is involved with non-homologous end-joining, not homologous recombination.

III-2) D CDK4 is a cyclin dependent kinase that plays an important role in the progression of cells through G_1 and into S phase. Artemis and DNA-PKcs play important roles in non-homologous end-joining of DNA double strand breaks, whereas RAD51 and BRCA1 are involved in the repair of double strand breaks through homologous recombination.

III-3) E SCID mice are immune deficient, making them good hosts for growing xenografts of human tumors. SCID mice are deficient in DNA-PK and are therefore radiosensitive. Cells from these mice have low levels of non-homologous end-joining.

III-4) A People with xeroderma pigmentosum are deficient in one of the several proteins involved in nucleotide excision repair. They are therefore extremely sensitive to UV irradiation because they are unable to repair the pyrimidine dimers produced in DNA, but they are not sensitive to ionizing radiation.

III-5) D Homologous recombinational repair requires the presence of a homologous DNA template, and is therefore most likely to occur following DNA replication in late S phase (when a sister chromatid is available as a template).

III-6) B A deficiency in MRE11 results in an ataxia telangiectasia-like disorder.

Taylor AM, Groom A, and Byrd PJ. Ataxia-telangiectasia-like disorder (ATLD)-its clinical presentation and molecular basis, DNA Repair 3:1219-1225, 2004. PubMed Link

III-7) B The BLM protein is a helicase. RPA serves to coat single stranded DNA regions generated during homologous recombination to prevent their degradation.

Moynahan ME, Jasin M. Mitotic homologous recombination maintains genomic stability and suppresses tumorigenesis, Nature Reviews Molecular Cell Biology, 11:196-207, 2010. PubMed link

Branzei D, Foiani M. Maintaining genome stability at the replication fork, Nature Reviews Molecular Cell Biology, 11:208-219, 2010. PubMed link

Negrini S, Gorgoulis VG, Halazonetis TD. Genomic instability — an evolving hallmark of cancer, Nature Reviews Molecular Cell Biology 11:220-228, 2010. PubMed link

Powell SN, Kachnic LA. Therapeutic exploitation of tumor cell defects in homologous recombination, Anticancer Agents Med Chem 8:448-460, 2008. PubMed link

Li X, Heyer WD. Homologous recombination in DNA repair and DNA damage tolerance. Cell Res 18:99-113, 2008. PubMed link

O'Driscoll M, Jeggo PA. The Role of Double-Strand Break Repair - Insights from Human Genetics. Nat Rev Genet 7:45-54, 2006. PubMed link

III-8) A The main role for Artemis is to cleave (through its nuclease activity) any residual DNA loops or hairpins that form during non-homologous end-joining.

Lieber MR. The mechanism of human nonhomologous DNA end joining, J Biol Chem 283:1-5, 2008. PubMed link

Weterings E, Chen DJ. The endless tale of non-homologous end-joining. Cell Res 18:114-124, 2008. PubMed link

Collis SJ, DeWeese TL, Jeggo PA*, et al.* The Life and Death of DNA-PK. Oncogene 24:949-961, 2005. PubMed link

Jeggo PA , Lobrich M. Artemis Links ATM to Double Strand Break Rejoining. Cell Cycle 4:359-362, 2005. PubMed link

III-9) A All of the proteins listed are substrates for ATM except for Ku70/80.

III-10) D The most common alterations produced in the DNA by radiation are base damages which are repaired by base excision repair, a repair process that is usually rapid and accurate. The proportion of the population that is heterozygous for the types of mutations that are found in people with AT – typically protein truncation mutations – is roughly 1-2%. Non-homologous end joining does not require a sister chromatid. Mutation of the genes involved with mismatch repair, primarily MSH2 and MLH1, are often present in people who develop hereditary non-polyposis colon cancer. Homologous recombination is a relatively error-free process. Sublethal damage repair is nearly non-existent following neutron-irradiation.

III-11) A Radiation injury would most likely occur in a person with ataxia telangiectasia. People with this syndrome are very sensitive to ionizing radiation due to the absence of functional ATM protein, which plays a central role in the repair of DNA double strand breaks and regulation of the cell cycle following irradiation.

III-12) B Non-homologous end-joining represents the principal means by which human cells repair DNA double strand breaks. Mismatch repair is primarily responsible for correction of errors made during DNA replication. Base excision repair removes base damages. Nucleotide excision repair mainly removes bulky adducts from DNA such as UV-induced pyrimidine dimers and chemical adducts. Photoreactivation involves the action of DNA photolyase which is activated by long wavelength UV and visible light to split the cyclobutyl bond of a pyrimidine dimer restoring it back to its original state.

Huen, MS, Sy SM, Chen J. BRCA1 and its toolbox for the maintenance of genome integrity, Nat Rev Mol Cell Bio, 11:138-148, 2010. PubMed link

Caldecott KW. Single-strand break repair and genetic disease. Nat Rev Genet,9:619-631, 2008. PubMed link

Helleday T, Petermann E, Lundin C, Hodgson B, Sharma RA. DNA repair pathways as targets for cancer therapy, Nat Rev Cancer, 8:193-204, 2008. PubMed Link

Bonner WM, Redon CE, Dickey JS, *et al*. GammaH2AX and cancer, Nat Rev Cancer, 8:957-967, 2008. PubMed link

Pollard JM, Gatti RA. Clinical radiation sensitivity with DNA repair disorders: An overview, Int J Radiat Oncol Biol Phys, 74:1323-1331, 2009. PubMed link

Lavin MF. Ataxia-telangiectasia: from a rare disorder to a paradigm for cell signaling and cancer, Nat Rev Mol Cell Biol, 9:759-769, 2008. PubMed link

Branzei D, Foiani M. Regulation of DNA repair throughout the cell cycle, Nat Rev Mol Cell Biol, 9:297-308, 2008. PubMed link

Helleday T, Petermann E, Lundin C, Hodgson B, Sharma RA. DNA repair pathways as targets for cancer therapy, Nat Rev Cancer, 8:193-204, 2008. PubMed

Wang W. Emergence of a DNA-damage response network consisting of Fanconi anaemia and BRCA proteins, Nat Rev Genet, 8:735-748, 2007. PubMed link

III-13) D RAD51 and BRCA2 function together in homologous recombinational repair of DNA double strand breaks.

IV. Chromosome and Chromatid Damage

IV-1) D Anaphase bridges generally result from the induction of isochromatid breaks, which are breaks induced in both chromatids of a sister chromatid pair following DNA replication in late S phase or G_2 of the cell cycle. They undergo an illegitimate union resulting in a bridge-like structure during anaphase of mitosis due to the inability of the sister chromatids to separate normally. Dicentric chromosomes result from breaks induced in two chromosomes in which the two broken chromosomes possessing the centromere join, resulting in a dicentric chromosome. An acentric fragment is produced following the breakage of a chromosome or chromosomes in which a portion of the chromosome that does not include the centromeric region is detached from the remainder of the chromosome. A single chromosome break would result in a terminal deletion.

IV-2) C The minimum whole body dose that can be detected through measurement of dicentric chromosomes in peripheral blood lymphocytes is approximately 0.25 Gy.

Leonard A, Rueff J, Gerber GB*, et al.* Usefulness and limits of biological dosimetry based on cytogenetic methods, Radiat Prot Dosimetry, 115:448-454, 2005. PubMed link

Rodrigues AS, Oliveira NG, Gil OM*, et al.* Use of cytogenetic indicators in radiobiology. Radiat Prot Dosimetry, 115:455-460, 2005. PubMed link

IV-3) A A terminal deletion is produced when a single chromosomal break results in deletion of a portion of the chromosome, that is, a “one-hit” aberration. An acentric ring results from two chromosomal breaks within the same arm of a chromosome. A dicentric results from breaks in two different chromosomes, while an inversion is produced by two breaks in the same chromosome. An anaphase bridge is produced by breaks produced in two sister chromatids.

IV-4) B The formation of a dicentric chromosome is most likely to trigger the events during mitosis that lead to mitotic catastrophe and the death of the cell (although it should be noted that some dicentrics are stable and long-lived). The other chromosomal aberrations listed are not as likely to result in cellular death (for example, inversions, translocations and insertions do not produce acentric fragments) although they could play an important role in carcinogenesis if the portion of the chromosome altered results in the inactivation of a tumor suppressor gene or activation of an oncogene.

IV-5) C The most reliable approach to estimate dose one month following a radiation exposure is to karyotype peripheral blood lymphocytes to detect chromosomal aberrations, particularly dicentric chromosomes, which are normally not found in unirradiated people. Alkaline elution would detect single strand DNA breaks while γ-H2AX, pulsed-field gel electrophoresis and the neutral comet assay can all measure DNA double strand breaks. These would not be useful assays to measure a dose that had been received one month prior to tissue being obtained as virtually all DNA single and double-strand breaks would be repaired by this time.

IV-6) A The number of dicentric chromosomes in X-irradiated cells follows a linear-quadratic function of dose.

IV-7) E Symmetrical translocations are stable chromosome aberrations as they generally do not interfere with the ability of the cell to replicate its DNA nor proceed through mitosis, although they may play a role in carcinogenesis, e.g., such as with the BCR-ABL fusion.

V. Mechanisms of Cell Death

V-1) E Pimonidazole detects hypoxic cells, whereas all the other assays listed would be useful for the identification of apoptotic cells. During the execution phase of apoptosis, nucleases are activated which cleave DNA into 180-200 base pair increments. Several assays are available to measure this phenotype. The TUNEL method identifies apoptotic cells by using terminal deoxynucleotidyl transferase (TdT) to transfer biotin-dUTP to strand breaks of cleaved DNA. The Annexin V Assay, a classical technique for detecting apoptosis, is the most commonly used method for detecting apoptosis by flow cytometry. Annexin V is a calcium-dependent phospholipid binding protein that has a high affinity for the phophatidylserine (PS), a plasma membrane phospholipid. One of the earliest features of apoptosis is the translocation of PS from the inner to the outer leaflet of the plasma membrane, thereby exposing PS to the external environment. Annexin V binds to PS exposed on the cell surface and identifies cells at an earlier stage of apoptosis than assays based on DNA fragmentation. DNA ladder formation is detected by gel electrophoresis of pooled DNA. Diamidino-2-phenylindole (DAPI) is DNA-specific dye that displays a blue fluorescence. This dye could be used to assess the nuclear morphology of normal versus apoptotic cells by fluorescence microscopy.

V-2) A The most appropriate approach to assess cellular survival to radiation for an actively dividing population of cells is to determine what fraction of the irradiated cells is capable of clonogenic survival (colony formation). Division delay would measure the amount of cell cycle perturbation caused by radiation, but occurs in all actively dividing cells regardless of whether they ultimately live or die. Apoptosis is just one form of death, and can occur at many different times after irradiation. The formation of giant cells with multiple nuclei is a manifestation of cells undergoing mitotic catastrophe following the formation of chromosome aberrations, but is not the only mechanism of radiation-induced cell death. Likewise, detection of necrotic cells would only provide the fraction of cells that undergo this form of cell death, and would not give an overall sense of cellular lethality that could also occur through either apoptosis, autophagy, mitotic catastrophe or senescence.

V-3) C Mitotic catastrophe is caused by the mis-segregation of genetic material into daughter cells resulting from radiation-induced chromosome aberrations and/or damage to the replication machinery of the cell. Apoptosis is a form of programmed cell death and can occur in response to initial radiation induced damage. However, this is rare and limited to specific tumor types such as low-grade lymphoma. Even when cells die by apoptosis, this usually occurs after mitotic catastrophe. In this case mitotic catastrophe is the reason for cell death, and apoptosis is just the mode of cell death. Oxidative damage to proteins can

occur, but is not significant at doses that are lethal to cells due to DNA damage. The generation of ceramide through the action of sphingomyelinase plays a role in the intrinsic pathway leading to apoptosis, and may be important in endothelial cells, but is not a major mechanism for the lethality of irradiation in solid tumors.

V-4) B Apoptosis predominates in some normal tissue cells derived from lymphoid tissues. In addition, radiation-induced apoptosis occurs in some normal epithelial tissues, such as the salivary gland and intestinal epithelium. However, apoptosis is not the most frequent mode of death for most cancer cells following radiation. Instead, mitotic death is more common. Apoptosis often occurs during interphase prior to mitosis. p53 plays a large role in regulation of the apoptotic program by increasing pro-death proteins like PUMA that block anti-death Bcl-2 proteins, which allow pro-death Bcl-2 proteins like BAX and BAK to kill the cell via apoptosis.

V-5) A Two breaks in a single chromosome can cause inversion, deletion or ring structure. Inversion is a chromosomal abnormality in which the segment between two breakpoints is inverted before sealing the breaks. Chromosomal inversions are stable aberrations and cells may continue to go through many divisions in their presence. Apoptosis and necrosis are forms of cell death and would reduce clonogenic survival. Autophagy, in some but not all circumstances can also lead to cell death. Senescence does not result in lethality per se, however senescent cells do not divide and therefore would not be able to contribute to colony formation.

Wouters BG. Cell death after irradiation: How, when and why cells die. Chapter 3 in: Basic Clinical Radiobiology. M Joinner and A van der Kogel, Eds, Fourth Edition (2009), Hodder Arnold, London UK.

V-6) D Annexin V stains phosphatidyl serine, a phospholipid, which is normally located on the inner leaflet of the cell membrane, but flips to the outer portion of the membrane during apoptosis. Plasma membrane integrity is maintained until the final stages of apoptosis, when the membrane blebs and pinches off to form apoptotic bodies. Cleavage of nuclear DNA at linker regions between nucleosomes is carried out by a DNAase, which is activated by caspases. Cells, such as lymphocytes and serous acinar cells that have a pro-apoptotic tendency, are generally radiosensitive, not radioresistant. In irradiated tissues, apoptotic cells often appear singly and in isolation.

V-7) A The majority of both normal and tumor cells die by mitotic catastrophe following one, or no more than a few, abortive mitotic cycles. However, until these cells attempt their first division post-irradiation, there is no morphological evidence of injury. In comparison to cells undergoing apoptosis, those undergoing necrosis demonstrate a loss of membrane integrity, a swelling of the cytoplasm and mitochondria, and random degradation of DNA (leading to a smear following agarose gel electrophoresis). An alternate pathway by which cells cease to proliferate following lethal doses of radiation is permanent growth arrest (also called replicative senescence); cells acquire a senescent-like morphology, characterized by increased granularity within the nucleus, accompanied by increased levels of $p16^{INK4A}$ (Cdkn2a) and SA-β-galactasidase. A number of pathways can be activated that lead to apoptosis, only some of which are p53-dependent.

Vandenabeele P, Balluzzi L, Vanden Berghe T, Kroemer G. Molecular mechanisms of necroptosis: An ordered cellular explosion, Nature Reviews Molecular Cell Biolog, 11:700-714, 2010. PubMed link

Cotter TG. Apoptosis and cancer: The genesis of a research field, Nat Rev Cancer 9:501-507, 2009. PubMed

Eisenberg A, Bialik S, Simon HU and Kimchi A. Life and death partners: Apoptosis, autophagy and the cross-talk between them, Cell Death Diff, 16: 966-975, 2009. PubMed link

Ohtani N, Mann DJ, Hara E. Cellular senescence: Its role in tumor suppression and aging, Cancer Sci, 100:792-797, 2009. PubMed

Letai AG. Diagnosing and exploiting cancer's addiction to blocks in apoptosis. Nat Rev Cancer, 8:121-132, 2008. PubMed

Kroemer G, Levine B. Autophagic cell death: The story of a misnomer, Nat Rev Mol Cell Biol, 9:1004-1010 2008. PubMed

Ow YP, Green DR, Hao Z, *et al.* Cytochrome c: Functions beyond respiration. Nat Rev Mol Cell Biol, 9:532-542, 2008. PubMed

Taylor RC, Cullen SP, Martin SJ. Apoptosis: Controlled demolition at the cellular level, Nat Rev Mol Cell Biol, 9:231-241, 2008. PubMed

Youle RJ, Strasser A. The BCL-2 protein family: Opposing activities that mediate cell death, Nat Rev Mol Cell Biol, 9:47-59, 2008. PubMed

Wouters BG, Brown JM. Apoptosis, p53, and tumor cell sensitivity to anticancer agents, Cancer Res, 59(7):1391-1399, 1999. PubMed link

V-8) C Cells undergoing apoptosis exhibit nuclear fragmentation. Apoptosis does not induce an inflammatory response, unlike necrosis. Apoptotic cells do not exhibit an increased expression of the *MSH2* gene, whose product is involved in mismatch repair. Apoptotic cells do not swell, but exhibit condensation and fragment into apoptotic bodies. Apoptosis can take place during interphase.

V-9) C The extrinsic apoptotic pathway involves stimulation of TNFR family members. Caspase 8 is an important initiator caspase for the extrinsic mechanism. p53 upregulates apoptosis. BAD is a pro-apoptotic protein. Leakage of cytochrome c from the mitochondrial membrane is a central aspect of the intrinsic apoptotic pathway.

V-10) A Bcl-xL prevents apoptosis primarily through inhibition of cytochrome c release from the mitochondria.

Youle RJ, Strasser A. The BCL-2 protein family: Opposing activities that mediate cell death, Nat Rev Mol Cell Biol, 9:47-59, 2008. PubMed link

V-11) E It is likely that following a dose of 4 Gy, many cells that may be reproductively dead will still be able to divide for several days following irradiation until they undergo mitotic catastrophe. It would be anticipated that a minority of carcinoma cells would undergo apoptosis and exhibit annexin V staining. Possession of a mutation in p53 would likely not substantially affect the radiosensitivity of carcinoma cells. It is only tumor cells, such as lymphomas that have a pronounced pro-apoptotic capacity, for which a p53 mutation results in radioresistance since the apoptotic pathway is inhibited in these mutant cells.

VI. Cell and Tissue Survival Assays

VI-1) D This and other *in vivo* clonogenic assays do not require that the investigator be able to unambiguously identify the stem cell or distinguish it from its differentiated progeny. Instead, the stem cell is identified functionally, by its ability to produce progeny; its survival is assayed by the ability to repopulate the depleted crypt after irradiation. All of the other factors would compromise the accuracy of the assay. A wide variation in the number of stem cells (e.g., 1 in some crypts, 10 or 50 in others) would result in large variations in the extrapolation number, n, of the radiation survival curve, and therefore in the vertical position of the exponential region of the survival curve. Such variability would make the assay unusable. The clonogenic assay also assumes that the presence of one (or more) surviving stem cells in an irradiated crypt leads to the regeneration of that crypt, and that a crypt where no stem cells survive does not regenerate. The migration of surviving stem cells from one regenerating crypt into a neighboring crypt that had no surviving stem cells, or the repopulation/survival of dying crypts as a result of the migration of unirradiated stem cells from outside of the irradiated volume, would result in an overestimation of the survival of the irradiated crypt stem cells. Conversely, if some stem cells survived, but did not proliferate for several days after irradiation, their crypts would not regenerate during the relatively short observation period used in this assay and the stem cells would erroneously be scored as dead. Stem cell survival would be underestimated in this case.

VI-2) A During the early 1960s, Till and McCulloch performed a series of experiments in which bone marrow cells were injected into lethally-irradiated mice, some of which went on to form colonies/nodules of bone marrow cells in the spleens of the recipient mice. This was the first demonstration that normal tissues possess pluripotent stem cells. In addition, for some experiments, they irradiated the donor mice and showed that with increasing dose, greater numbers of cells were necessary to produce spleen nodules in the recipient mice. This represented the first *in vivo* radiation dose response curve for a normal tissue (although radiation survival assays for cells *in vitro* had been developed a few years earlier). In recognition of this work, they were awarded the 2005 Albert Lasker Prize for Basic Medical Research.

Till JE, McCulloch EA. A direct measurement of the radiation sensitivity of normal mouse bone marrow cells, Radiation Res, 14:213-222, 1961.

VII. Models of Cell Survival

VII-1) D The formula for a single-hit survival curve is $S = e^{-\alpha D}$. Because the SF_2 (the surviving fraction following a dose of 2 Gy) is 0.37, $0.37 = e^{-\alpha D}$ or $\alpha D = 1 = \alpha$ (2 Gy). Hence, $\alpha = 0.5\ Gy^{-1}$

VII-2) C In classical target theory, the D_0 is the dose that reduces cell survival to 37% of some initial value, as measured on the exponential portion of the radiation survival curve. The D_0 dose also produces an average of one lethal lesion per cell in a population of irradiated cells; this can be derived from a Poisson distribution in which there is an average of one lethal hit in a series of targets. In this instance, 37% of the targets will not receive a lethal hit and will survive. It is the quasi-threshold dose, Dq, which is an approximation of the total amount of sublethal damage that a cell can accumulate before lethality occurs. The extrapolation number, n, represents the total number of targets that must be inactivated (or hits that must be received in a single target) for a cell to be killed. The Dq would be a manifestation of the width of the shoulder of a survival curve.

VII-3) C The D_0 for most oxygenated, mammalian cells falls in the range of 1 - 2 Gy.

VII-4) E A cell survival curve characterized by an extrapolation number equal to 1 is exponential. Therefore, if the D_0 is 1 Gy, then a dose of 3 Gy would yield a surviving fraction of (0.37) x (0.37) x (0.37) or approximately 0.05. Thus, 95% of the cells would be killed. An alternative solution can be obtained by applying the single hit single target equation $S = \exp(-D/D_o)$ with $D_o = 1$ Gy and D = 3 Gy; the surviving fraction will be $S = e^{-3/1} = 0.05$.

VII-5) E The survival curve resulting from a fractionated protocol is referred to as the effective survival curve. It is exponential and therefore appears as a straight line when plotted on a log-linear scale. Thus, the effective survival curve is not literally “linear” mathematically-speaking, but only takes on this appearance when the data are plotted in this manner. Bell-shaped implies that survival first increases with dose and then decreases, which does not occur. A parabolic dose response also does not occur.

VII-6) C For a cell line that exhibits significant curvature of its acute dose survival curve (as suggested by an n of 10), the effective D_0 would decrease with increasing fraction size compared to a multifraction survival curve employing smaller-sized dose fractions.

VII-7) D 20 colonies/2,000 cells plated = 0.01 absolute surviving fraction (1% survival). However, this value must be corrected for the plating efficiency of unirradiated cells, which is 40 colonies/200 cells plated = 0.2 (20% survival). Thus the normalized percent survival is 0.01/0.2 = 0.05 = 5%.

VII-8) B As is typical of most mammalian cell lines, the dose response curve for X-irradiated V79 Chinese hamster cells is linear-quadratic in shape, and can be modeled using the expression $S = e^{-(\alpha D + \beta D^2)}$. Using the parameters provided, the surviving fraction following a dose of 5 Gy would be $S = e^{-[(0.2)(5)+(0.05)(25)]} = e^{-(1+1.25)} = e^{-2.25} \sim 0.1$.

VII-9) C If the 5 Gy dose is delivered over a 10 h period, then the dose rate equals 5 Gy/10 h = 0.5 Gy/h. Assuming that relatively few cells divide during the 10 hour irradiation interval, the surviving fraction will increase due to repair of sublethal damage and the β parameter value will approach zero. ($\beta = 0$ means that all repairable damage has been repaired). Thus, the surviving fraction will equal $e^{-(0.2)(5)} = e^{-1} = 0.37$

VII-10) A Since the survival curve for high LET carbon ions is exponential, the surviving fraction following 5 irradiations with a dose that results in a surviving fraction of 0.4 would be $(0.4)^5 = 0.01$.

VII-11) B Genomic instability can be induced in cells surviving a prior irradiation, and this would be inherited by those cells' progeny, which may contribute to their showing a decreased clonogenic survival. All of the remaining explanations have the potential to increase, not decrease, survival.

VII-12) E The dose at which the level of single-hit equals the multi-hit killing is equal to the α/β ratio, which in this case is 0.4 Gy^{-1}/0.2 Gy^{-2} = 2 Gy.

VIII. Linear Energy Transfer

VIII-1) B Clinically relevant 75 MeV per nucleon argon ions have LET 250 keV/μm. 1 GeV/nucleon and 18 MeV/nucleon carbon ions have LET values of approximately 10 keV/μm and 108 keV/μm, respectively. 2.5 MeV alpha particles have an LET value of approximately 170 keV/μm. 150 MeV protons are considered low LET, with values in the range of 0.5 keV/μm.

VIII-2) C The carbon ion RBE is the dose required to produce a certain effect in X-irradiated cells divided by the carbon ion dose to produce the same biological effect. This ratio will be greater for cells irradiated under hypoxic conditions because of the much greater dose required to produce the effect in the X-irradiated cells where an oxygen effect is present, compared to the high LET irradiated cells where the oxygen effect is absent. The oxygen enhancement ratio, OER, for carbon ions would be lower than that for low LET radiations, but the absolute value of the OER is not related to the value of the RBE.

VIII-3) C OER decreases with increasing values of LET. Maximum effectiveness and therefore RBE reaches a peak for radiations whose LET is approximately 100 keV/μm. The RBE of high LET radiations is generally high, resulting in low values for D_0. The survival curves resulting from irradiation of cells with high LET radiations are typically exponential. LET is the term that describes the density of ionization or the average amount of energy lost (in keV) to the medium per unit of track length (μm).

VIII-4) B As the LET for different forms of radiation increases to about 100 keV/μm, both the RBE and the α/β ratio for the corresponding cell survival curves increase due primarily to an increase in the α parameter.

IX. Modifiers of Cell Survival: Oxygen Effect

IX-1) C Radiation type B likely has a higher LET than type A since less of an oxygen effect was observed for type B. Thus, if the radiation delivered by type B was delivered at a low dose rate, the amount of cell killing would not differ substantially from that produced at a high dose rate. The OER for radiation type A is 3.0 since three times the dose was required to produce the same biological effect (D_{37}) for the cells under hypoxic conditions than aerated conditions. Since types A and B are the same form of ionizing radiation, then type B would likely be lower energy than type A since LET is inversely proportional to energy of the particle.

IX-2) D In irradiated cells, oxygen increases the number and/or type of free radicals and thereby acts as a radiosensitizer, effectively increasing the level of damage produced. Oxygen reacts with free radicals resulting in the production of different radical species, which may be longer lived, and therefore more damaging than the original radicals. For example, oxygen may react with hydrogen radicals to produce peroxyl radicals. Through its reaction with free radicals formed from the radiolysis of water, oxygen plays a role in the indirect effect of radiation.

IX-3) D In order for oxygen radiosensitization to be observed, oxygen must be present either during or within microseconds following the irradiation. Irradiation under hypoxic conditions results in fewer DNA strand breaks than irradiation under aerated conditions. Irradiation in air results in more cellular damage and cell killing than irradiation under hypoxic conditions. The effect of oxygen upon radiobiologic response changes most between 0.05%-2%, with a half-maximum effect around 1%

IX-4) C The OER for most forms of low LET radiation delivered acutely is in the range of 2-3.5.

IX-5) D The OER is calculated as a ratio of doses, not effect. It is equal to the ratio of doses under hypoxic and aerobic conditions that yields the identical level of a biologic effect. For low LET radiation this value is approximately 2.5-3, and is somewhat lower at low doses (high levels of survival). The OER decreases with radiation of increased LET, due to an increased proportion of direct DNA damage.

X. Modifiers of Cell Survival: Repair

X-1) C The bystander effect has been documented in both cancer cell lines and normal, untransformed cells, with no indication that abnormal cellular signaling plays a role. The use of chemical gap junction inhibitors and connexin knock-out cells has shown a large inhibitory effect on bystander endpoints, as has the use of radical scavengers. Some aspect of bystander signaling however, is transmissible through medium transfer, and extracellular molecules such as TGF-beta have been implicated.

Prise KM, O'Sullivan JM. Radiation-induced bystander signalling in cancer therapy, Nat Rev Cancer, 9:351-360, 2009. PubMed link

X-2) E An X-ray dose delivered at a high dose rate results in greater cellular lethality since less repair of sublethal damage occurs during irradiation at a high dose rate. In contrast, during the course of irradiation at a low dose rate, many sublethal damages will be repaired and therefore will no longer be available to interact and form lethal damage. The fraction of cells undergoing apoptosis is primarily a reflection of the apoptotic tendency of the cell type rather than a reflection of the rate at which the dose was delivered. Activation of ATM, which in turn stimulates the production of molecules that cause inhibition of cell cycle progression, occurs regardless of whether the radiation is delivered at high or low dose rates. Cell proliferation is inhibited in cells irradiated at a high dose. Furthermore, cell proliferation would increase survival.

X-3) E A drug that inhibits the rejoining of chromosome breaks in irradiated cells would be expected to decrease the amount of sublethal damage repair (itself a manifestation of the rejoining of chromosome breaks), and therefore, to sensitize cells to low dose rate irradiation where sublethal damage would otherwise be repaired. The repair of potentially lethal damage would also be inhibited. The yield of terminal deletions would be expected to increase as there would be less repair of chromosomal breaks. The dose rate effect, manifested as increased cell survival for irradiation at low, compared to high dose rates, would also be diminished.

X-4) A Generally, increasing the time between fractions in a split dose treatment results in a higher cell surviving fraction due to repair at relatively short interfraction intervals of a few hours, or due to repopulation for longer times between fractions. However, under certain irradiation conditions and depending on the cell line, the initial dose may cause inhibition of progression from G_2 into M phase. Therefore, the second dose may be delivered when the majority of the surviving cells have reassorted into G_2, a radiosensitive phase of the cell cycle. Thus, even though repair of sublethal damages has occurred in these cells, which by itself would lead to a greater surviving fraction, this may be more than counterbalanced by reassortment sensitization, resulting in lower cell survival. Hypoxic conditions would not be expected for cells grown in tissue culture, so reoxygenation, which could lead to greater cell killing if it were to occur, is unlikely. The adaptive response in which cells treated with an initial low "priming" dose of radiation exhibit greater resistance to a second, higher, "challenge" dose, would increase, not decrease, cell survival.

X-5) C Cell lines whose X-ray survival curves have low α/β ratios generally display a large capacity for SLDR, whereas cells whose X-ray survival curves have high α/β ratios show relatively little SLDR. As the dose rate is lowered and exposure time increased, the biological effect of an X-ray dose diminishes due to SLDR. PLDR is best demonstrated with a "delayed plating" experiment, and is operationally defined as an increase in the surviving fraction resulting from prolonged incubation of cells under non-growth conditions following irradiation. There is little or no SLDR or PLDR following exposure to high LET radiation. Fractionated irradiation would be expected to increase survival (not decrease it) in normal lung tissue compared to lung cancer cells, and this would result from SLDR, not PLDR.

X-6) C Sublethal damage recovery is operationally defined as an increase in cell survival when a total dose is split into two fractions separated by a time interval compared with delivery of the same dose in one large fraction. The TCD_{50} is the total dose that locally controls, on average, 50% of tumors in laboratory animals, but by itself does not directly demonstrate sublethal damage recovery. A cell synchronization experiment would not demonstrate sublethal damage recovery, although it could be used to show variations in SLDR capacity in cells of different cell cycle "ages". An increase in cell survival when cells are maintained under a non-growth state after irradiation, is the operational definition of potentially lethal damage recovery. The paired survival curve technique is used to determine a tumor's radiobiological hypoxic fraction.

X-7) B As the dose rate decreases from about 1 Gy/min to 0.01 Gy/min, the greatest increase in cell survival due to SLDR is observed for most X-irradiated cell lines. Decreasing the dose rate further may permit an even greater increase in the surviving fraction, but this further increase would be due to repopulation that may take place if the dose is delivered at a very low dose rate over a long interval.

XI. Solid Tumor Assay Systems

XI-1) E The tumor regrowth delay assay measures the average time necessary for a treated tumor to reach a pre-determined size compared to the time it takes for control tumors. Of the assays listed, the tumor regrowth assay is most informative as to the effect of radiation and/or drug treatment. The techniques described in A and B are still used to measure the relative effectiveness of experimental chemotherapy drugs, however they provide only very limited information. The technique described in C is effective only if the treated tumors shrink immediately and dramatically following treatment, but is less effective with agents such as radiation that produce a delayed cell death or with drugs that have cytostatic effects, because these agents will not produce rapid and sizeable shrinkage of the tumors. The approach described in D may not allow meaningful comparisons between the different treatment groups, if some or all treatments have been relatively successful and tumors in several groups have not even begun to regrow by the time the control tumors become large.

XI-2) D Radiation-induced cell killing is random, and the probability follows a Poisson distribution; a tumor will be controlled only when no clonogenic cells remain. The dose at which a specific tumor is controlled will be determined by the probability of killing the last clonogenic cell in that tumor. However, this will not be the same for each tumor because of the random nature of radiation damage and of cell death. The result of this, statistically, is that the tumor control probability plotted as a function of dose on a linear scale will yield a steep, sigmoid-shaped curve that reflects only the random variation in the dose needed to kill the last clonogenic cell in the tumor. Heterogeneity between the tumors (e.g., differences in size/cell number), or heterogeneity within the tumor cell population (e.g., heterogeneity in the radiosensitivity of the cells because of their position in the cell cycle, oxygenation status, or genotype), would broaden the dose range over which the sigmoidal increase in tumor control probability occurred, and the resulting tumor control probability curve would be shallower.

XI-3) D The impact of a radiosenisitizer upon tumor control will be most readily detected for experimental protocols that result in a 50% rate of tumor cure, since even a small level of sensitization will significantly decrease the TCD_{50} in this portion of the curve. This curve demonstrates that 50% of the tumors will be controlled by a dose of 60 Gy (ie. TCD_{50} = 60 Gy), whereas 70 Gy increases tumor cure to >90%. NTCP stands for normal tissue complication probability. The additional dose to increase cures from 50% to 60% is relatively small because the TCD_{50} is on the steep part of the dose-response curve, but to increase cure rates from 90% to 100%, a much larger dose is required. At 50 Gy, approximately 10% of the tumors will be controlled**.**

XII. Tumor Microenvironment

XII-1) D Acute changes in blood flow cause acute, or perfusion limited hypoxia. This can be partial or total occlusion of blood vessels that causes hypoxia in cells being fed by the vessel in question. Acute hypoxia can change over a period of 15 min-2 hrs and will thus alter overall tumor oxygenation during a period of 24 hrs between radiation fractions. Hypoxia can be distributed throughout the entire tumor mass, and can potentially be present surrounding any blood vessel in the tumor. No relationship has been observed between tumor hypoxia and tumor size. Tumor hypoxia varies widely amongst patient tumors and is thought to be an important contributor to the overall variation in response to therapy.

Cao Y. Off-tumor target –beneficial site for antiangiogenic cancer therapy? Nat Rev Clin Oncol, 7:604-609, 2010. PubMed link

Dewhirst MW, Cao Y, Moeller B. Cycling hypoxia and free radicals regulate angiogenesis and radiotherapy response, Nature Reviews Cancer, 8, 425-437, 2008. PubMed link

XII-2) B Clinical studies indicate that hypoxia does not show a strong relationship with tumor size. This is due to the fact that hypoxia arises through deficiencies in blood vessel perfusion and from a limited ability to diffuse through metabolically active tissue. Hypoxia is observed at distances from 100-200 microns from functional vessels. Thus, even very small tumors may have high hypoxic fractions. Hypoxic cells are radioresistant and exhibit genomic instability and increased probability of metastasis. Each of these factors translates into a worse patient prognosis.

Bristow RG, Hill RP. Hypoxia and metabolism. Hypoxia, DNA repair and genetic instability, Nat Rev Cancer, 8:180-192, 2008. PubMed link

XII-3) B The maximum distance that oxygen can diffuse from a capillary before hypoxia is detected, is roughly 150 μm, and is determined by the oxygen consumption rate of cells surrounding blood vessels. This distance also depends on the starting concentration in the blood, which can be influenced by hemoglobin levels. An increase in oxygen utilization would reduce the diffusion limit.

XII-4) B Without reoxygenation, it is unlikely that a tumor comprised of any significant proportion of hypoxic cells (even as low as 1%), would be controlled following total doses used in typical radiotherapy protocols.

XII-5) D Under normoxic conditions, HIF-1α is hydroxylated in a reaction that uses oxygen as a co-factor. When hydroxylated, HIF-1α is recognized by VHL and degraded. During hypoxia, hydroxylation is prevented and HIF-1α becomes stabilized and active as a transcription factor.

XII-6) E The oxygen enhancement ratio (OER) for X-rays is lower (~1.5-2.0) for X-ray doses <2 Gy and higher (~3.0) for doses >10 Gy. Chronic hypoxia develops in regions of a tumor distant from blood vessels, which is mainly due to the limited diffusion distance of oxygen. Acute hypoxia is associated with transient changes in vascular perfusion that could be due to either temporary blockage in a blood vessel, vascular status or other factors. Reoxygenation of both chronically and acutely hypoxic cells has been demonstrated in experimental tumors, however, both the mechanisms and the time course of reoxygenation are different for chronic and acute hypoxia. Hypoxia plays a role in tumor control through the induction of hypoxia-inducible factor alpha (HIF-1α) (HIF1A). HIF-1α is degraded under well-oxygenated conditions, but is stabilized under hypoxic conditions. In hypoxia, stabilized HIF-1α dimerizes with constitutively expressed HIF-1β (ARNT) to form a transcription factor that regulates expression of pro-angiogenic genes, including that for vascular endothelial growth factor (*VEGF*).

Dewhirst MW. Relationships between cycling hypoxia, HIF-1, angiogenesis and oxidative stress, Radiat Res, 172:653-665, 2009. PubMed link

Kaelin WG Jr. The von Hippel-Lindau tumour suppressor protein: O2 sensing and cancer. Nat Rev Cancer, 8:865-873, 2008.PubMed link

Bertout JA, Patel SA, Simon MC. The impact of O2 availability on human cancer, Nat Rev Cancer, 8:967-975, 2008. PubMed link

Bristow RG, Hill RP. Hypoxia and metabolism. Hypoxia, DNA repair and genetic instability, Nat Rev Cancer, 8:180-192, 2008. PubMed link

Dewhirst MW, Cao Y, Moeller B. Cycling hypoxia and free radicals regulate angiogenesis and radiotherapy response, Nat Rev Cancer, 8:425-437, 2008. Erratum in: Nat Rev Cancer, 8:654, 2008. PubMed link

Galanis A, Pappa A, Giannakakis A, Lanitis E, Dangaj D, Sandaltzopoulos R. Reactive oxygen species and HIF-1 signalling in cancer, Cancer Letters, 266:12-20, 2008. PubMed link

XII-7) A [18F]-fluorodeoxyglucose (FDG) – PET would be most useful to measure glycolytic activity in the tumor, but not hypoxia. The other compounds can all be used to detect hypoxic regions in tumors non-invasively.

Lapi SE, Voller TF, Welch MJ. PET imaging of hypoxia, PET Clin 4:17-38, 2009. PubMed link

Brindle K. New approaches for imaging tumour responses to treatment, Nat Rev Cancer, 8:94-107, 2008. PubMed link

Lee ST, Scott AM. Hypoxia positron emission tomography imaging with 18f fluoromisonidazole, Semin Nucl Med, 37:451-461, 2007. PubMed link

XII-8) A A non-invasive method for the detection of hypoxic regions or measurement of oxygen concentration in tumors would help to select patients to receive drugs or specialized therapies aimed at targeting hypoxia. Studies with tirapazamine and use of carbogen have indicated that the benefit of these therapies are limited to patients with hypoxic tumors.

XII-9) D Under hypoxic conditions, HIF-1α regulates the transcription of the gene encoding VEGF.

XII-10) D Although p53 is activated by hypoxia, this does not occur as a result of HIF activation. p53 is activated at oxygen concentrations lower than that required to activate HIF. HIF regulates glycolysis (e.g GLUT-1), angiogenesis (e.g. VEGF), erythropoiesis (e.g. EPO), and pH (e.g. CA9).

XII-11) B A breaking survival curve, in which the survival curve initially displays a steep slope followed by a shallower response, would be predicted for irradiation of a mixed population of aerated and hypoxic cells. This type of dose response would be anticipated since the initial portion of the survival curve reflects the killing of radiosensitive aerated cells; whereas the survival curve obtained at higher doses primarily reflects the killing of radioresistant hypoxic cells. A fractionated protocol would be expected to decrease the effect of a hypoxic cell radiosensitizer to enhance tumor control, compared with an acute treatment, since reoxygenation would cause aeration of many of the hypoxic cells between fractions thereby diminishing the apparent effectiveness of the radiosensitizer. The OER is the dose to produce an effect in hypoxic cells divided by the dose to produce the same effect in aerated cells. The diffusion distance in air for oxygen is much greater than 100 μm. Maximum OER is typically observed only when the oxygen concentration reaches about 3-5%.

XII-12) B The paired survival curve technique is used to determine the proportion of viable clonogenic cells in a tumor that is hypoxic. In this assay, animals possessing tumors are irradiated while breathing either room air (typical tumor response), or where they are clamped to block blood flow. The ratio of the surviving fractions for the cells, under aerated to fully anoxic conditions, provides an estimate of the fraction of the cells in the tumor that are hypoxic under normal conditions.

XIII. Cell and Tissue Kinetics

XIII-1) B Mitotic cells generally possess little or no survival curve "shoulder" and therefore are characterized by high α/β ratios.

XIII-2) C Assuming that all cells are proliferating, the number of cells in a tumor that doubled in diameter would increase approximately 8-fold as the number of cells can be approximated from the volume of a sphere which is equal to $\pi d^3/6$. An 8-fold increase in the cell number would require three cell doublings. Since it took 18 days to achieve this increase, the cell cycle time can be estimated at 6 days.

XIII-3) D The CDK1/cyclin B complex plays an important role in the transition of cells from G_2 phase into mitosis.

XIII-4) B Cell loss is often the main factor that determines the tumor volume doubling time, since tumors with a low cell loss factor will grow more rapidly than tumors with a high cell loss factor. The growth fraction of a tumor is the number of proliferating cells in a tumor divided by the number of proliferating and quiescent cells in the tumor. The growth rate generally decreases with increasing tumor size. Volume doubling times are longer than the value that would be predicted from the cell cycle time of individual cells because the growth fraction is usually less than one and the cell loss factor may be large. The volume doubling time is a reflection primarily of the growth fraction and cell loss factor.

XIII-5) E Since the cell loss factor is equal to 1.0, the tumor would remain the same size since for every new cell produced, one existing cell would die.

XIII-6) A T_{pot} represents the time it would take a tumor to double its cell number in the absence of cell loss (i.e., $\phi = 0$).

XIII-7) B The T_{pot} for most head and neck tumors is in the range of 2-6 days.

XIII-8) E The T_{pot} is equal to λT_S /LI = (0.7)(10 hours)/0.2 = 35 hours

XIII-9) D If the treatment had been initiated 20 days earlier, then the number of cells in the tumor in patient B would have been one-half of the number of cells present when the cancer was diagnosed. In contrast, the tumor in patient A is growing more rapidly with a T_{pot} of 5 days. Therefore, if diagnosed 20 days earlier, the cancer in this patient would be only one-sixteenth as many cells. Thus, the ratio of the number of cells in the tumors in patients A and B would be 1:8, if the cancers had been diagnosed 20 days earlier.

XIII-10) A Although a low growth fraction would contribute to a long volume doubling time, the most likely reason why a tumor made up of cells with a short cell cycle time would grow slowly is most likely due to a high cell loss factor.

XIII-11) E The volume doubling time can be estimated from the equation $\phi = 1-(T_{pot}/T_{vol})$ where ϕ is the cell loss factor, T_{pot} is the potential doubling time and T_{vol} is the measured volume doubling time. Therefore, $0.9 = 1 - (20 \text{ days}/T_{vol})$ or $T_{vol} = 200$ days.

XIII-12) A SMC1 is a substrate for ATM and plays a role in regulation of progression through S phase. It is not part of the p53 pathway. In contrast, p53 regulates p21, which in turn associates with CDK1/cyclin B complexes and inhibits their phosphorylation by CAK or cyclin activating complex. GADD45 is a p53 target gene whose product binds CDK1, preventing cyclinB/CDK1 complex formation. 14-3-3σ is induced by p53 and plays a role in G_2 arrest.

Hurley PJ, Bunz F. ATM and ATR: Components of an integrated circuit, Cell Cycle, 6:414-417, 2007. PubMed link

Kitagawa R, Kastan MB. The ATM-dependent DNA damage signaling pathway, Cold Spring Harb Symp Quant Biol, 70:99-109, 2005. PubMed Link

Lukas J, Lukas C, Bartek J. Mammalian cell cycle checkpoints: signalling pathways and their organization in space and time, DNA Repair (Amst) 3:997-1007, 2004. PubMed Link

XIV. Molecular Signaling

XIV-1) D Growth factor receptors generally have three domains: an extracellular ligand-binding domain, a trans-membrane domain that spans the plasma membrane of the cell, and an intracellular kinase domain. Mutations can occur in all three domains in ways that contribute to cancer development. The resultant changes in the protein often lead to constitutive kinase activity, which signals the cell to proliferate, not to undergo senescence. Kinases are proteins that attach phosphate groups to other molecules. Such receptor mutations have not been shown to stimulate general protein translation, cause DNA damage that would stimulate formation of γ-H2AX foci or affect caspase 3, which is normally activated by cleavage, not ubiquitination, to cause apoptosis.

XIV-2) C In order to become active, the RAS protein must be prenylated by the action of farnesyl transferases. Hence, RAS activation in cells can be prevented by farnesyl transferase inhibitors (FTIs). It has been postulated that this could decrease the growth of cancer cells and should cause radiation sensitization, since some studies have found a correlation between RAS expression and radioresistance. In clinical studies however, FTIs have had less effect than anticipated on cancer cells because RAS can also be geranylated by geranylgeranyl transferases, which the FTIs do not block. It now appears that FTIs may have additional cellular effects, which are still under investigation. HDAC (histone deacetylase) inhibitors alter chromatin configuration and may be radiation sensitizers; cyclin-dependent kinases are intracellular enzymes involved in regulating the cell cycle; I-κB is an intracellular inhibitory molecule that regulates the transcription factor NF-κB; and Iressa is an inhibitor of ERBB1.

XIV-3) E All of the processes listed, except binding of FAS ligand to FAS receptor on the plasma membrane, have been associated with p53 activation. Binding of FAS ligand to FAS receptor activates the extrinsic pathway to apoptosis, which does not appear to involve p53.

XIV-4) A RAS is a GTPase.

Vigil D, Cherfils J, Rossman KL, Der CJ. Ras superfamily GEFs and GAPs: Validated and tractable targets for cancer therapy?, Nature Reviews Cancer 10:842-857, 2010. PubMed link

Schubbert S, Shannon K, Bollag G. Hyperactive Ras in developmental disorders and cancer, Nat Rev Cancer, 7:295-308, 2007. PubMed link

XIV-5) D FADD (FAS-associated death domain) protein plays an important role in the extrinsic apoptotic pathway through activation of caspase 8. Activated RAS stimulates cellular proliferation through activation of multiple pathways including the RAF, MEK, JNK, RAC/RHO, PLC and PI3K/AKT pathways.

XIV-6) C Epigenetic regulation of genes can occur at the level of the histone proteins intimately associated with the DNA. Modification of the histones that surround the DNA can lead to complex signaling that directs the packing and unpacking of the DNA double helix. Epigenetic regulation of histones can occur through acetylation, phosphorylation, methylation and ubiquitination. Glycosylation does not occur.

Camphausen K, Tofilon PJ. Inhibition of histone deacetylation: A strategy for tumor radiosensitization, J Clin Oncol, 25:4051-4056, 2007. PubMed Link

Lohrum M, Stunnenberg HG, Logie C. The new frontier in cancer research: Deciphering cancer epigenetics, Int J Biochem Cell Biol, 39:1450-1461, 2007. PubMed Link

XIV-7) A EGFR is activated in tumors by overexpression or mutation and functions to induce proliferation. The pathways activated by EGFR may also stimulate DNA repair, and promote angiogenesis. As such, it is an important target for therapy.

XV. Cancer

XV-1) D Telomerase adds specific repeat sequences onto and caps the ends of chromosomes, thereby creating telomeres. This both prevents the ends of chromosomes from shortening with each cell division as well as from unraveling and/or inappropriate identification by the cellular DNA repair enzymes as double strand breaks. Telomerase is generally active in normal stem cells and many tumor cells, but not other differentiated, normal cells, which confers on them unlimited replicative potential, i.e., "immortality". Telomerase does not play a central role in base excision repair and tends to be present at low levels in senescent cells. Inhibition, not stimulation, of telomerase represents a potential means to inhibit proliferation of cancer cells.

O'Sullivan RJ, Karlseder J. Telomeres: protecting chromosomes against genome instability, Nature Reviews Molecular Cell Biology, 11:171-181, 2010. PubMed link

Harley CB. Telomerase and cancer therapeutics, Nat Rev Cancer, 8:167-179, 2008. PubMed link

Gilson E, Géli V. How telomeres are replicated, Nat Rev Mol Cell Biol, 8:825-838, 2007. PubMed link

XV-2) B Since p53-mediated apoptosis is the main way lymphoma cells die following irradiation, possession of a mutation in the p53 gene renders these cells radioresistant, not radiosensitive.

Murray-Zmijewski F, Slee EA, Lu X. A complex barcode underlies the heterogeneous response of p53 to stress, Nat Rev Mol Cell Biol, 9:702-712, 2008. PubMed link

Szumiel I. Intrinsic radiation sensitivity: Cellular signaling is the key, Radiat Res, 169:249-258, 2008. PubMed link

Sengupta S and Harris CC, p53: Traffic cop at the crossroads of DNA repair and recombination. Nat Rev Mol Cell Biol 6:44-55, 2005. PubMed link

Gudkov AV and Komarova EA. The role of p53 in determining sensitivity to radiotherapy, Nat Rev Cancer, 3:117-129, 2003. PubMed link

XV-3) A The RB protein suppresses cell growth by binding to the E2F transcription factor, preventing it from activating the transcription of cell cycle-related proteins that allow the cell to transition from G_1 to S phase. Cell cycle dependent kinases add phosphate, not hydroxyl, groups to the RB gene product causing it to release E2F. A mutant *RB* gene is inherited from one parent in the familial form of retinoblastoma, not the sporadic form. The RB protein product is phosphorylated by CDK4, not CDK1. In the familial form, people who inherit a mutated copy of the *RB* gene exhibit an increased incidence not only of retinoblastoma, but also osteosarcomas, as well as carcinomas of the lung, kidney and bladder.

Mittnacht S. The Retinoblastoma Protein--from Bench to Bedside, Eur J Cell Biol, 84(2-3):97-107, 2005. PubMed link

Massague J. G1 Cell-Cycle Control and Cancer, Nature, 432:298-306, 2004. PubMed link

XV-4) D Although a DNA repair deficiency may lead to greater cancer proneness, it is **not** true that cells derived from all human tumors have such deficiencies.

XV-5) D Oncogenes are frequently activated by point mutations. Examples include single nucleotide mutations in K-ras or in receptor tyrosine kinases that result in constitutive activation. Oncogene activation drives tumor proliferation and carcinogenesis. Epigenetic silencing and gene loss are events that inactivate tumor suppressors. Familial cancers are caused by inheritance of defective tumor suppressors.

XV-6) B $p16^{INK4A}$ is an inhibitor of CD4 and CDK6. The gene coding for it is a tumor suppressor that is found mutated in many cancers, particularly melanomas and pancreatic cancers. Inactivation of the gene is associated with an increased metastatic potential, but presumably plays no role vis-à-vis tumor hypoxia.

XV-7) A People with Cockayne's syndrome are deficient in transcription-coupled nucleotide excision repair and are characterized by stunting of growth, impaired development of the nervous system, photosensitivity and premature aging. However, there is no evidence for cancer proneness. The other syndromes are associated with the following cancers:

Bloom's syndrome – leukemia and lymphoma
Fanconi's anemia – leukemia
Nijmegen breakage syndrome - lymphoma
ataxia telangiectasia – leukemia, lymphoma

XV-8) D Following irradiation, ATM activates CHEK2 which then phosphorylates CDC25C phosphatase, preventing it from dephosphorylating CDK1, a step necessary for progression from G_2 into M. Although the mechanism for activation of ATM following irradiation is not clear, it has been suggested that the MRN complex stimulates, not inhibits, its activation. Following irradiation, ATM is autophosphorylated and converted from an inactive dimer to an active monomer. ATM causes phosphorylation of MDM2 and inhibits its inhibitory activity against p53. H2AX is a substrate for ATM kinase activity causing addition of phosphate groups resulting in γH2AX.

Boutros R, Lobjois V, Ducommun B. CDC25 phosphatases in cancer cells: Key players? Good targets?, Nat Rev Cancer, 7:495-507, 2007. PubMed link

Bode AM, Dong Z. Post-translational modification of p53 in tumorigenesis, Nat Rev Cancer, 4:793-805, 2004. PubMed Link

XV-9) B BRCA1 is not a phosphatidyl inositol 3-kinase like kinase, whereas ATM, ATR, RAD3 and DNA-PK all fall into this category of protein.

XV-10) A NFκB does not inhibit non-homologous end-joining of DNA double strand breaks.

XV-11) B The products of tumor suppressor genes generally inhibit cell growth, not stimulate it.

XV-12) E PTEN is a tumor suppressor gene.

Vogelstein B and Kinzler KW, Cancer Genes and the Pathways They Control, Nat Med 10(8): 789-799, 2004. PubMed link

XV-13) D People with ataxia telangiectasia do not exhibit an increased sensitivity to UV induced damage which is repaired by nucleotide excision repair.

XV-14) C A loss of function mutation in a tumor suppressor gene would be dominant in a pedigree. This is observed because inheritance of a mutated copy of a tumor suppressor would result in the inactivation of one copy of the tumor suppressor gene in all cells in the body. It is likely that, during the course of such an individual's life, the other copy of the tumor suppressor gene would be lost through loss of heterozygosity in at least some cells, thereby creating conditions to promote malignant transformation. A gain of function mutation of an oncogene would be dominant on a cellular level since the protein encoded by the oncogene would then be overexpessed and stimulate malignant progression. A gain of function mutation in a tumor suppressor gene may, if anything, inhibit malignant progression of a tumor since it would likely be inhibitory of cell growth. A loss of function mutation in a tumor suppressor gene is recessive on a cellular level since the remaining normal copy of the gene should encode sufficient protein. A loss of function mutation in an oncogene would probably have either no effect or potentially inhibit cancer susceptibility since there may be a diminished level of the gene product which could reduce cell growth.

XV-15) A Although a mutation in BRCA1 results in a susceptibility for the development of breast cancer, it is not deleted in the majority of breast cancers.

Fackenthal JD, Olopade OI. Breast cancer risk associated with BRCA1 and BRCA2 in diverse populations, Nat Rev Cancer, 7:937-948, 2007. PubMed link

XV-16) D p21 levels **increase** in irradiated cells.

XV-17) A Loss of heterozygosity of a tumor suppressor gene, not an oncogene, often occurs during malignant progression, and involves the loss of a protein that otherwise would play a role in inhibiting cell proliferation.

XV-18) A Hereditary non-polyposis carcinomas of the colon have displayed mutations in mismatch repair genes. Neurofibromatosis and retinoblastoma are associated with the loss of tumor suppressor genes. Ovarian cancers and glioblastomas have been reported to harbor numerous gene defects.

XV-19) A BCL2 is an anti-apoptotic protein that counters the release of cytochrome c from the mitochondria, a necessary step in the intrinsic apoptotic pathway. Therefore, BCL2 over-expressing cells are resistant to apoptosis. BCL2 over-expressing cells do not proliferate rapidly, do not have increased angiogenesis, are not necessarily hypoxic, and do not have decreased DNA double strand break repair.

XVI. Total Body Irradiation

XVI-1) A The time to death from the hematopoietic syndrome is about 1-2 months. The latent period before death from the cerebrovascular syndrome is 1-2 days. The threshold doses (the minimum dose at which these syndromes may be detectable in some people in an irradiated population), for hematopoietic and gastrointestinal syndromes are approximately 1 Gy and 5 Gy, respectively. However, it should be noted that doses of approximately 2.5 Gy and 8 Gy are necessary before a substantial portion of an irradiated population would exhibit pronounced symptoms of hematopoietic and gastrointestinal syndromes, respectively. The latent period until death from GI syndrome is about 3-10 days.

XVI-2) C Death from the hematopoietic syndrome usually results from infection and hemorrhage due to radiation-induced loss of white cells and platelets.

XVI-3) E A person exposed to 3 Gy of γ-rays should be carefully watched for symptoms of infection and hemorrhage resulting from loss of white blood cells and platelets, with the critical period being 2-4 weeks following irradiation. Prophylactic administration of antibiotics should be initiated immediately following the accident, rather than waiting for overt signs of infection. A bone marrow transplant would likely be of no value at this dose, so tissue typing is not necessary, since use of antibiotics and transfusion of blood components, as necessary, would substantially enhance the probability for survival without the use of a transplant. The dose the worker received was too low for her to develop symptoms of the GI syndrome, which include dehydration and bloody diarrhea, likely culminating in death. If the dose received was less than 2 Gy, it would be reasonable to be monitored from home, but following a dose of 3 Gy a person should be hospitalized in reverse air flow isolation with supportive care, including antibiotic administration immediately.

ACR Disaster Preparedness for Radiology Professionals, A Primer for Radiologists, Radiation Oncologists and Medical Physicists, Government Version 3.0 available through the ASTRO website at: Astro pdf link

Planning Guidance for Nuclear Detonation, first edition Jan 2009, Homeland Security Council Interagency Policy Coordination Subcommittee for Preparedness and Response to Radioological and Nuclear Threats. Available on the ASTRO website at: Astro pdf link

Goans RE, Waselenko JK. Medical management of radiological casualties, Health Phys 89:505-512, 2005. PubMed link

Turai I, Veress K, Gunalp B, *et al*. Medical response to radiation incidents and radionuclear threats, BMJ, 328:568-572, 2004. PubMed Link

Waselenko JK, MacVittie TJ, Blakely WF, *et al.* Medical Management of the Acute Radiation Syndrome: Recommendations of the Strategic National Stockpile Radiation Working Group, Ann Intern Med, 140:1037-1051, 2004. PubMed link

XVI-4) D Death from the gastrointestinal syndrome could occur within one week following irradiation, but is unlikely following a whole body dose of 5 Gy. However, a person irradiated with this dose who did not receive appropriate medical care has a greater than 50% chance of dying within a 1-2 month period from bone marrow syndrome. Following a whole body dose of 5 Gy, infections are likely due to loss of white blood cells and lack of treatment with antibiotics. Nausea would be observed during the early prodromal period. Epilation and bleeding would occur during the period before the person dies from hematopoietic syndrome.

XVI-5) D A drop in the level of white cells and platelets may be observed following a whole body dose of approximately 1 Gy, although it has been detected at doses as low as 0.5Gy.

XVI-6) D A whole body dose that results in severe diarrhea within 4 days of irradiation is likely to be lethal (probably 8 Sv or higher). Therefore, all of the people would be expected to die within 1-2 weeks following irradiation due to GI syndrome.

XVI-7) E A person who dies one year following total body irradiation would not die from any of the conventional whole-body radiation syndromes. These syndromes cause death at about 1-2 days (cerebrovascular), 1-2 weeks (gastrointestinal) or 1-2 months (hematopoietic), respectively, following irradiation. Since the dose received was not sufficiently high to cause death from the GI syndrome (i.e., at least 8 Sv), it would likewise not be high enough to cause brain necrosis. However, the treatment dose may have been high enough to cause lung fibrosis, which may result in death, within one year after irradiation.

XVI-8) B Immunosupression observed within 24 hours after irradiation would be the consequence of the rapid death of lymphocytes due to radiation-induced apoptosis. A much longer period than 24 hours would be required for the death of progenitor cells and a loss of granulocytes. Doses much greater than 5 Gy would be necessary to cause decreased activity of NK cells and inactivation of circulating antibodies.

XVI-9) A The $LD_{50/60}$ for an acute, whole body irradiation is estimated to be 3.5 Gy without medical intervention and approximately 7 Gy with optimal medical care. The principal causes of death for people who receive a dose close to the $LD_{50/60}$ are infections and hemorrhage. A person who received a dose of about 3.5 Gy would not exhibit the symptoms associated with the GI syndrome, such as severe diarrhea. The $LD_{50/60}$ is the dose that leads to death within 60 days of 50% of the population.

XVI-10) B The use of low dose rate irradiation in preparation for a bone marrow transplant results in substantial sparing of the lung with respect to the development of radiation fibrosis. In contrast, there is more modest sparing of either serous acinar cells in the parotid glands, basal cells in the skin, the oral mucosa, or lymphocytes.

XVI-11) A The chronological sequence over which the components of peripheral blood decline after irradiation are lymphocytes, granulocytes, platelets and erythrocytes.

XVII. Clinically Relevant Normal Tissue Responses to Radiation

XVII-1) B Increasing the radiation dose decreases the latent period for cataract formation. The lens does not have the ability to eliminate damaged fibers. The RBE for cataract formation following irradiation with a series of small doses is in the range of 50-100 since there is substantial sparing associated with the X-irradiation, thereby substantially increasing the threshold dose to induce a cataract by X-rays. In contrast, the neutron dose to induce a cataract is relatively unaffected by the magnitude of the individual doses. Hence, the RBE, which is the ratio of the X-ray dose divided by the test radiation (neutrons) dose to induce an effect (cataract formation), increases with decreasing fraction size. The threshold dose for the induction of a radiation-induced cataract following an acute X-ray dose is 2 Gy or less. A radiation-induced cataract is one of the few examples of a radiation injury which does have distinct pathognomonic characteristics that identify it as having been induced by ionizing radiation; radiation-induced cataracts typically begin in the posterior portion of the lens, unlike the case of age-related cataracts.

Ainsbury A, Bouffler SD, Dörr W, *et al*. Radiation cataractogenesis: A review of recent studies, Radiat Res, 172:1-9, 2009. PubMed link

XVII-2) A Only about 1% of children develop severe restrictive pulmonary disease, although the majority develop some symptoms.

Faraci M, Barra S, Cohen A *et al.* Very late nonfatal consequences of fractionated TBI in children undergoing bone marrow transplant, Int J Radiat Oncol Biol Phys, 63:1568-1575 2005. PubMed Link

XVII-3) D Dose fractionation increases the risk for sterility in the male; the TD_5 and TD_{50} for sterility are 2 Gy and 8 Gy, respectively, for a single dose of X-rays, whereas these values decrease to 1 Gy and 2 Gy for fractionated irradiation. This effect results from spreading the dose over time permitting reassortment sensitization to occur for spermatogonia, which have a large variation in radiation sensitivity through the course of their cell cycle, and more than compensating for any repair that might occur between fractions. Thus, spermatogonia located in a relatively radioresistant portion of the cell cycle may progress into a more radiosensitive part of the cell cycle at the time of the second and subsequent irradiations. Spermatids and spermatozoa are relatively radioresistant, whereas spermatogonia are radiosensitive. A drop in testosterone levels would not be detectable following a scattered dose of 0.1 Gy to the testes, particularly to an adult. Following a moderate dose of radiation, which kills a large number of spermatogonia, there may be relatively little effect on the levels of spermatocytes, spermatids and spermatozoa initially, since a period of 67 days is required for maturation of a spermatogonial stem cell to a mature spermatozoan. Hence, there may be very little drop in sperm count for the first month following irradiation, although the sperm count will decrease at a later time. Full recovery of a normal sperm count following radiation-induced azoospermia caused by exposure of the testes to a dose of 6 Gy, would require a period of at least 2 years.

XVII-4) D Similar to other hierarchical tissues, the gastrointestinal mucosa is considered a rapidly renewing system. The transit time from a gut stem cell to a terminally differentiated epithelial cell, being lost from the tip of a villus, is on the order of a week.

XVII-5) B Diarrhea usually occurs about 3 weeks after the start of fractionated radiotherapy.

XVII-6) A Early myelopathy differs from transient demyelination because it is more severe and progressive, not less so.

XVII-7) E Arterial cerebrovasculopathy is an infrequent, not common, occurrence.

Kelsey CR, Marks LB. Somnolence syndrome after focal radiation therapy to the pineal region: Case report and review of the literature, J Neurooncol, 78(2):153-156., 2006. PubMed link

Ryan J. Radiation somnolence syndrome, J Pediatr Oncol Nurs, 17(1):50-53, 2000. PubMed link

Johannesen TB, Lien HH, Hole KH*, et al.* Radiological and Clinical Assessment of Long-Term Brain Tumour Survivors after Radiotherapy, Radiother Oncol, 69:169-176, 2003. PubMed link

Tofilon PJ, Fike JR. The Radioresponse of the Central Nervous System: A Dynamic Process, Radiat Res, 153:357-370, 2000. PubMed link

XVII-8) C The kidney has a relatively low tolerance dose because of the limited number of clonogens within each nephron, although the cells comprising the functional subunits of the kidney are not particularly radiosensitive. The kidney exhibits substantial sparing with fractionation and displays little or no tolerance to re-irradiation. A much longer latent period than 3 months is required before the appearance of radiation nephropathy.

Cohen EP, Robbins ME. Radiation Nephropathy, Semin Nephro, 23(5):486-499, 2003. PubMed link

Stewart FA, Luts A, Lebesque JV. The lack of long-term recovery and reirradiation tolerance in the mouse kidney, Int J Radiat Biol, 56:449-462, 1989. PubMed Link

XVII-9) B RILD typically occurs between 2 weeks and 3 months after completion of radiotherapy.

Fajardo LF, Berthrong M, Anderson RE: *Radiation Pathology*. University Press, Oxford, 2001.

Lawrence TS, Robertson JM, Anscher MS, *et al.* Hepatic toxicity resulting from cancer treatment, Int J Radiat Oncol Biol Phys, 31:1237-1248, 1995. PubMed Link

XVII-10) C Atrophic villi would likely be observed within a week following the start of irradiation of the small intestine, since the cells lining the villi have relatively short life spans.

XVII-11) B The best way to spare the parotid gland is to decrease the volume of the gland irradiated. The parotid exhibits relatively little sparing with fractionation so use of either a hyperfractionated or hypofractionated protocol would have only a modest impact. Prolongation or acceleration of treatment would have little effect on the parotid.

Konings AW, Coppes RP, Vissink A. On the mechanism of salivary gland radiosensitivity, Int J Radiat Oncol Biol Phys, 62(4):1187-1194, 2005. Review. Erratum in: Int J Radiat Oncol Biol Phys, 64:330, 2006. PubMed Link

XVII-12) C The kidney exhibits little or no re-irradiation tolerance, whereas the other organs, including the spinal cord, exhibit at least some recovery following irradiation.

Cohen EP and Robbins ME, Radiation Nephropathy, Semin Nephrol, 23, 5:486-499, 2003. PubMed link

XVII-13) D There is clinical evidence that pentoxifylline may be helpful for the treatment of radiation fibrosis and osteoradionecrosis.

Delanian S, Lefaix JL. Current management for late normal tissue injury: Radiation-induced fibrosis and necrosis, Semin Radiat Oncol, 17:99-107, 2007. PubMed Link

XVII-14) A The lacrimal gland is comparable to the parotid in terms of both its structure and the tendency of secreting cells to undergo radiation-induced interphase death.

XVII-15) B The ureter has a $TD_{5/5}$ of 70 Gy. In contrast, the $TD_{5/5}$ values for whole organ irradiation of the kidney, colon, stomach and liver are 23 Gy, 45 Gy, 50 Gy and 30 Gy, respectively.

XVII-16) E Temporary epilation can be caused by a 3 Gy acute exposure, and is observed around 3 weeks after irradiation. The doses and times to appearance for the other skin reactions are:

temporary erythema - 2 Gy - 1 day
permanent epilation - 7 Gy - 3 weeks
moist desquamation - 18 Gy - 4 weeks
dry desquamation - 14 Gy - 4 weeks

Geleijns J, Wondergem J. X-ray imaging and the skin: Radiation biology, patient dosimetry and observed effects, Radiat Prot Dosimetry, 114(1-3):121-125, 2005. PubMed Link

XVII-17) D There is an extensive series of laboratory studies that have established a clear role for the renin-angiotensin system in the pathogenesis of radiation nephropathy. Administration of angiotensin-converting enzyme inhibitors (ACEI), such as captopril, and angiotensin type 1 receptor antagonists (AT_1RA), such as L-158,809, have been shown to be effective as prophylactic agents and as mitigators of injury when administered after irradiation. The decline in renal function observed in a patient presenting with radiation nephropathy following TBI was reported to be prevented by administration of losartan, an AT_1RA. At present, there are no data to suggest that renal function will improve following treatment with ACEI or AT_1RA. The ability of these agents to modulate radiation nephropathy is not due to a reduction in blood pressure; ACEI are effective at doses that do not affect blood pressure. Moreover, administration of antihypertensive agents does not ameliorate radiation nephropathy. The decline in kidney function is not accelerated at low radiation doses.

Cohen EP, Robbins ME. Radiation nephropathy, Semin Nephrol, 23:486-499, 2003. PubMed link

Cohen EP, Hussain S, Moulder JE. Successful treatment of radiation nephropathy with angiotensin II blockade. Int J Radiat Oncol Biol Phys, 55:190-193, 2003. PubMed link

Zhao W, Diz DI, Robbins ME. Oxidative damage pathways in relation to normal tissue injury, Br J Radiol, 80 Spec No 1:S23-31, 2007. PubMed link

Moulder JE, Cohen EP. Future strategies for mitigation and treatment of chronic radiation-induced normal tissue injury, Semin Radiat Oncol, 17:141-148, 2007. PubMed link

Robbins ME, Diz DI. Pathogenic role of the renin-angiotensin system in modulating radiation-induced late effects, Int J Radiat Oncol Biol Phys, 64:6-12, 2006. PubMed link

XVII-18) B Mucositis is an acute response, not a late effect, and is one of the main dose-limiting toxicities in the management of head and neck and digestive track carcinomas with radiation therapy. The remaining toxicities are some of the chief late complications seen in these patients.

Mantini G, Manfrida S, Cellini F, *et al.* Impact of dose and volume on radiation-induced mucositis, Rays, 30:137-144, 2005. PubMed link

Cooper JS, Fu K, Marks J, Silverman S. Late effects of radiation therapy in the head and neck region, Int J Radiat Oncol Biol Phys, 31:1141-1164, 1995. PubMed link

XVII-19) C Although increased permeability of the mucosa in the GI tract is also a key determinant, the altered immunity associated with effects on the lymphoreticular system plays a leading role in the infection that characterizes mortality from the gastrointestinal syndrome. B cells, those that mature in the bone marrow, are more radiosensitive than T cells, due to the sensitivity of the progenitor cells. However, there can be a persistent depression in T cell numbers. Localized radiation to the thymus can predispose a patient to a series of late effects due to the radiation sensitivity of both thymocytes and other thymic cell populations. There is a decrease in spleen size following radiation, as well as marked fibrosis, thickened capsule, and obliteration of the sinusoids.

XVIII. Mechanisms of Normal Tissue Radiation Responses

XVIII-1) D Killing of serous cells in the parotid gland, which causes xerostomia in many head and neck cancer survivors who received radiotherapy, would not be substantially affected by fraction size.

Eisbruch A, Rhodus N, Rosenthal D*, et al.* The prevention and treatment of radiotherapy-induced xerostomia, Semin Radiat Oncol, 13:302-308, 2003. PubMed link

Chao KS, Majhail N, Huang CJ*, et al.* Intensity-modulated radiation therapy reduces late salivary toxicity without compromising tumor control in patients with oropharyngeal carcinoma: A comparison with conventional techniques, Radiother Oncol, 61:275-280, 2001. PubMed

XVIII-2) B Assuming that the mature differentiated cells comprising a tissue do not have a pro-apoptotic tendency, the time to expression of radiation damage in an early-responding tissue correlates best with the lifespan of the mature functional cells. This occurs because tissues with a hierarchical structure (i.e., most early-responding tissues) depend on the constituent stem cells to reproduce and supply new cells to replace the mature ones, when they reach the end of their lifespan. However, because stem cells are likely to be killed by radiation, there is a lack of "replacement" cells when the mature cells reach the end of their lifespan. Therefore, the time scale for the appearance of the radiation injury mimics to a first approximation the lifespan of the mature cells.

XVIII-3) A bFGF protects against, rather than enhances, radiation-induced apoptosis of endothelial cells.

Brush J, Lipnick SL, Phillips T, *et al.* Molecular mechanisms of late normal tissue injury, Semin Radiat Oncol, 17:121-130, 2007. PubMed Link

Fleckenstein K, Gauter-Fleckenstein B, Jackson IL, *et al*. Using biological markers to predict risk of radiation injury, Semin Radiat Oncol, 17:89-98, 2007. PubMed Link

Milano MT, Constine LS, Okunieff P. Normal tissue tolerance dose metrics for radiation therapy of major organs, Semin Radiat Oncol, 17:131-140, 2007. PubMed Link

Bentzen SM. Preventing or reducing late side effects of radiation therapy: Radiobiology meets molecular pathology, Nature Rev Cancer, 6:702-713, 2006. PubMed Link

Denham JW, Hauer-Jensen M. The radiotherapeutic injury - a complex "wound", Radiother Oncol, 63:129-145, 2002. PubMed Link

Anscher MS, Vujaskovic Z. Mechanisms and Potential Targets for Prevention and Treatment of Normal Tissue Injury after Radiation Therapy, Semin Oncol, 32(2)Suppl 3:S86-91, 2005. PubMed link

Robbins ME, Zhao W. Chronic Oxidative Stress and Radiation-Induced Late Normal Tissue Injury: A Review, Int J Radiat Biol, 80:251-259, 2004. PubMed link

XVIII-4) B Insulin-like growth factor (IGF) is a polypeptide protein hormone. Its primary action is mediated by binding to specific IGF receptors present on many cell types in many tissues. IGF-1 is a potent activator of the AKT signaling pathway, a stimulator of cell growth and inhibitor of apoptosis. TGFβ, bFGF, CTGF and PDGF all appear to play a role in radiation-induced lung fibrosis.

XVIII-5) B The latent period prior to the manifestation of a late effect generally decreases with increasing dose to the irradiated organ.

XVIII-6) D The dose response for the induction of late normal tissue damage is sigmoidal in shape.

XVIII-7) C The majority of patients who develop clinically-detectable pneumonitis will progress to fibrosis. It is strongly suspected that many of the patients who develop lung fibrosis in the apparent absence of pneumonitis did, in fact, have pneumonitis, but that it was asymptomatic and had gone unrecognized. Lung is a very sensitive, dose-limiting organ with a steep dose response curve for single dose, whole organ irradiation, characterized by a $TD_{5/5}$ of 7 Gy (the $TD_{5/5}$ for fractionated radiotherapy using a conventional dose per fraction is about 17.5 Gy). Both volume irradiated and fractionation pattern have large effects on the tolerance dose. A number of investigators have identified regions of pneumonitis that extend outside of the treatment field, known as abscopal effects, however the mechanism for their development remains unclear.

Roberts KB, Rockwell S. Radiation pneumonitis. In: *Fishman's Pulmonary Diseases & Disorder*, *4th Ed*, (A.P. Fishman, Ed.) McGraw-Hill, New York, 2009.

Werner-Wasik M, Yu X, Marks LB, *et al.* Normal-tissue toxicities of thoracic radiation therapy: esophagus, lung, and spinal cord as organs at risk, Hematol Oncol Clin N Am, 18:131-160, 2004. PubMed link

McDonald S, Rubin P, Phillips TL, Marks LB. Injury to the lung from cancer therapy: clinical syndromes, measurable endpoints, and potential scoring systems, Int J Radiat Oncol Biol Phys, 31:1187-1203, 1995. PubMed link

XVIII-8) A FSUs contain a relatively constant number of clonogens. FSU's *can* be repopulated from a single surviving clonogen, and, for certain tissues, from clonogens that migrate from an adjacent FSU. For some tissues, FSUs are anatomically discrete structures (such as the nephron in the kidney), although for other tissues, there may not be any clear structural or anatomical unit that corresponds to an FSU (such as in the CNS and skin). FSUs are thought to be functionally independent of each other, even though they may be structurally interdependent.

Stewart FA, Van Der Kogel AJ. Proliferative and cellular organization of normal tissues. In: Basic Clinical Radiobiology, Third Edition, Ed. GG Steel, Arnold, London, 2002.

Wheldon TE, Michalowski AS. Alternative models for the proliferative structure of normal tissues and their response to irradiation, Br J Cancer Suppl, 7:382-385, 1986. PubMed link

Withers HR, Taylor JM, Maciejewski B. Treatment volume and tissue tolerance, Int J Radiat Oncol Biol Phys, 14:751-759, 1988. PubMed Link

XVIII-9) B The volume of normal tissue included in the irradiation field can have significant effects in the subsequent development of late effects. Despite being a serially arranged tissue like the rectum and spinal cord, several recent studies have shown that increasing the length of the esophagus in the treatment field does not predict the severity or duration of radiation-induced esophagitis. The morphological structure of the lung makes it difficult to define precise threshold limits. However, the best predictor for late effects has been found to be the V_{20}/V_{30}, that is, the percentage of normal lung volume that receives 20 Gy or 30 Gy, respectively. In contrast, in the rectum, it is the percentage of the wall that has received 40-50 Gy that determines the likelihood of rectal bleeding, although the extent of reserve, unirradiated tissue is also a factor. The liver is deemed an organ whose FSU's are arranged in parallel. Early estimates of V_{eff} gave a value of 0.32, but with changes in the standard of care over time, this value has risen to 0.94, emphasizing the importance of treatment volume in the probability of late complications. In the brain, the complex structure and morphology allows for focal radiation necrosis to be distinguished from diffuse white matter changes. The latency period for cerebral necrosis ranges from 6 months to several years post-radiation.

Kong FM, Pan C, Eisbruch A, Ten Haken RK. Physical models and simpler dosimetric descriptors of radiation late toxicity, Semin Radiat Oncol, 17:108-120, 2007. PubMed link

XVIII-10) D TGFβ generally has an inhibitory effect on epithelial cell proliferation. TGFβ is an important fibrogenic cytokine. It increases proliferation of mesenchymal cells and extracellular matrix deposition, and appears to be mechanistically involved in radiation fibrosis. It is secreted as a biologically inactive (latent) homodimer that is complexed with latency-associated peptide (LAP), and requires activation in order to exert its biological activities. TGFβ is one of the strongest known chemotactic factors for granulocytes, and on a molar basis, has been estimated to be about 1000-fold more potent than cyclosporine as a T-cell suppressor.

Ikushima H, Miyazono K. TGFβ signalling: A complex web in cancer progression, Nature Reviews Cancer, 10:415-424, 2010. PubMed link

Travis EL. Genetic susceptibility to late normal tissue injury, Semin Radiat Oncol, 17:149-55, 2007. PubMed link

Bentzen SM. Preventing or reducing late side effects of radiation therapy: Radiobiology meets molecular pathology, Nat Rev Cancer, 6:702-713, 2006. PubMed link

Bierie B, Moses HL. Tumour microenvironment: TGFbeta: The molecular Jekyll and Hyde of cancer, Nat Rev Cancer, 6:506-520, 2006. PubMed Link

Anscher MS, Vujaskovic Z. Mechanisms and potential targets for prevention and treatment of normal tissue injury after radiation therapy, Semin Oncol, 32:S86-91, 2005. PubMed link

Robbins ME, Zhao W. Chronic oxidative stress and radiation-induced late normal tissue injury: A review, Int J Radiat Biol, 80:251-259, 2004. PubMed link

Dent P, Yacoub A, Contessa J*, et al.* Stress and radiation-induced activation of multiple intracellular signaling pathways, Radiat Res, 159:283-300, 2003. PubMed link

XVIII-11) A Evidence from animal studies suggests that at least a partial recovery and re-irradiation tolerance occurs in the spinal cord provided at least 6 months have passed since an initial course of treatment. Soft tissue or bone necrosis *has* been observed in clinical studies involving re-irradiation of recurrent or new primary head and neck tumors. Mouse lungs are capable of tolerating a second course of fractionated irradiation, depending on the total dose given during the first course (the higher the initial total dose, the less tolerance to re-irradiation, and vice versa). Full re-irradiation tolerance for acute damage in rapidly dividing mucosal tissues is generally observed, provided at least a month or two has passed since the initial treatment course. Animal experiments have shown that the kidney does not appear to recover from radiation injury, as it will not tolerate re-irradiation even after a period of several years following the original treatment course.

Ang KK, Price RE, Stephens LC, et al. The tolerance of primate spinal cord to re-irradiation, Int J Radiat Oncol Biol Phys, 25:459-464, 1993. PubMed link

XVIII-12) B The TD_5 (as a function of length irradiated for the spinal cord) decreases with increasing cord length and then remains relatively constant.

XVIII-13) B Radiation-induced epilation occurs before dermatitis due to the short cell cycle time of the cells in the germinal matrix of the hair bulb, compared to that of the basal cells of the epidermis.

XVIII-14) A Irradiation of a small volume of the spinal cord to 70 Gy can cause myelopathy because of the serial arrangement of the FSUs in this organ (i.e., inactivation of a single FSU can compromise the function of the entire organ), whereas the FSUs in the other organs are arranged in parallel, meaning that these organs have a large functional reserve and therefore can tolerate high doses provided the irradiated volume is small.

XIX. Therapeutic Ratio

XIX-1) E In order to achieve a 37% tumor control probability, the total dose delivered must reduce the number of surviving clonogenic cells to an average of 1. This is based on the equation $P = e^{-(M)(SF)}$, where P is the probability of tumor cure (37% or 0.37 in this case), M is the initial number of tumor clonogens (10^6), and SF is the surviving fraction resulting from the irradiation protocol. Thus, for 10^6 clonogenic cells, a total dose that reduces the surviving fraction to 10^{-6} (i.e., 1 surviving clonogen) must be used to achieve a 37% control rate. Since the survival curve is exponential with a D_{10} of 5.75 Gy (D_{10}, = D_0 X ln 10 = 2.5 X 2.3 = 5.75 Gy) it would be necessary to use a dose of 34.5 Gy.

XIX-2) C Three cell divisions would result in an 8-fold increase in the number of cells. Therefore, the dose would need to be increased by a dose D, where $e^{(D/D0)} = 8$. Therefore, D = 2.5 x ln 8 = 5.2 Gy of additional dose would be needed to achieve the same level of tumor control. It is also worth remembering that 3.3 times the number of cell doublings corresponds to one $\log_{10}$ of cell kill.

XIX-3) B Since the chemotherapy results in a surviving fraction of 10^{-4}, the number of clonogens in the tumor would be reduced from $8x10^6$ to $8x10^2$. Since the D_{10} for this tumor is 5.75 Gy, then a dose of approximately 17 Gy would produce a 37% control rate. Another way to more precisely determine the answer to this problem is to recognize that since the chemotherapy results in a surviving fraction of 10^{-4}, the amount of radiation dose, D, NOT needed is given by $SF = e^{(-D/D0)} = 10^{-4}$. Therefore $-D/D_0 = \ln 10^{-4}$ or $D = -(D_0)(-\ln 10^{-4}) = -(2.5)(-9.2) = 23$ Gy and so the final dose required is 34.5 + 5.2 – 23 = 16.7 Gy. Alternatively, with use of chemotherapy, the number of clonogens is reduced from $8x10^6$ to $8x10^2$, so the dose D now required for 37% cure is given by $D = (2.5)[\ln(8 \times 10^2)] = (2.5)(6.7) = 16.8$ Gy.

XIX-4) B Tumor A has a low α/β ratio and therefore this tumor will exhibit a high degree of sparing with dose fractionation. In contrast, tumor B, which has a high α/β ratio will exhibit correspondingly less sparing with fractionation. Thus, the TCD50 for a fractionated protocol will be higher for tumor A compared with tumor B.

XIX-5) D During a 3 week (21 day) break, cells with a 3 day doubling time will undergo 7 additional doublings, leading to an increase in the number of tumor cells by a factor of 128. Solving for x in the equation $(0.3)^x = 1/128$, where x is the number of fractions, yields $x \approx 4$. (Taking the logarithm of both sides of the equation gives x log 0.3 = - log 128, so x = 2.10/0.52). Thus, “compensating” for the extra cells produced by proliferation would require an additional 4 fractions of 2 Gy, or 8 Gy.

XIX-6) D In order to achieve a 90% tumor control probability, it is necessary to reduce the number of tumor cells to 0.1 (on average). Since the extrapolation number is 1 for the cells comprising the tumor, it can be assumed that there is little or no "shoulder" on the survival curve. Thus, for a tumor with 10^8 cells initially, the surviving fraction would need to be 10^{-9}. This would be achieved by a dose of 4 Gy x 9 logs = 36 Gy.

XIX-7) A If a tumor increases its volume by a constant fraction per unit time, then it would display exponential growth as per the equation $V = e^{(.693)(T/Tv)}$, where T is the total elapsed time and T_v is the tumor's volume doubling time. In practice however, this is rarely observed because as a tumor grows, generally the growth fraction decreases and cell loss increases. This type of progressively slowing growth curve is best fit using the Gompertz equation, $V = V_0 e^{A/B(1-e^{-Bt})}$, where V_0 is the volume at time zero and A and B are growth parameters specific for the particular tumor. At small times for t, the equation is exponential with $V = V_0 e^{At}$. At long times, e^{-Bt} becomes very small, so the volume reaches a maximum of $V_0 e^{A/B}$.

Joiner M and van der Kogel A, Eds. Basic Clinical Radiobiology, 4th Ed. Hodder Arnold, London, 2009; page 79.

XIX-8) E The dose reduction factor (DRF) is a parameter used to measure the effectiveness of a radioprotector. The DRF equals the dose to produce a certain effect in the presence of a radioprotector divided by the dose to produce the same effect in the absence of the protector. Thus, 1.3 = x/30 Gy, so x = 39 Gy.

XIX-9) E To produce a TCD_{90} for a series of tumors containing 10^6 clonogenic cells would require a total dose that would reduce the surviving fraction to 10^{-7}. Since 56 Gy produced this level of control, the D_{10} for these cells must be approximately 56 Gy/7 logs = 8 Gy. The relative increase in the number of clonogens resulting from an increase in tumor diameter from 0.1 cm to 1 cm is $(1/0.1)^3 = 10^3$, so the number of cells would increase from 10^6 to 10^9. To produce 90% control, would require 8 Gy x 10 logs = 80 Gy. Depending on the normal tissue(s) of concern in the radiation field, its tolerance dose, and how much of its volume would need to be irradiated, delivering a total dose of 80 Gy may or may not be feasible.

XX. Time, Dose, Fractionation

XX-1) C An analysis of multifraction isoeffect data for normal tissues and tumors *in vivo* forms the basis for the determination of the α/β ratio. This is accomplished by generating a so-called reciprocal dose plot ("F_e plot"), a type of isoeffect curve in which the reciprocal of the total dose to produce an isoeffect is plotted as a function of the dose per fraction used in multifractionation experiments. Based on such an isoeffect curve (which should be linear in shape assuming the linear-quadratic model provides a good fit to the data), the α/β ratio would be equal to the intercept of the curve extrapolated to zero dose divided by its slope. The α/β is generally high for early responding tissues and low for late responding tissues. The flexure dose, not the α/β ratio, is the dose at which the survival curve first begins to bend away from its initial slope. The α/β ratio tends to be high, not low, for cell types with a pro-apoptotic tendency. The α/β ratio is the *dose* at which the linear and quadratic contributions to cell killing are equal.

XX-2) D The α/β ratio for this tissue can be determined by setting $n_1d_1\,[1 + d_1/(\alpha/\beta)] = n_2d_2\,[1 + d_2/(\alpha/\beta)]$, where n_1 and n_2 are the number of fractions and d_1 and d_2 are the doses per fractions used for the first and second protocols, respectively. Thus, $(25)(1.8\text{ Gy})(1+1.8\text{ Gy}/\alpha/\beta) = (17)(2.5\text{ Gy})(1+2.5\text{ Gy}/\alpha/\beta) = 45\text{ Gy} + 81\text{ Gy}^2/\alpha/\beta = 42.5\text{ Gy} + 106.25\text{ Gy}^2/\alpha/\beta$ or $\alpha/\beta = 25.25\text{ Gy}^2/2.5\text{ Gy} = 10.1\text{ Gy}$.

XX-3) A Since the α/β ratio for head and neck cancers tends to be high, whereas the α/β ratios for late effects are low, it would be anticipated that a hyperfractionated schedule could produce a decrease in late effects while maintaining a level of tumor control similar to that produced by the standard protocol.

XX-4) D When plotted as the log of the total dose to produce a given isoeffect as a function of the log of the dose per fraction (plotted on a reverse scale), most late responding normal tissues are characterized by steep isoeffect curves, whereas those for early responding normal tissues and most tumors tend to be shallow.

Joiner M and van der Kogel A, Eds. Basic Clinical Radiobiology, 4th Ed. Hodder Arnold, London, 2009; page 103.

XX-5) B The dose per fraction, at which the isoeffect curves for tumor control and late effects intersect, helps to define the range over which the desired tumor control probability can be achieved while also staying at or below the tolerance dose for the late responding normal tissue. Since the use of smaller-than-conventional fraction sizes generally results in greater sparing of late effects relative to tumor control, treatment protocols involving the use of fraction sizes smaller than the point of intersection between the two isoeffect curves would yield the desired level of tumor control while not exceeding normal tissue tolerance. This type of analysis would *not* provide any information as to the actual extent of tumor control or the extent of normal tissue damage anticipated since these are already specified by the chosen isoeffect. (It would be necessary to determine TCP and NTCP curves to obtain this information, independent of any isoeffect analysis.) Also, these isoeffect curves provide no information as to the effects of changing overall treatment time, since the type of isoeffect curve plot as stated evaluates the influence of dose per fraction and not time (and further, it is assumed that overall time remains fairly constant in this analysis, and that it is only dose per fraction that changes). Likewise, the effect of a split course treatment could not be evaluated in this case, because data as to the tumor's potential doubling time are not provided.

XX-6) C If the α/β ratio is less for a patient's tumor than their dose-limiting normal tissue, such a patient may benefit from the use of large fraction sizes, because the tumor would be more sensitive to fraction size than the dose limiting normal tissue and would be preferentially damaged by hypofractionation.

XX-7) B Tumor cell repopulation during treatment would cause a decrease in the BED, since the cell divisions that take place during the course of therapy could counteract some, if not all, of the toxicity of the radiation. This can be calculated from the equation $BED = nd[1+d/(\alpha/\beta)] - [(0.693)(T)/(\alpha)(T_{pot})]$, where n is the number of fractions, d is the dose per fraction, α and β are the parameters characterizing the underlying dose response curve for the tumor, T is the length of time during treatment that repopulation occurs and T_{pot} is the potential doubling time (the time it would take the tumor to double its cell number in the absence of cell loss).

XX-8) E An accelerated treatment schedule is used primarily to limit the amount of tumor cell repopulation that may occur before the completion of radiotherapy. The repopulation that may occur, particularly for tumors with short T_{pot} values, can severely limit the effectiveness of treatment.

XX-9) E The BED equation that can be used for this problem is BED = nd[1+d/(α/β)], where n is the number of fractions and d is the dose per fraction. (It is not necessary to correct for either tumor cell proliferation, since the regimens are specified as having the same overall treatment time, or incomplete repair, since these are both once-per-day treatments.) Thus, the late effects BED associated with the use of 2 Gy fractions is (36)(2 Gy)(1+2 Gy/2 Gy) = 144 Gy_2. Since it is indicated that the new treatment schedule is isoeffective with respect to late effects, then the BED for the second protocol will also be 144 Gy_2. The number of 3 Gy fractions to use can be calculated using 144 Gy_2 = n(3 Gy)(1+ 3 Gy/2 Gy) = 7.5n or n = 19 fractions. The tumor BED for the first schedule is (36)(2 Gy)(1+2 Gy/10 Gy) = 86 Gy_{10}. The BED for the second protocol is (19)(3 Gy)(1+3 Gy/10 Gy) = 74 Gy_{10}. Thus, there is a decrease of 12 Gy_{10} for the second compared with the first protocol, or a [(86 Gy_{10} – 74 Gy_{10})/86 Gy_{10}] (100%) = 14% decrease. An alternative method to compute the answer to this problem is to use the biologically equivalent in 2 Gy fractions dose (EQD2), which is EQD2 = D[(d+α/β)/(2 Gy+α/β)]) where D is the total dose and d is the dose per fraction. Thus, the EQD2 for the standard 2 Gy protocol is (72 Gy)[(2 Gy+ 2 Gy)/(2 Gy +2 Gy) = 72 Gy (clearly, the EQD2 equals D for all protocols involving a fraction size of 2 Gy). Since it is indicated that the new treatment schedule is isoeffective with respect to late effects, then the EQD2 for the second protocol will be 72 Gy. With α/β = 2 Gy for late effects, the total dose (D) to use in 3 Gy fractions can be calculated using 72 Gy = D(3 Gy+ 2 Gy)/(2 Gy+ 2 Gy) = 1.25D or D = 57.6 Gy. For the nearest integral number of 3 Gy fractions (19), this is a total dose of 57 Gy. With α/β = 10 Gy for tumor, the tumor EQD2 for the second protocol is (57 Gy)[(3 Gy + 10 Gy)/(2 Gy+ 10 Gy)] = 61.75 Gy. Thus, there is a decrease in EQD2 of 10.25 Gy for the new treatment compared with the standard protocol which had an EQD2 of 72 Gy (once again, the EQD2 is equal to D for all 2 Gy protocols) or a [10.25 Gy/72 Gy] (100%) = 14% decrease. Note, it is critical to recognize the distinction between the BED (biologically **effective** dose) and the EQD2 (biologically **equivalent** dose in 2 Gy fractions), which has also been referred to as the NTD (normalized total dose) or the LQED (linear quadratic equivalent dose). A loss of this distinction can result in miscalculations that may lead to crucial errors in treatment dose calculations.

Joiner M and van der Kogel A, Eds. Basic Clinical Radiobiology, 4th Ed. Hodder Arnold, London, 2009; page 123.

Fowler JF, Dale RG. When Is a “BED” not a “BED”?—When It Is an EQD2: In Regard to Buyyounouski et al. (Int J Radiat Oncol Biol Phys, 76:1297–1304, 2010); Int J Radiat Oncol Biol Phys, 78(2):640-641, 2010. PubMed link

XXI. Brachytherapy

XXI-1) A Ir-192 is most commonly used for HDR brachytherapy. Pd-103 and I-125 are used in LDR brachytherapy. Co-60 is used in external beam radiotherapy. Y-90 is used in radioimmunotherapy.

XXI-2) B Interstitial multicatheter and intracavitary balloon brachytherapy techniques for partial breast irradiation are designed to treat only that portion of the breast at highest risk for harboring subclinical disease following breast-conserving surgery. Because of the more limited treatment volumes irradiated with these techniques compared to external beam therapy, higher radiation doses can be given in a shorter treatment course (typically 3.4 Gy per fraction, 10 fractions, in one week) with minimal toxicity and good cosmesis. HDR brachytherapy with Ir-192 after-loading also reduces radiation exposure of medical personnel. However, interstitial multicatheter placement is considered technically challenging and the balloon applicator has a more limited ability to adapt to the tumor bed.

Dickler A. Technology insight: MammoSite--A new device for delivering brachytherapy following breast-conserving therapy, Nat Clin Pract Oncol, 4:190-196, 2007. PubMed link

Patel RR, Arthur DW. The emergence of advanced brachytherapy techniques for common malignancies, Hematology/Oncology Clinics of North America, 20:97-118, 2006. PubMed link

Patel RR, Das RK. Image-guided breast brachytherapy: An alternative to whole-breast radiotherapy, Lancet Oncology, 7:407-415, 2006. PubMed link

XXI-3) D I-131 tositumomab (Bexxar) is a radiolabeled antibody against the CD20 cell surface antigen found in a very high percentage of B cell non-Hodgkin's lymphomas. The β- and γ-emitting (*not* α-emitting) radioisotope I-131 is used for treatment of thyroid cancer, and is administered singly, not attached to any antibody. The primary clinical toxicity from I-131 tositumomab is a dose-related, reversible, hematopoietic suppression.

Macklis RM. Iodine-131 tositumomab (Bexxar) in a radiation oncology environment, Int J Radiat Oncol Biol Phys, 66:S30-S34, 2006. PubMed link

Pohlman B, Sweetenham J, Macklis RM. Review of Clinical Radioimmunotherapy, Expert Rev Anticancer Ther, 6:445-461, 2006. PubMed link

XXI-4) C Most clinical evidence now indicates that prostate cancers have unusually low α/β ratios, possibly as low as 1.5 Gy, and significantly less than the α/β ratio of roughly 3 Gy assumed for late complications in the normal tissues surrounding the prostate. This low α/β ratio suggests that prostate tumors should be especially sensitive to the large fraction sizes used for HDR brachytherapy. Since the OER usually increases with dose and dose rate, it would be expected to be greater for HDR than LDR brachytherapy. The probability of late normal tissue complications could increase with HDR because of the high doses per fraction used, but the high conformality of the dose makes this less of an issue compared with the use of external beam irradiation. The radioisotopes such as I-125 and Pd-103 used for LDR brachytherapy require relatively little shielding (HVLs of 0.025 mm and 0.008 mm lead, respectively), and are generally delivered as a permanent seed implant. In contrast, Ir-192, an isotope commonly used for HDR brachytherapy, has an HVL of 2.5 mm lead and is typically administered through a catheter-based after-loading technique.

XXII. Radiobiological Aspects of Alternative Dose Delivery Systems

XXII-1) D Although stereotactic radiosurgery or intraoperative radiotherapy employ large fraction sizes in which the entire treatment dose may be delivered in one irradiation, the incidence of late complications from these regimens has generally not been significantly elevated compared with a standard protocol because the dose is delivered to avoid irradiation of normal tissue. In addition, the biologic mechanisms for achieving tumor control and production of normal tissue damage may differ substantially for very large dose fractions compared with standard 2 Gy dose fractions. For many trials, a sufficient follow-up period has been realized so that most late effects, if they were to develop, would have appeared. Normal tissue radioprotectors are not routinely used in conjunction with these procedures. Although radioresistance by tissue hypoxia is more pronounced when large doses are used and there is less opportunity for hypoxic tissue to reoxygenate with only one or a small number of fractions, in most instances, normal tissues do not contain hypoxic regions. There is no evidence that DNA repair systems would saturate more readily in tumor cells than normal cells, if at all.

XXII-2) B Electrons are useful only for relatively superficial treatments. Based on the energies used for radiotherapy, they are not capable of penetrating very far into tissue.

XXII-3) B Although carbon ions exhibit a reduced OER, the OER for protons is high and similar to that for X-rays.

XXII-4) C Protons used for radiotherapy must be of a very high energy (> 100 MeV) in order to be sufficiently penetrating and are therefore of relatively low LET, typically less than 10 keV/μm. Since radiotherapy protons are low LET, they exhibit an OER in the range of 2-3 and therefore, like X-rays, would not be particularly effective at eradicating hypoxic tumor cells. Protons are only slightly more biologically effective than X-rays and have an RBE of ~1.1.

XXIII. Chemotherapeutic Agents and Radiation Therapy

XXIII-1) D Irinotecan is a synthetic analogue of camptothecin (CPT) and inhibits topoisomerase I by trapping the cleavable complex formed between this enzyme and DNA. CPT is a natural product derived from the bark and stem of Camptotheca (Happy Tree) with remarkable anticancer activity, but also low solubility and high adverse reactions. Because of these disadvantages, synthetic derivatives have been developed. The other CPT synthetic analogue used in cancer chemotherapy is topotecan. Proteasome inhibitors are drugs that block the action of proteasomes, the cellular complexes that break down proteins, such as p53. Examples of proteasome inhibitors include bortezomib, the first proteasome approved for use in the US, and salinosporamide A currently in clinical trials for multiple myeloma. Cyclophosphamide (Cytoxan) is an alkylating agent.

Helleday T, Petermann E, Lundin C, Hodgson B, Sharma RA. DNA repair pathways as targets for cancer therapy, Nat Rev Cancer, 8:193-204, 2008. PubMed link

Pommier Y. Topoisomerase I inhibitors: Camptothecins and beyond, Nat Rev Cancer, 6:789-802, 2006. PubMed Link

XXIII-2) B Cetuximab is a monoclonal antibody that blocks the epidermal growth factor receptor. The combination of cetuximab and radiation has been shown to be an effective treatment for cancers of the head and neck. Bevacizumab is a monoclonal antibody against VEGF and acts by interfering with angiogenesis. Celecoxib is a nonsteroidal anti-inflammatory drug that inhibits the cyclo-oxygenase 2 enzyme. Sirolimus is an immunosuppressant whose mode of action is to bind the FK-binding protein 12 (FKBP12), which in turn inhibits the mammalian target of rapamycin (mTOR) pathway. Bortezomib is a proteasome inhibitor that is used to treat multiple myeloma.

Murphy JD, Spalding AC, Somnay YR, *et al*. Inhibition of mTOR radiosensitizes soft tissue sarcoma and tumor vasculature, Clin Cancer Res,15(2):588-596, 2009. PubMed link

Atkins M, Jones CA, Kirkpatrick P. Sunitinib maleate, Nat Rev Drug Discov, 5:279-280, 2006. PubMed link

Bonner JA, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck, NEJM 354:567-578, 2006. PubMed link

Chinnaiyan P, Allen GW, Harari PM. Radiation and new molecular agents, part II: Targeting HDAC, HSP90, IGF-1R, PI3K, and RAS, Semin Radiat Oncol, 16:59-64, 2006. PubMed link

Mendelsohn J, et al. Epidermal growth factor receptor targeting in cancer, Semin Oncol, 33: 369-385, 2006. PubMed link

Mesa RA. Tipifarnib: Farnesyl transferase inhibition at a crossroads, Expert Rev Anticancer Ther, 6:313-319, 2006. PubMed link

Minucci S, Pelicci PG. Histone deacetylase inhibitors and the promise of epigenetic (and more) treatments for cancer, Nat Rev Cancer, 6:38-51, 2006. PubMed link

Sabatini DM. mTOR and Cancer: Insights into a complex relationship, Nature Reviews Cancer, 6: 729-734, 2006. PubMed link

Spalding AC, Lawrence TS. New and emerging radiosensitizers and radioprotectors, Cancer Invest, 24:444-456, 2006. PubMed Link

Wilhelm S, Carter C, Lynch M, et al. Discovery and development of sorafenib: A multikinase inhibitor for treating cancer, Nat Rev Drug Discov, 5:835-844, 2006. PubMed link

Sartor CI, Raben D, O'Neil B. Biologicals and their interactions with radiation. In: G. Tepper (ed.), Clinical Radiation Oncology, 2nd edition, pp. 99-109: Churchill Livingstone Elsevier, 2006.

Hynes NE, Lane HA. ERBB receptors and cancer: The complexity of targeted inhibitors, Nat Rev Cancer, 5:341-354, 2005. PubMed link

XXIII-3) E Herceptin is an anti-HER2 antibody. An example of a mTOR/FRAP inhibitor is Rapamycin, which inhibits translation initiation. Activating mutations of FMS-like tyrosine kinase 3 (FLT3) are present in approximately 30% of patients with de novo acute myeloid leukemia (AML) and are associated with lower cure rates from standard chemotherapy-based treatment. Targeting the mutation by inhibiting the tyrosine kinase activity of FLT3 is cytotoxic to cell lines and primary AML cells harboring FLT3 mutations. An example of FLT3 inhibitor is CEP-701. RAS mutations may result in constitutive activation of the RAS/RAF/MEK/ERK kinase signaling pathway, and have been found to occur frequently in human tumors. Multiple kinase inhibitors of this pathway are being evaluated.

XXIII-4) D Iressa is a small molecule EGFR-tyrosine kinase inhibitor. Monoclonal antibodies directed against vascular endothelial growth factor (VEGF) such as Avastin may benefit some patients with colorectal, breast and lung cancers. Nitrogen mustards are used as antineoplastic agents in cancer therapy as nonspecific DNA alkylating agents. The antitumor activity of nitrogen mustards has been connected with their ability to cross-link the twin strands of DNA which if not repaired, can inhibit DNA replication and transcription, eventually leading to cell cycle arrest, apoptosis, and the inhibition of tumor growth. Cyclooxygenase (COX) inhibitors are compounds that block the action of COX enzymes, which are produced in response to inflammation and by precancerous and cancerous tissues. An example of a COX inhibitor is Celecoxib. Antibodies against HER-2 receptor, which is overexpressed in some breast cancers, include trastuzumab (Herceptin).

Pao W, Chmielecki J. Rational, biologically based treatment of EGFR-mutant non-small-cell lung cancer, Nature Reviews Cancer, 10:760-774, 2010. PubMed link

XXIII-5) D Cyclooxygenase (COX)-2 mediates synthesis of eicosanoids from arachidonic acid. It tends to be over-expressed in tumors, is not constitutively produced in most normal tissues and stimulates, rather than inhibits, prostaglandin synthesis. EGFR is inhibited by erlotinib.

XXIII-6) C 5-FU affects thymidylate synthase and inhibits the synthesis of nucleotides required for DNA synthesis. Accordingly, it primarily affects cells in S phase of the cell cycle. All of the other agents can create damage throughout the cell cycle, and do not have any phase specificity.

XXIII-7) B Gemcitabine is a nucleoside analog of deoxycytidine in which the hydrogens at the 2' carbons in the sugar are replaced by fluorines. Once incorporated into DNA, the presence of this analog inhibits further DNA synthesis. In contrast, the other drugs listed cause toxicity either due to the damage they produce or by interfering with normal cellular processes. Melphalan and mitomycin c are alkylating agents. Etoposide is a topoisomerase II poison. Taxol stabilizes microtubule formation.

XXIII-8) E Methotrexate is a competitive inhibitor of dihydrofolate reductase (DHFR) and thus prevents the formation of reduced folate. Reduced folate is required for transfer of methyl groups in the biosynthesis of purines and in the conversion of deoxyuridine monophosphate (dUMP) to thymidine monophosphate (dTMP). Reduced folate becomes oxidized to folic acid in this reaction and its regeneration is dependent on DHFR for reduction to its active form.

XXIII-9) E Both vincristine and paclitaxel affect microtubules. However, vincristine binds to tubulin dimers, inhibiting assembly of microtubule structures. Taxol affects microtubule formation through hyper-stabilization.

XXIII-10) E Cisplatin causes cellular lethality due to the formation of crosslinks between the two DNA strands. This prevents normal DNA synthesis.

Kelland L. The resurgence of platinum-based cancer chemotherapy, Nat Rev Cancer, 7:573-584, 2007. PubMed link

XXIII-11) D Bortezomib is a proteasome inhibitor.

Richardson PG, Mitsiades C, Hideshima T, et al. Bortezomib: Proteasome inhibition as an effective anticancer therapy, Annu Rev Med, 57:33-47, 2006. PubMed Link

Schwartz R, Davidson T. Pharmacology, Pharmacokinetics, and Practical Applications of Bortezomib, Oncology, 18:14-21, 2004. PubMed link

XXIII-12) C Avastin is a monoclonal antibody against VEGF.

Ellis LM, Hicklin DJ. VEGF-targeted therapy: Mechanisms of anti-tumour activity, Nat Rev Cancer, 8:579-591, 2008. PubMed link

Jain RK, Duda DG, Clark JW, et al. Lessons from Phase III Clinical Trials on Anti-VEGF Therapy for Cancer, Nat Clin Pract Oncol, 3:24-40, 2006. PubMed link

XXIV. Radiosensitizers, Radioprotectors and Bioreductive Drugs

XXIV-1) D It has been suggested that the transient increase in radiation response reflects the transient normalization of the tumor vasculature, which results in increased perfusion and increased oxygen delivery, leading to a decrease in tumor hypoxia and decreased hypoxia-induced radioresistance.

Jain RK. Normalization of tumor vasculature: An emerging concept in antiangiogenic therapy, Science, 307:58-62, 2005. PubMed Link

Jain RK. Antiangiogenic therapy for cancer: Current and emerging concepts, Oncology, 19(4 Suppl 3):7-16, 2005. PubMed Link

XXIV-2) D The DAHANCA trial of nimorazole reported that this 5-nitroimadazole hypoxic cell radiosensitizer can be delivered without serious, dose-limiting side effects. Because nimorazole has its NO_2 group at the 5 rather than the 2 position on the imidazole ring, it is a less efficient radiosensitizer than either misonidazole or etanidazole. Loco-regional failure and disease-specific mortality were more frequent in patients assigned to the radiation plus placebo arm of the trial than for those patients given radiation plus nimorazole. Thus, it was the recommendation of the authors of this study that nimorazole **should** be used routinely in the treatment of these types of head and neck cancer.

Rockwell S, Dobrucki IT, Kim EY, *et al*. Hypoxia and radiation therapy: Past history, ongoing research, and future promise, Current Mol Med, 9:441-459, 2009. PubMed link

Overgaard J, Eriksen JG, Nordsmark M *et al.* Danish Head and Neck Cancer Study Group.Plasma osteopontin, hypoxia, and response to the hypoxia sensitiser nimorazole in radiotherapy of head and neck cancer: Results from the DAHANCA 5 randomised double-blind placebo-controlled trial, Lancet Oncol, 6:757-764, 2005. PubMed Link

XXIV-3) E The critical factor in determining whether a new agent will be clinically valuable when combined with radiation is whether it produces a therapeutic gain, that is, it increases tumor toxicity or reduces normal tissue toxicity without a commensurate increase or decrease, respectively, in the other tissue. Synergy with radiation will not produce a therapeutic gain if it occurs equally in both tumor and critical normal tissues. A therapeutic gain will not be produced unless the proliferation in tumors and critical normal tissues show significant differences that result in the modulator producing a selective increase in the radiation response of the tumor. A therapeutic gain cannot be achieved unless the vasculature in tumors and critical normal tissues show differences that result in the modulator producing a selective increase in the radiation response of the tumor. The cytotoxicity of most biological response modulators is minimal and manageable; their efficacy as cancer treatments result primarily from their ability to modulate radiation sensitivity. Minimal normal tissue toxicity alone does not necessarily lead to a therapeutic gain; in fact, a therapeutic gain can be obtained despite significant toxicity in normal tissue, provided the relative cytotoxic effect is greater in the tumor.

XXIV-4) E Overgaard has published a meta-analysis using data obtained from over 10,000 patients in 86 randomized trials who received radiotherapy and either oxygen or nitroimidazoles as hypoxic cell radiosensitizers, compared to radiotherapy alone. His findings were that these attempts at modification of tumor hypoxia significantly improved the effect of radiotherapy, with an odds ratio of 0.77 for loco-regional tumor control and an associated significant survival benefit (with an odds ratio of 0.87).

Overgaard J. Hypoxic radiosensitization: Adored and ignored, J Clin Oncol, 10;25(26):4066-4074, 2007. PubMed Link

XXIV-5) B dFdCDP formed in cells treated with gemcitabine interferes with ribonucleotide reductase, causing depletion of deoxynucleotide triphosphates necessary for DNA synthesis. This is thought to be a mechanism leading to radiosensitization.

Shewach DS, Lawrence TS. Antimetabolite radiosensitizers, J Clin Oncol, 25:4043-4050, 2007. PubMed link

XXIV-6) D The use of an hypoxic cell radiosensitizer, such as nimorazole, would not be expected to affect the response of normal tissues to radiotherapy since normal tissues generally do not possess regions of hypoxia. A change in fraction size may affect both the incidence and the severity of the radiation response in normal tissues, particularly late-responding tissues. A step down in field size would spare at least some normal tissues the full treatment dose. A gap in treatment may lessen the severity of the response in acutely-responding normal tissue, as repopulation of surviving cells during the gap would compensate to some extent for the damage caused by the radiation. Administration of amifostine, a radioprotector, also may protect normal tissues.

XXV. Hyperthermia

XXV-1) E Radiofrequency ablation is accomplished by inserting a RF probe into or near a tumor mass, and then heating it to temperatures that produce frank tissue necrosis. RF ablation is typically used singly, not simultaneously with radiation therapy.

XXV-2) C The greatest heat radiosensitization is produced when the heat is delivered as close to the time of irradiation as possible, since a likely mechanism for the sensitizing effect is heat denaturation of the proteins (enzymes) associated with the repair of radiation damage.

Moyer HR, Delman KA. The role of hyperthermia in optimizing tumor response to regional therapy, Int J Hyperthermia, 24:251-261, 2008. PubMed link

XXV-3) E The thermal enhancement ratio (TER) is defined as the radiation dose to produce an effect in cells or tissues irradiated at normal physiologic temperature divided by the dose of radiation for cells or tissues irradiated at elevated temperature to produce the same effect. There are large differences in the sensitivity of cells to heat depending on their position in the cell cycle ("age response"), with S phase cells being most sensitive. This is the opposite of radiation's age response, in which S phase cells exhibit the greatest resistance. This "complementarity" of toxicities of heat and radiation forms part of the basis for combining the two modalities. A second justification for combining radiation and heat is that heat enhances radiation injury by denaturing proteins/enzymes needed for the repair of radiation damage; heat does not create additional DNA damage in and of itself. Thermotolerance is an acquired resistance to heat, and is thought to be mediated by so-called heat shock proteins, cellular chaperones that help stabilize structures damaged by heating (membranes, proteins, cytoskeleton, etc.). The time course for the appearance, maintenance and eventual disappearance of heat shock proteins in cells undergoing hyperthermia mirrors the time course for the development and decay of thermotolerance. The development of thermotolerance is not a genetic change and therefore is **not** heritable in the progeny of previously-heated cells. Step-up heating may be useful clinically only if it can be used to protect normal tissues selectively; the procedure involves a pre-heating at mild hyperthermic temperatures so as to induce thermotolerance, followed by high temperature heating sufficient to produce cytotoxicity. Step-down heating has also been attempted for the purposes of sensitizing tumors to hyperthermia. In this case, a tumor is pre-heated at a very high temperature – which temporarily inhibits the development of thermotolerance – followed by heating at a somewhat lower, but still cytotoxic temperature.

XXV-4) B Tissues maintained under conditions of low pH tend to be sensitive to heat. G_2 cells are quite radiosensitive, but somewhat more resistant to heat killing, comparatively speaking. It is the chronically hypoxic cells in tumors (that typically exist in acidic microenvironments) that tend to be more sensitive to heat than acutely hypoxic cells. In laboratory rodents, hyperthermia usually results in increased blood flow in normal tissues and decreased blood flow in most tumors, not vice versa. Because the vasculature in normal tissues is generally more "mature" and responsive to external stimuli than tumor vasculature, it can more readily respond to elevated temperatures by dilating and increasing blood flow so as to carry away excess heat and restore normal physiologic temperature. The amount of cytotoxicity produced by a hyperthermic treatment at 43ºC for 10 minutes would be less, not more, than that produced by 46ºC for 5 minutes. This would be predicted from the thermal dose calculation (applicable for heat exposures at 43ºC and above) $t_2/t_1 = 2^{T1-T2}$, where t_1 and t_2 are the exposure times at temperatures T1 and T2 to produce equal biological effects. Thus, if T1 is 46 ºC and T2 is 43ºC, then the treatment at the lower temperature would need to be 8 times as long as at the higher temperature to produce the same amount of cell killing.

XXVI. Radiation Carcinogenesis

XXVI-1) C Individuals treated as infants with radiation therapy for an enlarged thymus were found to have an increased incidence of thyroid cancer.

Boice JD. Radiation-induced thyroid cancer -- What's new?, J Natl Cancer Inst, 97:703-705, 2005. PubMed link

XXVI-2) A Because different tissues have different sensitivities with respect to radiation carcinogenesis, for risk estimation and radiation protection purposes, tissues are assigned "weighting factors" (W_T) that correct the absorbed dose a tissue receives for biological equivalence. For example, the breast is assigned a W_T = 0.12, whereas bladder and gonads have W_T's = 0.05, and brain and kidney, 0.01.

XXVI-3) C Thyroid cancer was the most common cancer observed among children who lived in the Chernobyl area at the time of, and subsequent to, the accidental radiation release., This was a result of the high level of environmental contamination with radioactive iodine which homed to the thyroid.

XXVI-4) D In the Childhood Cancer Survivor Study, there was no evidence of an increase in pancreatic cancer, however increased incidences of skin cancer, sarcoma, meningioma and thyroid cancer were observed in childhood cancer survivors who received radiotherapy as part of their treatment.

Armstrong GT, Stovall M, Robison LL. Long-term effects of radiation exposure among adult survivors of childhood cancer: Results from the childhood cancer survivor study, Radiat Res, 174:840-850, 2010. PubMed link

Sadetzki S, Mandelzweig L. Childhood exposure to external ionising radiation and solid cancer risk, Br J Cancer, 7;100(7):1021-1025, 2009. Review. PubMed link

XXVI-5) D Using a low dose rate risk estimate for the working population of 0.04 radiation-induced fatal cancers per Sv, and assuming a linear extrapolation of the risk estimate to 0.25 Sv, it would be anticipated that this person would have a 1% excess risk for the development of a cancer resulting from his/her activities as a radiation oncologist.

Preston DL, Cullings H, Suyama A, et al. Solid cancer incidence in atomic bomb survivors exposed in utero or as young children, J Natl Cancer Inst, 100:428-436, 2008. PubMed link

Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII Phase 2 (2006) National Research Council, National Academies Press, 2006.

Charles MW. LNT -- An apparent rather than a real controversy? J Radiol Prot 26:325-329, 2006. PubMed link

Tubiana M, Aurengo A, Averbeck D, et al. The debate on the use of linear no threshold for assessing the effects of low doses, J Radiol Prot, 26:317-324, 2006. PubMed link

Wakeford R, Little MP. Risk coefficients for childhood cancer after intrauterine irradiation: A review, Int J Radiat Biol, 79:293-309, 2003. PubMed link

Preston DL, Ron E, Tokuoka S, Funamoto S, Nishi N, Soda M, Mabuchi K, Kodama K. Solid cancer incidence in atomic bomb survivors: 1958-1998, Radiat Res, 168:1-64, 2007. PubMed link

XXVI-6) D Using the risk estimate of 0.05/Sv for a general population exposed to X-rays from CT scanning, it would be anticipated that (10^7 people) x (0.01 Sv per person) x (0.05 radiation-induced fatal cancer deaths) = 5,000 excess cancer deaths.

XXVI-7) B Radiation-induced leukemias have a medium latent period of 3-7 years, whereas solid tumors do not appear for at least 10 years following irradiation, if not several decades later.

Finch SC. Radiation-induced leukemia: Lessons from history, Best Pract Res Clin Haematol 20(1):109-118, 2007. Review. PubMed link

Nakachi K, Hayashi T, Hamatani K, et al. Sixty years of follow-up of Hiroshima and Nagasaki survivors: Current progress in molecular epidemiology studies, Mutat Res, 659:109-117, 2008. PubMed link

XXVI-8) D The EPA has estimated that approximately 20,000 of the annual 160,000 lung cancer deaths in the U.S. each year are due to exposure to indoor radon through the production of α-particles resulting from the decay of radon to α-emitting daughter products.

http://epa.gov/radon/healthrisks.html

XXVI-9) B Treatment of ankylosing spondylitis, which at one time involved radiation therapy, has been associated with an increased incidence of leukemia.

XXVII. Heritable Effects of Radiation

XXVII-1) C The current estimate for the development of a hereditary disorder in the children of an irradiated person is 0.002/Sv.

Fujiwara S, Suyama A, Cologne JB, et al. Prevalence of adult-onset multifactorial disease among offspring of atomic bomb survivors, Radiat Res,170:451-457, 2008. PubMed link

Boice JD Jr, Tawn EJ, Winther JF, et al. Genetic effects of radiotherapy for childhood cancer. Health Phys 85:65-80, 2003. PubMed link

Schull WJ. The children of atomic bomb survivors: A synopsis, J Radiol Prot, 23: 369-384, 2003. PubMed link

XXVII-2) B The GSD or genetically significant dose, which represents the average dose to the gonads weighted to reflect the child-bearing potential of the people that comprise that population, is estimated at 0.3 mSv for radiation exposures from imaging procedures in the US.

XXVII-3) E A dose of 0.83 will cause a significant drop in the sperm count that may result in oligospermia and infertility for about a year following the irradiation. After a period of about six months following irradiation, the more differentiated members of the spermatogenic series that were susceptible to mutation will have all matured and been lost. Based on studies with laboratory rodents, this period of time should also be adequate to permit a return to the baseline population risk for mutations in offspring. Also, a dose of 0.83 Gy would be too low to cause a hormonal dysfunction.

XXVIII. Radiation Effects in the Developing Embryo and Fetus

XXVIII-1) D Prenatal irradiation puts individuals at a dose-dependent, increased risk for the development of a radiation-induced cancer at some time later in life. The woman should not be advised to discontinue treatment until reaching term, as the scattered dose to her fetus is likely small. Her personal risk in delaying therapy, while her cancer continues to progress, would effectively present a much greater concern. In addition to carcinogenesis, the fetus would also be at (an even higher) risk for radiation-induced congenital abnormalities, because irradiation took place during the first trimester of pregnancy when most of the organs are undergoing active development. The scattered dose to the fetus would certainly not be large enough to result in death and miscarriage or stillbirth, however it is likely greater than 0.01 cGy.

XXVIII-2) C The thyroid of a developing fetus will incorporate radioactive iodine from about the 10^{th} week of gestation onward.

XXVIII-3) E The dose to the breasts associated with a screening mammogram is on the order of 10 mSv, with the scattered dose to the ovaries being only a small fraction of this dose. The estimated risk for a mutation being produced in the child of an irradiated individual is only about 0.2% per Sv, so the probability that this woman's future children would inherit a radiation-induced mutation is very small. For this low a dose, no hormonal effects would be expected and no ova should be killed. It would be incorrect to tell the woman that her ovaries received **no** dose since there would always be some amount of scattered radiation, although the total dose received would be extremely low. The dose to her ovaries would be far lower than the estimated 1-2 Sv assumed to be the approximate "genetic doubling dose" for humans. The doubling dose is the dose that doubles the spontaneous incidence of mutations among offspring of irradiated parents.

XXVIII-4) B Temporary growth inhibition would most likely be observed if a developing mouse was irradiated during the organogenesis period of gestation. Mice irradiated during this gestational stage tend to have low birth weights, however they usually catch up in size during infancy.

XXVIII-5) B The organs that are actively undergoing development, (i.e., those that have high rates of cell division and ongoing differentiation), at the time of irradiation are the most susceptible to radiation injury during gestation.

XXVIII-6) C A dose of 0.1 Gy to an embryo or fetus at the 10 day to 25 week period of gestation is generally accepted as the minimum dose above which a physician should discuss with a pregnant patient the risk of radiation-induced birth defects (including possible congenital abnormalities and mental retardation), and possible actions to be taken, including therapeutic abortion.

XXIX. Radiation Protection

XXIX-1) D Historically, the annual dose equivalent received from medical diagnostic tests in the US is quoted as approximately 0.4-0.5 mSv per year, which constitutes about 15% of average yearly radiation exposure. This is in comparison to the 3 mSv received from natural background radiation sources (including radon), and the 0.1 mSv from other sources. However, as a result of the large increase in the use of CT scanning in the U.S. over the past 25 years, for which the doses are higher than for most other diagnostic tests, the average annual dose equivalent resulting from use of medical X-rays may now be as high as 3 mSv (or closer to 50% of the total average annual dose). Also, background radiation exposure generally increases with increasing altitude since there would be less atmosphere to attenuate the cosmic rays from space.

Mettler FA Jr, Bhargavan M, Faulkner K, *et al*. Radiologic and nuclear medicine studies in the United States and worldwide: Frequency, radiation dose, and comparison with other radiation sources -- 1950-2007, Radiology, 253:520-531, 2009. PubMed link

XXIX-2) C It is estimated that an average of 0.3 mSv to the gonads are received each year resulting from use of diagnostic X-rays, although this value may now be somewhat greater due to the increased use of CT scanning. In contrast, the human genetic doubling dose is estimated at 1-2 Gy. Thus the ratio of these values is closest to 3,000.

XXIX-3) C An order for a diagnostic X-ray examination may only be based upon medical need and not for the purpose of limiting legal liability for the radiologist. Using the current estimate, that the average annual effective dose equivalent associated with diagnostic radiology is 3 mSv, calculations suggest that $(3 \times 10^{-3}$ Sv$)(5 \times 10^{-2}$ radiation-induced fatal cancers/Sv$)(3 \times 10^{8}$ people) = 45,000 fatal, radiation-induced cancers would be produced per year from imaging procedures. This would constitute about 8% of all cancer deaths each year in the U.S. This risk estimate is based on the currently accepted, linear, no threshold model of radiation carcinogenesis. There is reason to believe that this number may be an over-estimate since the majority of people receiving these medical exposures tend to be older adults who are less susceptible to radiation carcinogenesis than young people. Nevertheless, even accounting for age differences in sensitivity to radiation carcinogenesis, the risk estimate for radiation-induced cancers still would suggest that more than 1% of fatal cancers are induced by medical radiation. However, not all scientists agree that use of the linear, no threshold model is appropriate in the case of such small radiation doses, especially given the amount of extrapolation necessary, and therefore that these risk estimates are probably over-estimates. Nevertheless, how much of an over-estimate remains to be seen.

XXIX-4) A According to NCRP guidelines, a member of the public may receive a maximum of 1 mSv per year resulting from exposure to radioactive waste materials. Background radiation and the radiation exposure resulting from medical exposures, that are performed to either diagnose or treat disease, do not count towards this annual limit.

NCRP Report 116. Limitation of Exposure to Ionizing Radiation, 1993. PubMed link

ICRP (1991). *1990 Recommendations of the International Commission on Radiological Protection. ICRP Publication 60*. *Ann of the* ICRP 21, 1-3 Pergamon Press, Oxford.

XXIX-5) C Radiation-induced mental retardation resulting from in utero irradiation is a deterministic effect that has a threshold dose below which the effect is not observed. However, some forms of mental retardation induced by mutations to the egg or sperm would be stochastic. In contrast, cancer (breast and leukemia) and inherited genetic disorders (phenylketonuria and galactosemia) are stochastic effects, characterized by a no dose threshold and endpoints that are "all or nothing".

XXIX-6) C The term stochastic is used to describe an effect of radiation in which the probability of occurrence is a function of dose, with no threshold.

XXX. Molecular Techniques used in Radiation and Cancer Biology

XXX-1) C An exonuclease is an enzyme that hydrolyzes the phosphodiester bonds of DNA to cleave nucleotides sequentially from the end of a polynucleotide chain.

XXX-2) C RNA polymerase is an enzyme that transcribes a copy of a DNA template into RNA. This would likely not serve as a useful reporter gene since it does not produce a product that can be detected easily.

XXX-3) B An antibody would be useful to screen an expression library, which synthesizes the protein encoded by each gene in the library. If nucleotide sequences are not available as probes for library screening (eg. sequence is not known), antibodies could be used for screening, if available. To do this one must create an expression library (ie. a library that not only contains the DNA fragments of interest but one that can actually manufacture the protein coded by the fragment) so that it may be detected by the antibody. This requires that the cDNA fragment within the vector be inserted downstream of a bacterial promoter, which will cause the inserted fragment to be expressed.

XXX-4) D The temperature sequence used in PCR would be first to incubate the sample at 95°C to denature the DNA, then decrease the temperature to 57°C to permit binding of primers to the DNA (depending on the primers and amplicon, the temperature may vary around this range), and then incubation at 72°C (the optimal temperature for synthesis of DNA by Taq polymerase).

XXX-5) B Subtractive hybridization is a technique that compares amounts of mRNA in different samples. All the other assays are used to analyze genomic alterations. Single nucleotide polymorphisms are ancestral genetic variations that occur when a single nucleotide in a genome is altered. Variations in the DNA sequences of humans can affect how humans develop diseases and respond to pathogens, radiation, chemicals, drugs, etc. This research is generally performed by comparing regions of the genome between matched cohorts with and without a disease or reaction. The increased interest in SNPs has been reflected by the development of a diverse range of SNP genotyping methods, including the single-strand conformation polymorphism (SSCP) assay, TaqMan assay, invader assay and the use of molecular beacons. TaqMan is based on PCR and is limited to applications that involve a small number of SNPs, since optimal probes and PCR reaction conditions must be designed for each SNP. Molecular beacons make use of a specially engineered probe. If the probe encounters a complementary sequence, it undergoes a conformational change, which allows the molecule to fluoresce. Alternatively, if the probe encounters a target

sequence with as little as one non-complementary nucleotide, the molecular beacon will remain in its original state and no fluorescence will be observed. The invader assay utilizes a specific endonuclease that catalyzes structure-specific cleavage. This cleavage is highly sensitive to mismatches and can be used to interrogate SNPs with a high degree of specificity. Single strand conformation polymorphism (SSCP) involves the electrophoretic separation of single-stranded nucleic acids, based on subtle differences in sequence (often a single base pair) which results in a different secondary structure and a measurable difference in mobility through a gel. The mobility of double-stranded DNA in gel electrophoresis is dependent on strand size and length, but is relatively independent of the particular nucleotide sequence. The mobility of single strands, however, is noticeably affected by very small changes in sequence, possibly one changed nucleotide out of several hundred. Small changes are detectable because of the relatively unstable nature of single-stranded DNA; in the absence of a complementary strand, the single strand may experience intrastrand base pairing, resulting in loops and folds that give the single strand a unique 3D structure, regardless of its length. A single nucleotide change could dramatically affect the strand's mobility through a gel by altering the intrastrand base pairing and its resulting 3D conformation

Abravaya K, Huff J, Marshall R, Merchant B, Mullen C, Schneider G, and Robinson J. Molecular beacons as diagnostic tools: Technology and applications, Clin Chem Lab Med, 41: 468-474, 2003. PubMed link

McGuigan FE, Ralson SH. Single nucleotide polymorphism detection: Alleic discrimination using TaqMan, Psychiatr Genet, 12: 133-136, 2002. PubMed link

Olivier M. The Invader assay for SNP genotyping, Mutat Res, 573:103-110, 2005. PubMed link

Orita M, Iwaha H, Kanazawa H, Hayashi K, and Sekiya T. Detection of polymorphism of human DNA by gel electrophoresis as single-strand polymorphism conformation, PNAS 66:2766-2770, 1989. PubMed link

XXX-6) A Exons can generally be identified by their lack of stop codons, since only a single one appears per mature mRNA strand. Exons are coding regions of a gene and introns are intervening sequences whose function is unknown. It is estimated that up to 99% of DNA is intronic, non-coding DNA. The primary transcript (RNA) is the exact copy of the entire gene, including introns as well as exons. The difference between the primary transcript and DNA is that T (DNA)→ U (RNA). The process of splicing removes the introns from the RNA and joins the exons together to create the messenger RNA (mRNA).The mRNA contains the coding sequence (CDS), which is translated into a string of amino acids based on the three-letter mRNA genetic code. CDS starts with the start codon, AUG (methionine). The mRNA also includes an untranslated region on each end, the 5'UTR and 3'UTR. The 3'UTR sequence starts with one of three stop codons (UAG, UAA, or UGA) that end the process of translation.

XXX-7) E A DNA ligase rejoins simple strand breaks. A DNA polymerase performs the resynthesis step during nucleotide excision repair. DNA ligase IV plays an important role in the **final** step of non-homologous end joining repair of DNA double strand breaks. During nucleotide excision repair, DNA endonuclease recognizes a particular type of damage and produces single strand cuts on either side of the damaged nucleotide to remove it. An AP endonuclease recognizes and removes a damaged base from DNA as an initial step in base excision repair.

XXX-8) E A Northern blot, in which RNA is subjected to gel electrophoresis and screened with a probe for a particular RNA transcript, would best be used to study the expression of a particular gene. A Western blot is used to examine an SDS gel for the presence of a particular protein, using an antibody to detect it. The electrophoretic mobility gel shift assay, or EMSA, is used to map transcription factor binding sites in the regulatory portions of genes, and is based on the reduced electrophoretic mobility of a DNA-protein complex compared to unbound DNA. For a Southern blot, DNA run on a gel is screened with a probe for a particular DNA sequence. DNAase I footprinting is used to identify a protein binding site in DNA.

XXX-9) D Fluorescent *in situ* hybridization or FISH involves the use of a fluorescently-labeled probe for a particular gene in order to identify the location of that gene on a chromosome. Promoter bashing is used to identify that portion of a promoter where a transcription factor binds. The Enzyme-Linked ImmunoSorbent Assay, or ELISA, is used to detect the presence of an antibody or an antigen in a sample. A two-hybrid screen is used to characterize protein-protein interactions. A restriction fragment length polymorphism (RFLP) results when the location cut by restriction enzymes varies between individuals, due to insertions, deletions or transversions.

Braselmann H, Kulka U, Baumgartner A, et al. SKY and FISH analysis of radiation-induced chromosome aberrations: A comparison of whole and partial genome analysis, Mutat Res, 578:124-133, 2005. PubMed Link

Tucker JD, Cofield J, Matsumoto K*, et al.* Persistence of Chromosome Aberrations Following Acute Radiation: I, Paint Translocations, Dicentrics, Rings, Fragments, and Insertions, Environ Mol Mutagen, 45:229-248, 2005. PubMed link

XXX-10) B Sequencing of a cDNA can be used to predict the amino acid sequence of the protein encoded by the original gene, since this represents the expressed portion of a gene. The cDNA is synthesized from the mature, processed mRNA, and therefore contains only the information from the DNA's exons. A functional complementation assay involves the transfer of a gene to a mutant cell in order to determine whether doing so restores the normal phenotype. A cDNA library is created from mature mRNAs, not whole genomic DNA. A unique oligonucleotide probe for a particular gene cannot be backwards engineered from the amino acid sequence of the protein encoded by that gene due to the redundancy in the genetic code (i.e., a particular amino acid can be designated by more than one triplet codon).