Chapter 6: Radiobiology

NPRE441:Principles of Radiation Protection Spring 2024
MW 12-1.50 pm 2018 Campus Instructional Facility

Co-Instructor: Kim A Selting, DVM, MS, DACVIM (Oncology), DACVR (Radiation Oncology), seltingk@illinois.edu

Slides retrieved and adapted from:

- Slide deck NPRE441 Spring 2023 by Dr. Elena Zannoni (UIUC, USA)
- Slide deck NPRE441 Spring 2021 by Prof.L.J. Meng (UIUC, USA)
- Slide deck prepared in 2015 by Dr.M. Cremonesi (IEO European Institute of Oncology, Milano, Italy)
- Slide deck prepared by Dr.E.Okuno (Institute of Physics of S. Paulo University, S. Paulo, Brazil)
- Slide deck prepared in 2006 by Dr.E.B. Podgorsak (McGill University, Montreal)

IAEA
International Atomic Energy Agency

OBJECTIVE: TO FAMILIARIZE THE STUDENTS WITH THE BASIC PRINCIPLES OF RADIOBIOLOGY

Primary reading resource:
J. Turner, "Atoms, Radiation, and Radiation Protection", Third Edition, Wiley-VHC, Inc. 2007

CHAPTER 6. TABLE OF CONTENTS (classes April 3rd, 8th, 10th, 15th)

CHAPTER 6. TABLE OF CONTENTS
(classes April 3rd, 8th, 10th, 15th)

- 2. Irradiation of cells (second half of first lecture)
  - A. Time Frame of Radiation Effect
  - B. Interaction with DNA
  - C. DNA damage
  - D. DNA repair
  - E. Cell death

CHAPTER 6. TABLE OF CONTENTS (classes April 3rd, 8th, 10th, 15th)

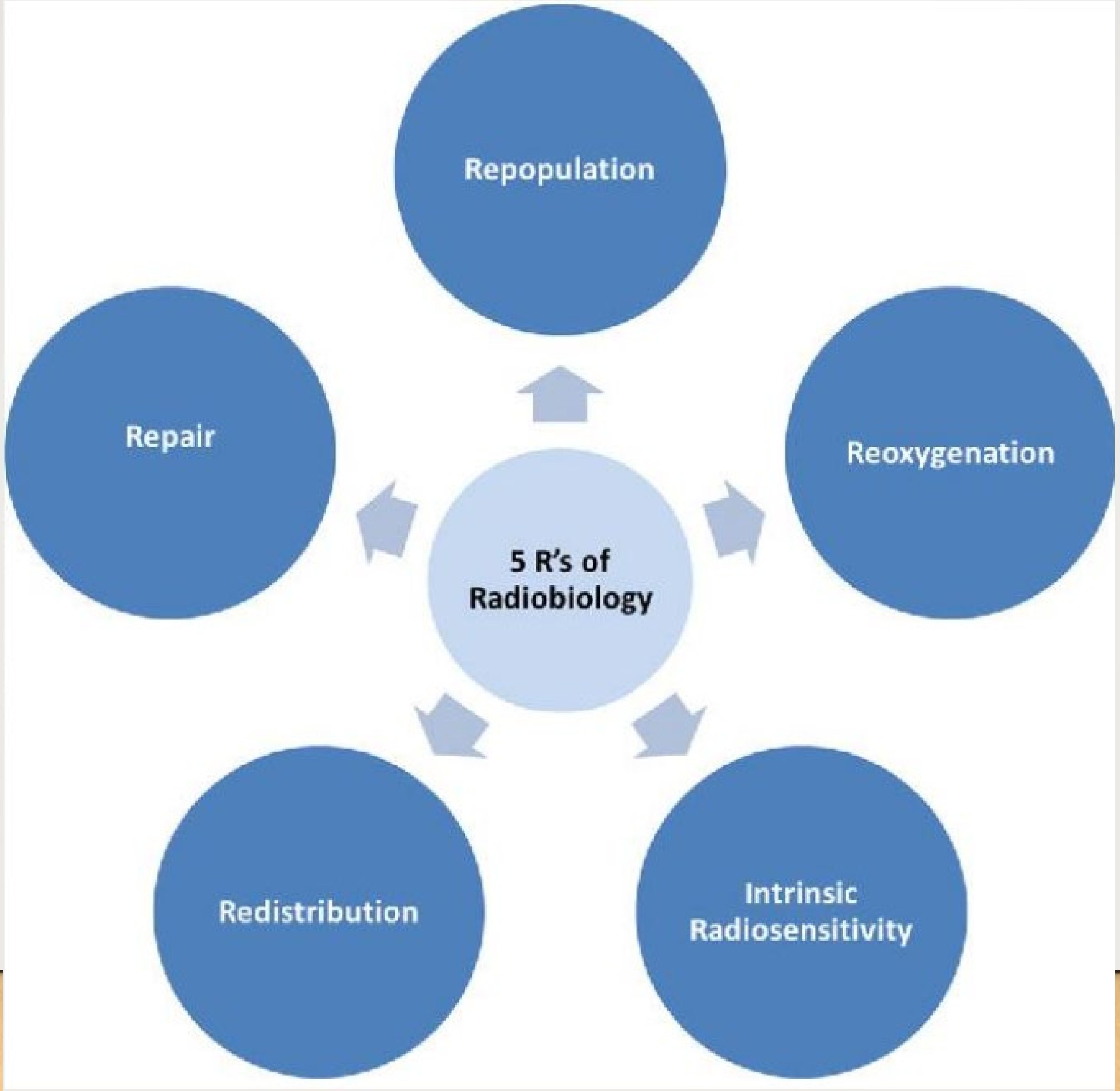
CHAPTER 6. TABLE OF CONTENTS
(classes April 3rd, 8th, 10th, 15th)

4. Factors affecting, and modeling of response to, radiation (third and fourth lectures)

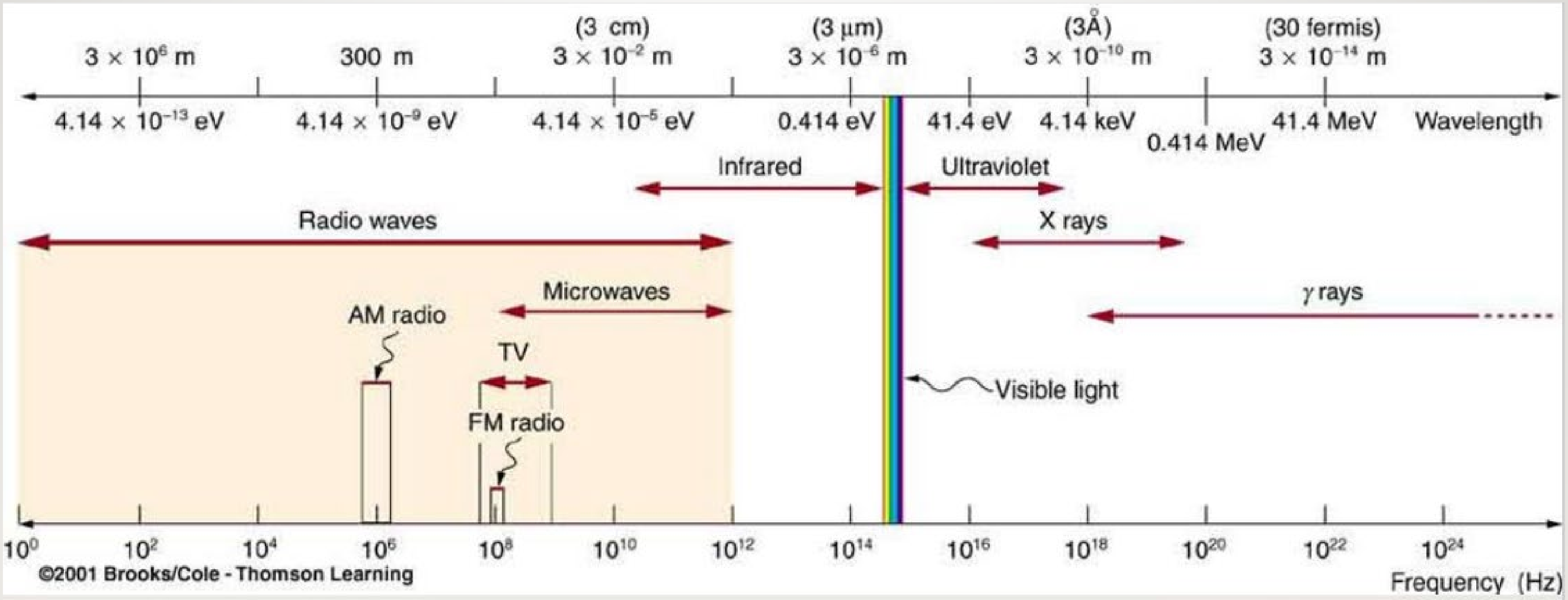
- A. Cell survival curves
  - (1) linear-quadratic model
  - (2) single-hit single-target model
  - (3) multi-target-single hit model
- B. The α/β ratio
- C. Dose response curves
- D. Normal and tumor cells: Therapeutic ratio

- Concepts
  - E. Relative biological effectiveness (RBE)
  - F. Oxygen effect
  - G. Dose rate and fractionation
  - H. Radioprotectors and radiosensitizers
  - I. The 5 R's of Radiobiology

CHAPTER 6. PART 4



EMR spectrum-



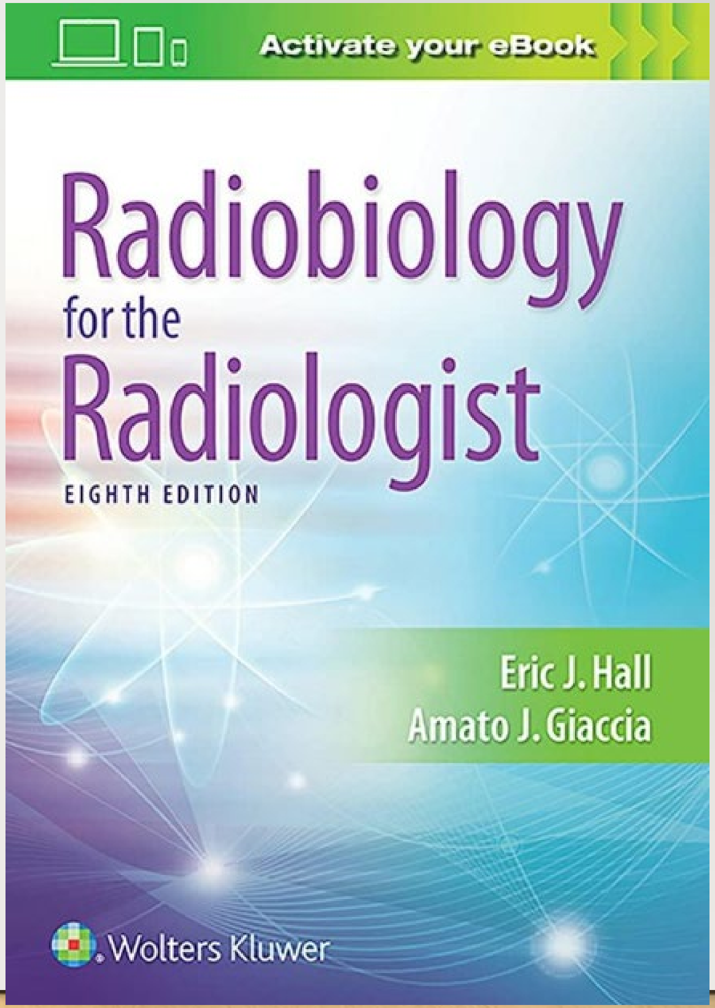
UV 3.10 -12.4 eV

Near IR 0.12 -1.77 eV

CHAPTER 6. TABLE OF CONTENTS (classes April 3rd, 8th, 10th, 15th)

6.1.A

- 6.1 INTRODUCTION
  - A. Definition
    - Radiobiology (or radiation biology) is a branch of science which combines the basic principles of physics and biology and is concerned with the interaction of ionizing radiation on living matter.
    - Addresses the biological effects produced by energy absorption in small volumes corresponding to single cells or parts of cells.



6.1.B INTRODUCTION
International Organizations on Radiation effects

BEIR
(National Academy of Sciences, Biological Effects of Ionizing Radiation)

UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation)

Collect and analyze data from the recent literature regarding biological effects of ionizing radiation

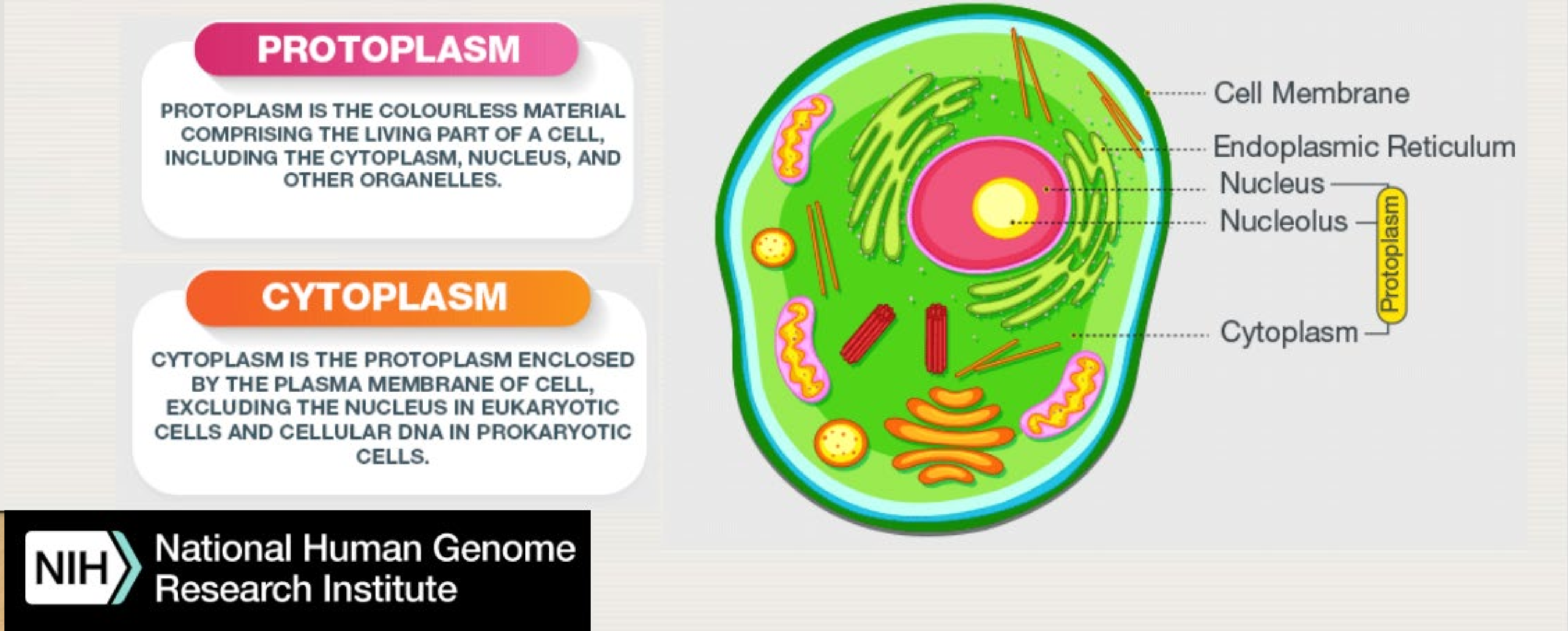
Report periodically on **risk estimates** for radiation induced cancer and hereditary effects

ICRP
(International Commission on Radiological Protection)

is involved in **recommendation and development of guidelines** in the field of radiation protection

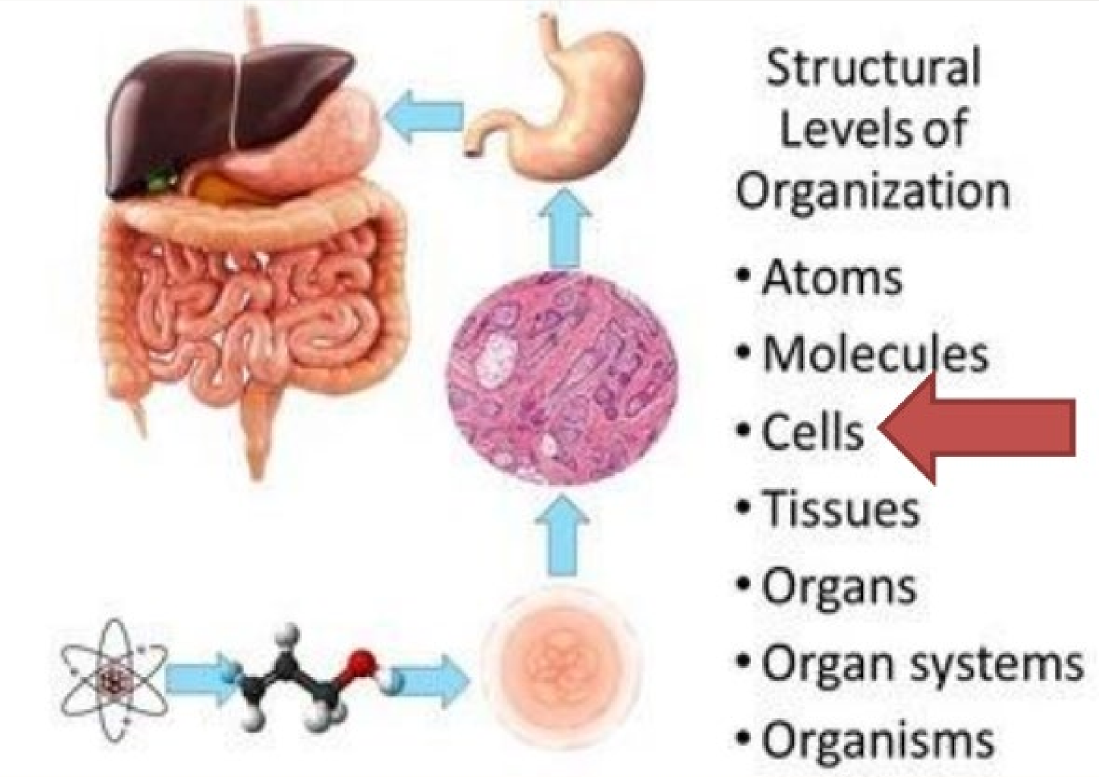
6.1.C INTRODUCTION
Basic Concepts of Cell Biology

- All living entities are made up of protoplasm, which consists of inorganic and organic compounds dissolved or suspended in water.
- The smallest unit of protoplasm capable of independent existence is the cell, the basic microscopic unit of all living organisms.



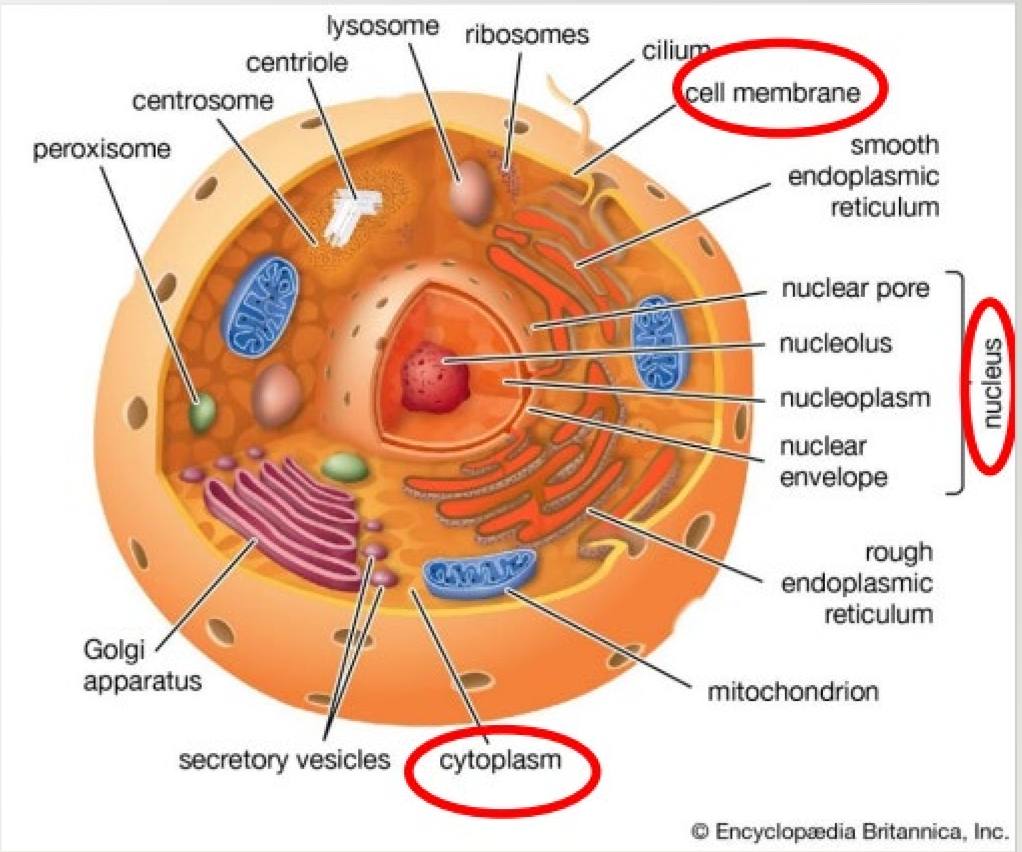
6.1.C INTRODUCTION
Basic Concepts of Cell Biology

- <u>Tissue</u> = Group of cells that together perform one or more functions.
- <u>Organ</u> = Collection of tissues that form the structure of a functional unit specialized to perform a particular function.
- <u>Organ system/organism</u> = Group of organs that perform one or more functions.



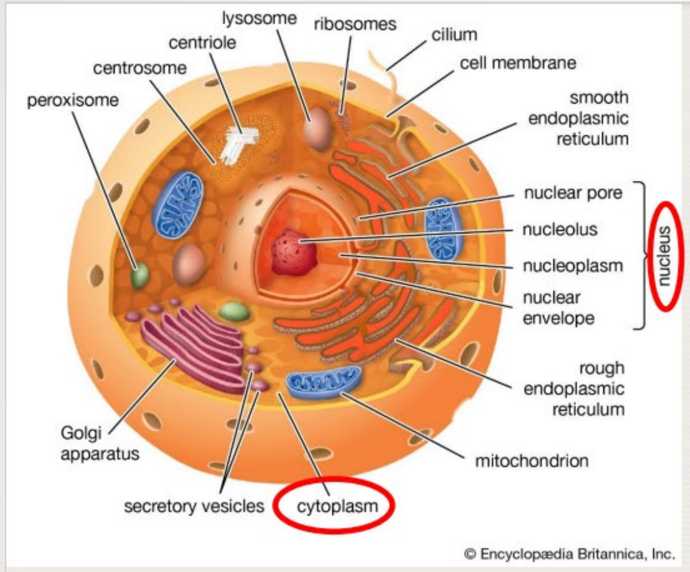
6.1.C INTRODUCTION
Basic Concepts of Cell Biology

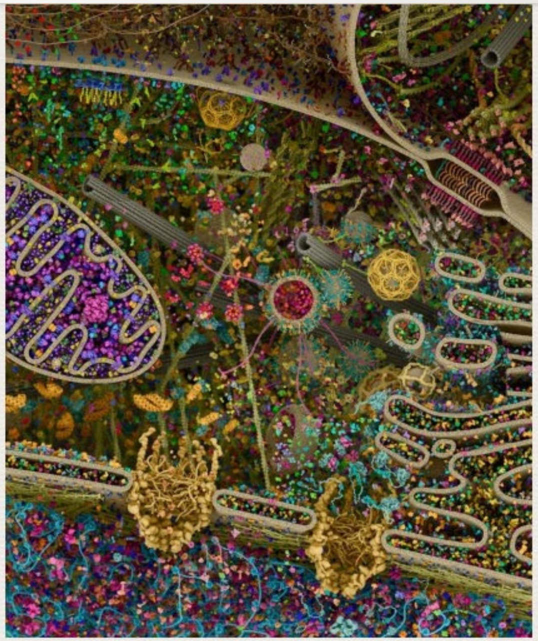
- Cells are separated from the surrounding environment by a cell membrane and contain:
  - Inorganic compounds (water and minerals)
  - Organic compounds (proteins, carbohydrates, nucleic acids, lipids) ❑
- The two main constituents of a cell are:
  - **Cytoplasm** supports all metabolic functions within a cell.
  - **Nucleus** contains the genetic information (DNA).
- **Organelles**: subcellular structures in the cytoplasm that have one or more specific functions in the cell.
  - Mitochondria produce chemical energy
  - Ribosomes assemble proteins



https://www.genome.gov/genetics-glossary

6.1.C INTRODUCTION
Basic Concepts of Cell Biology

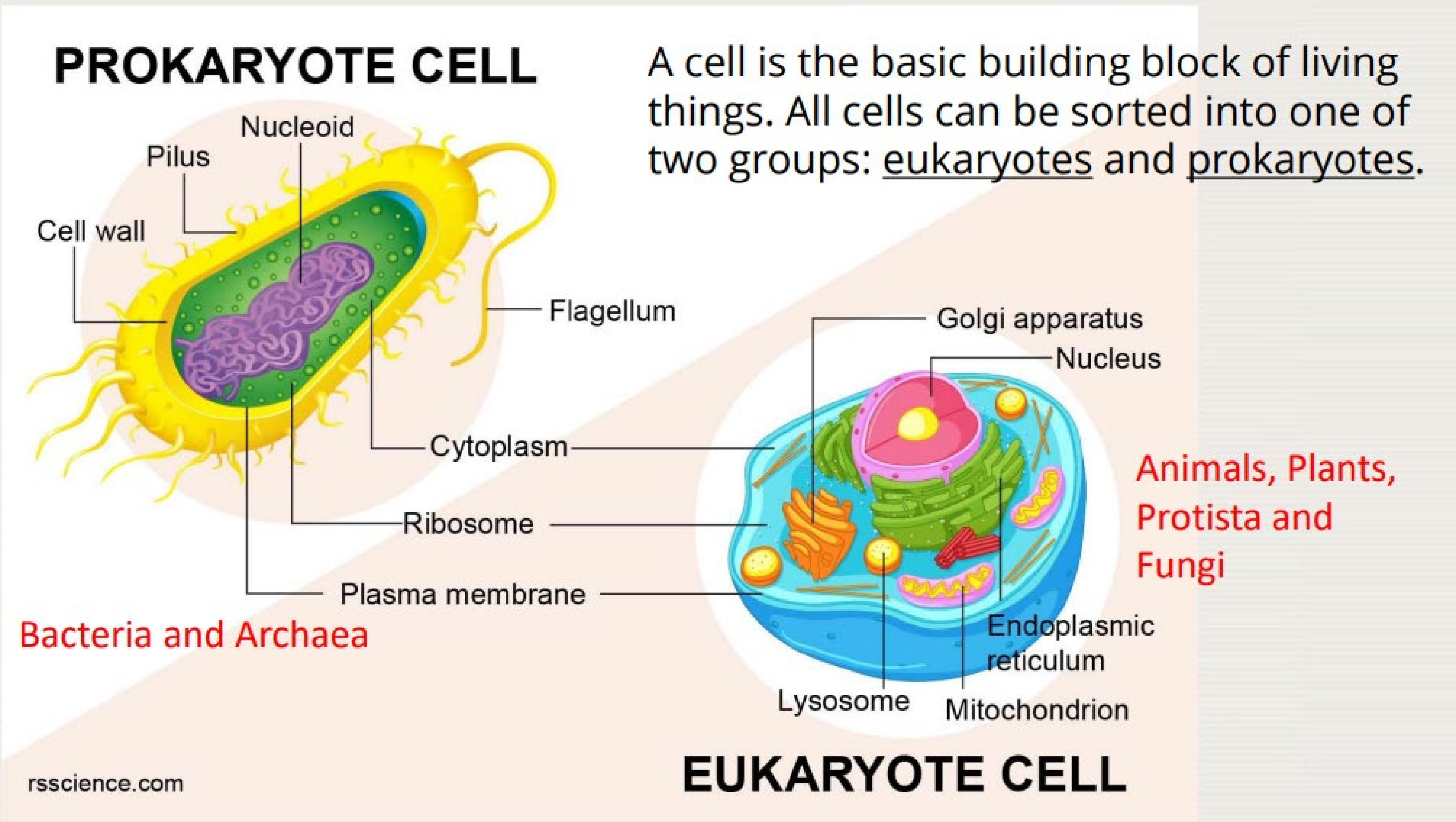




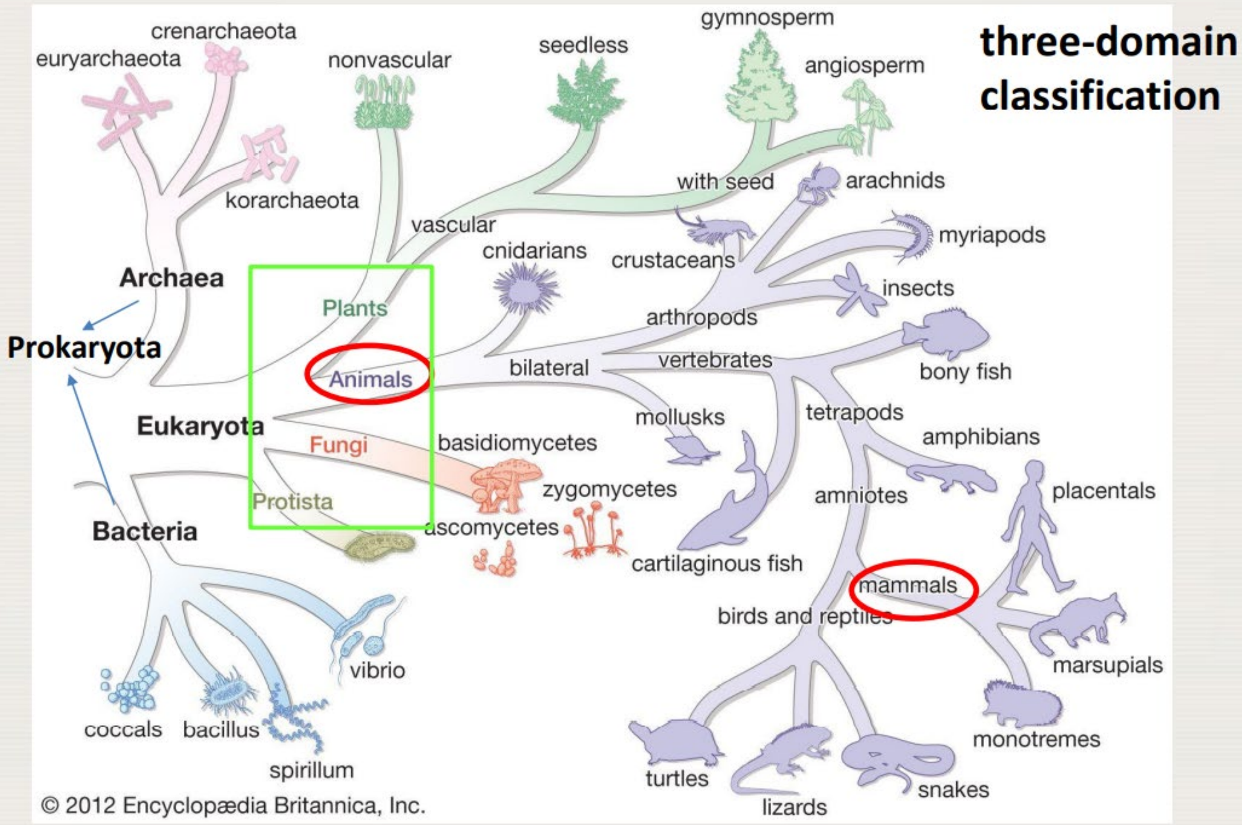
3D rendering (NOT direct image) of a eukaryotic cell that was modeled using X-ray, nuclear magnetic resonance (NMR), and cryo-electron microscopy datasets. From "Cellular landscape cross-section through a eukaryotic cell." by Evan Ingersoll and Gael McGill (Nov 2020). https://www.digizyme.com/cst_landscapes.html

IAEA

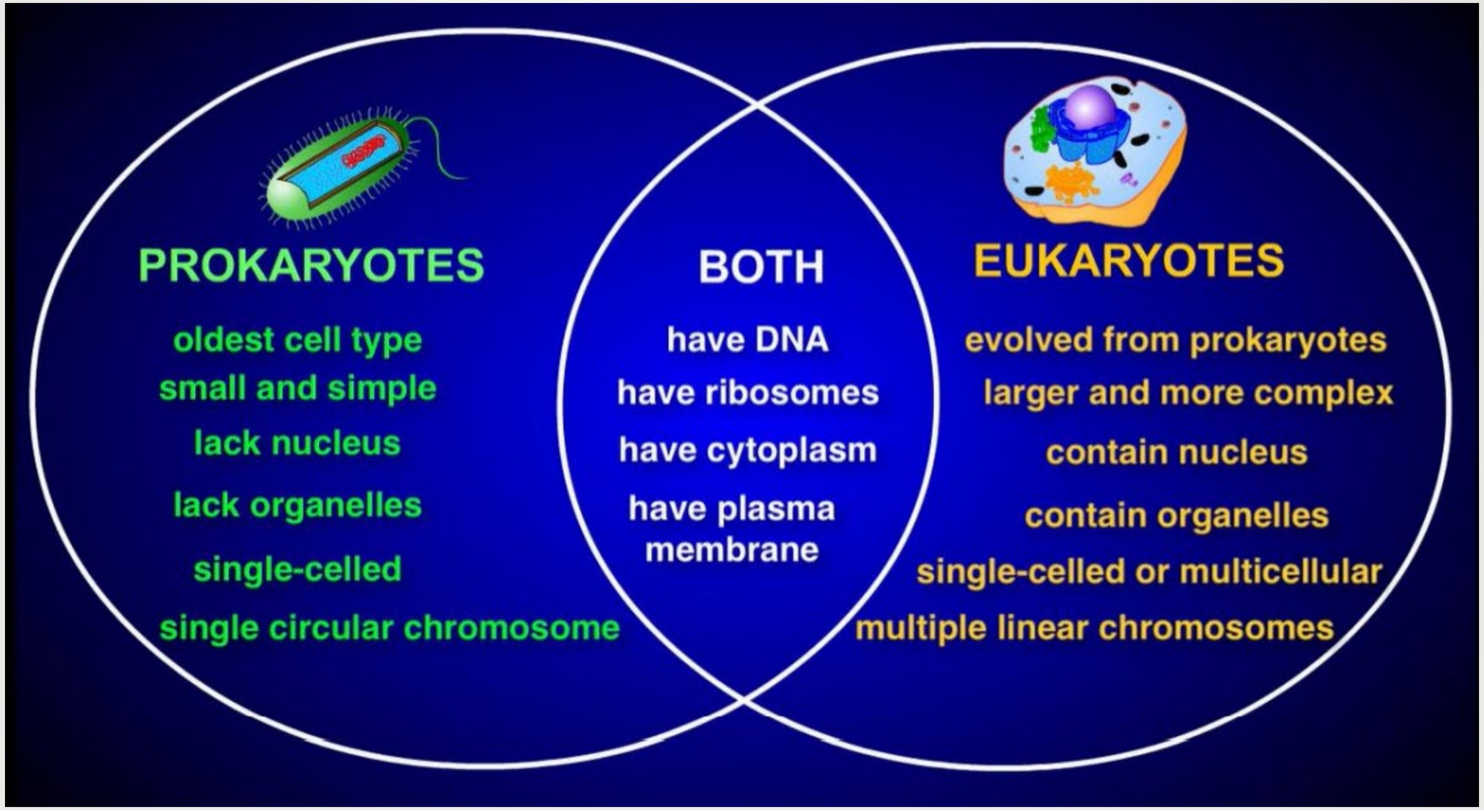
6.1.C INTRODUCTION
Basic Concepts of Cell Biology



6.1.C INTRODUCTION
Basic Concepts of Cell Biology



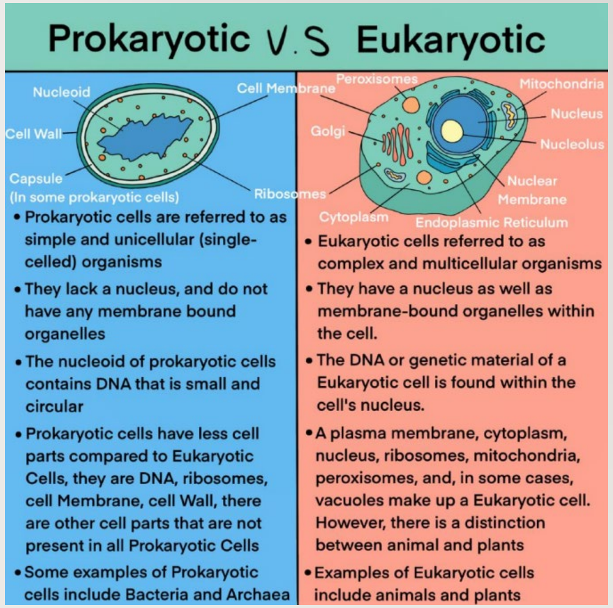
6.1.C INTRODUCTION
Basic Concepts of Cell Biology



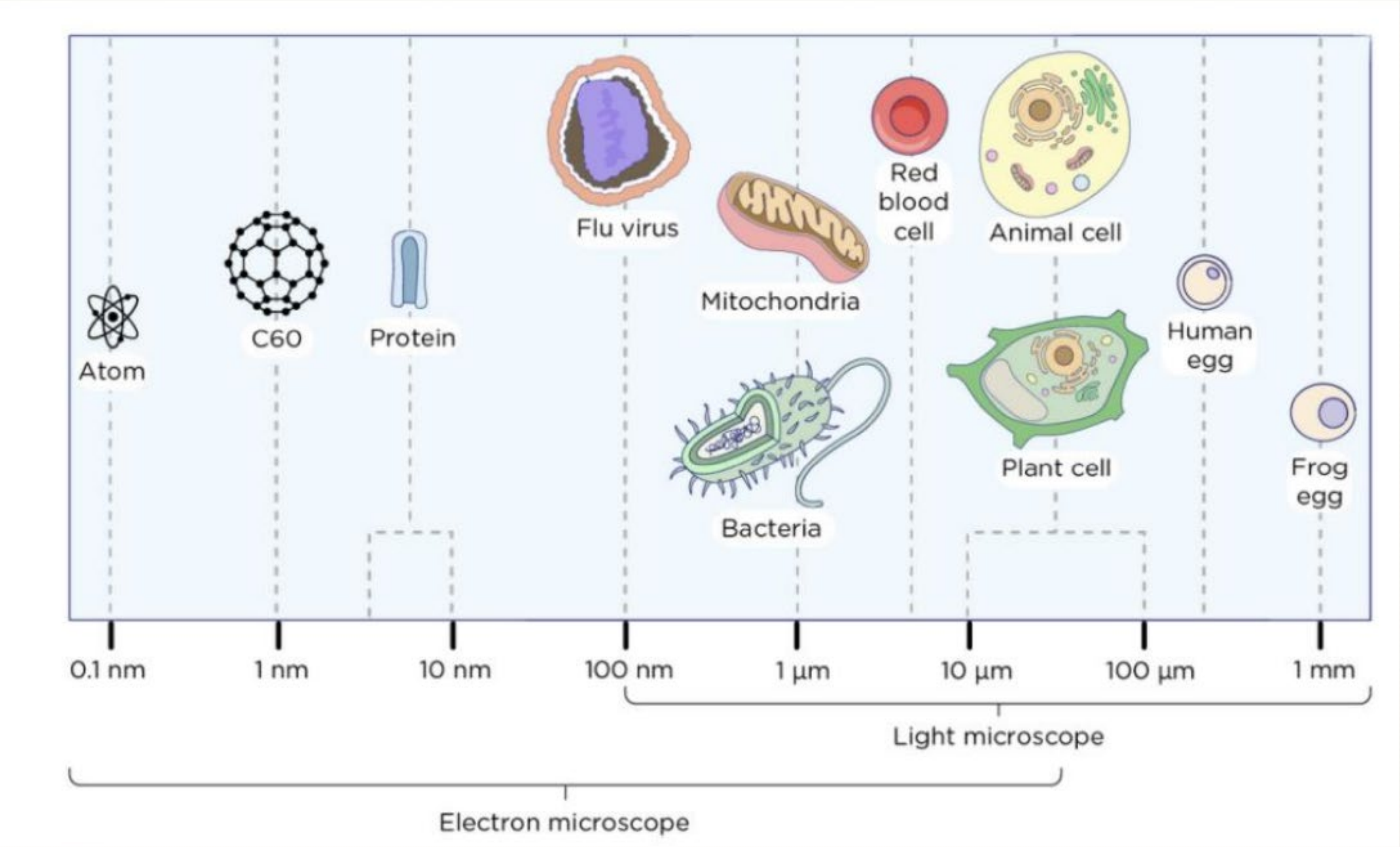
6.1.C INTRODUCTION
Basic Concepts of Cell Biology

DNA repair

- Why is this important in a radiation protection class?
- How much radiation does it take to kill bacteria?
  - Deinococcus radiodurans
    - Can grow in 60 Gy/hr
    - Can survive 15,000 Gy acutely
  - Food safety
    - E.coli killed with 1000-2000 Gy
- Therapeutic radiation (eukaryote) = 30-70 Gy total

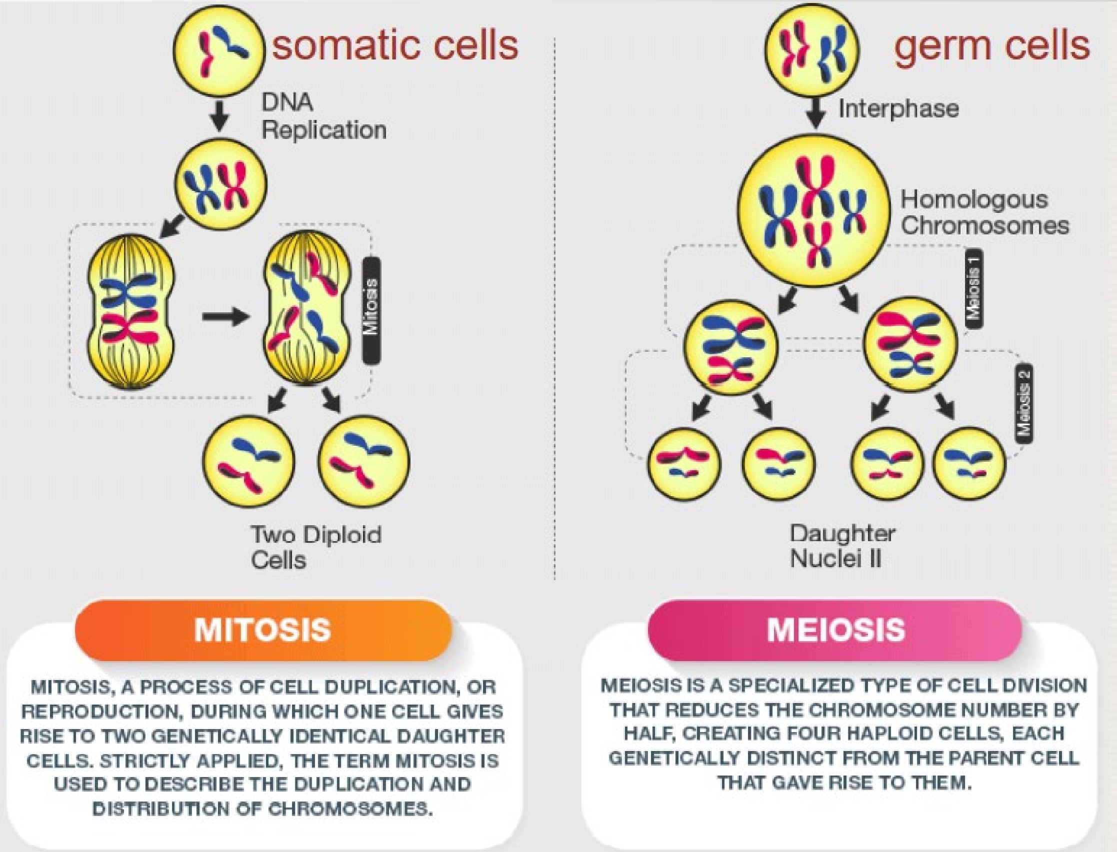


6.1.C INTRODUCTION
Basic Concepts of Cell Biology



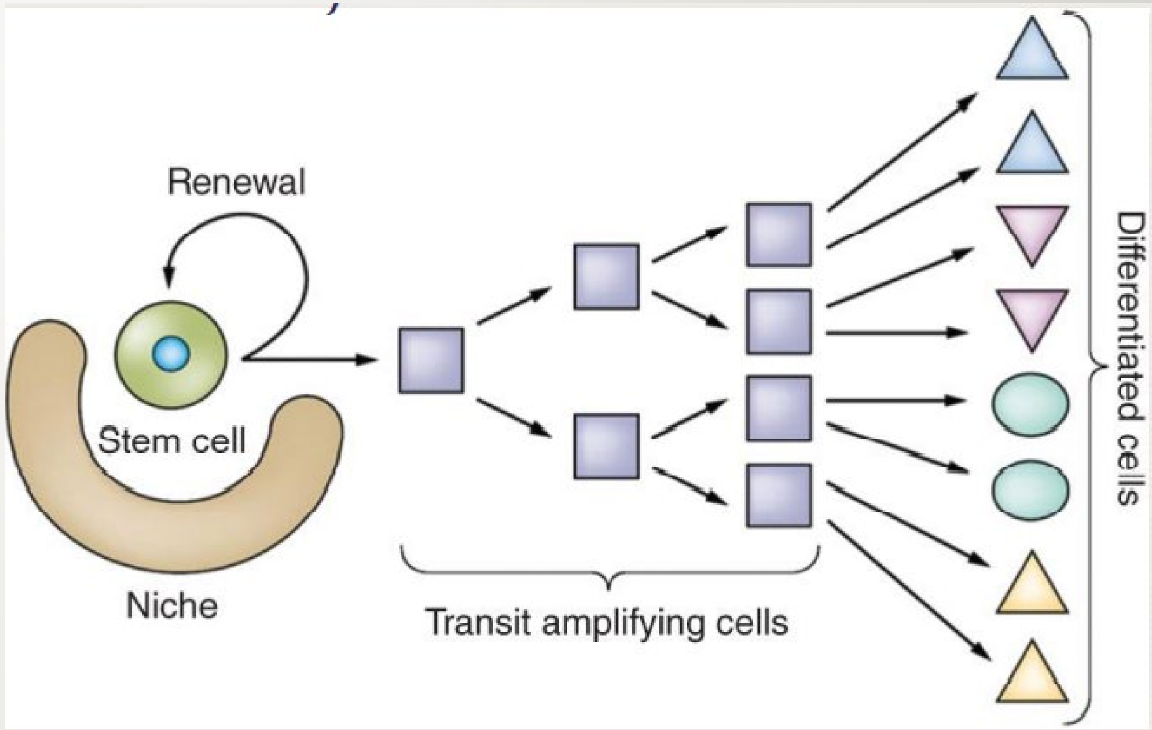
6.1.C INTRODUCTION
Basic Concepts of Cell Biology

- Human cells are either somatic cells or germ cells.
- Germ cells are either a sperm or an egg, all other human cells are called somatic cells
- Germline (heritable) vs somatic (after cells develop) mutations lead to susceptibility to cancer or carcinogenesis



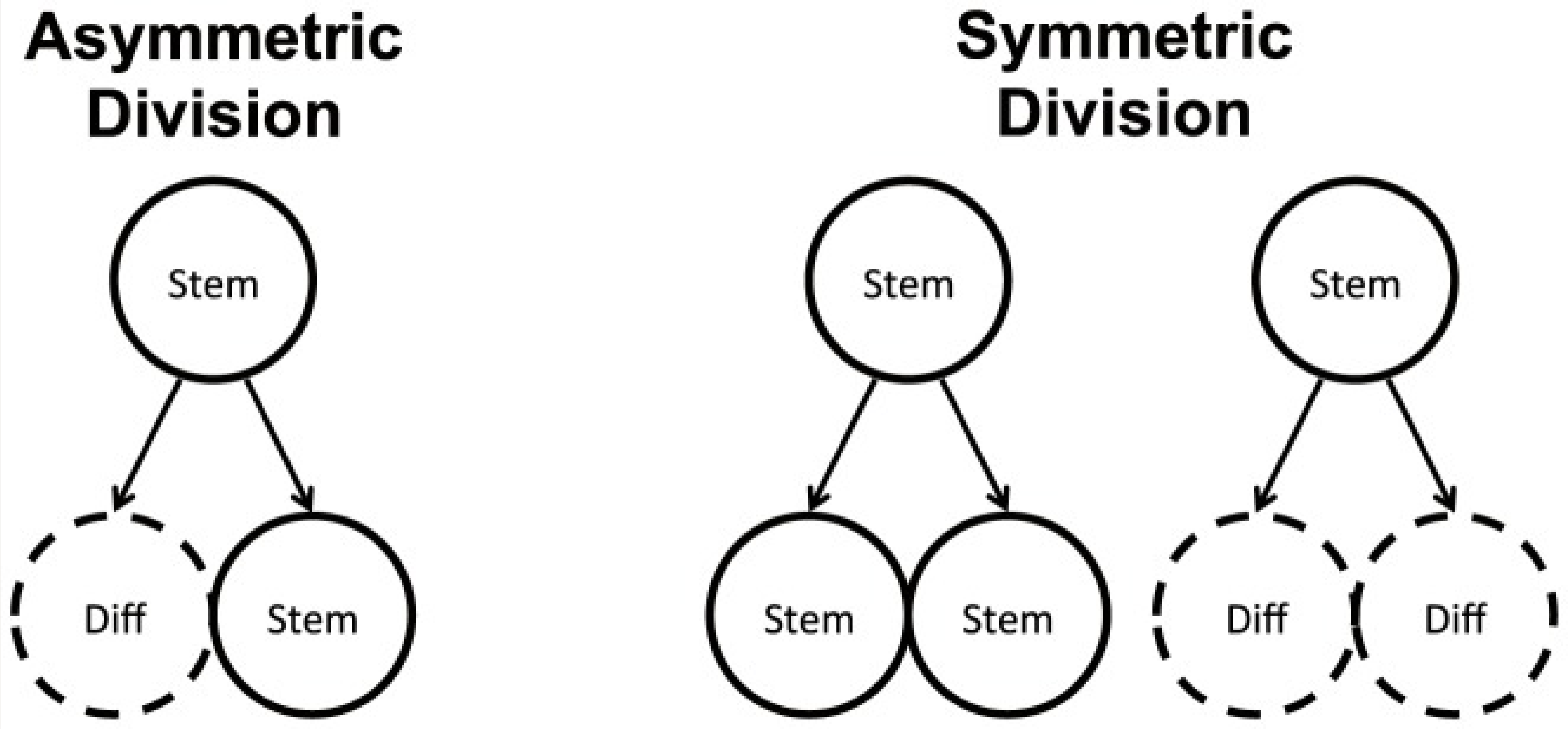
6.1.C INTRODUCTION
Basic Concepts of Cell Biology

- Somatic cells are classified as:
  - Stem cells (SCs), which exists to self-perpetuate and produce cells for a differentiated cell population.
  - Transit amplifying cells (TACs) are an undifferentiated population in transition between SCs and differentiated cells.
  - Mature cells, which are fully differentiated (have developed a specific morphology and function) and do not exhibit mitotic activity (static).



Stem cells – response to injury (tissue tolerance)

Homeostasis



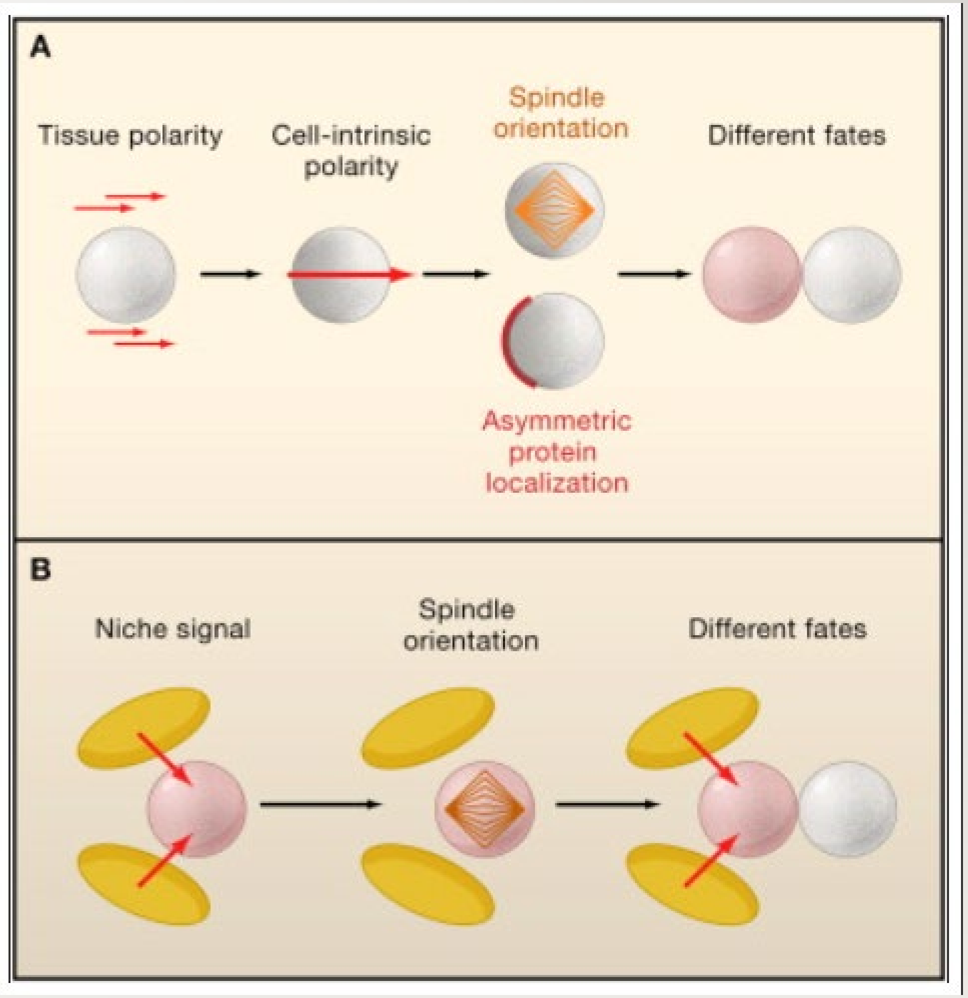
Cellular damage

doi: 10.1371/journal.pone.0076195

Figure 1 Extrinsic and Intrinsic Regulation of Stem Cell Self-Renewal

(A) Stem cells can set up an axis of polarity during interphase and use it to localize cell fate determinants asymmetrically in mitosis. Orientation of the mitotic spindle along the same polarity axis ensures the asymmetric segregation of determinants into only one of the two daughter cells.

(B) Stem cells may depend on a signal coming from the surrounding niche for self-renewal. By orienting their mitotic spindle perpendicularly to the niche surface, they ensure that only one of the two daughter cells continues to receive this signal and maintains the ability to self-renew.

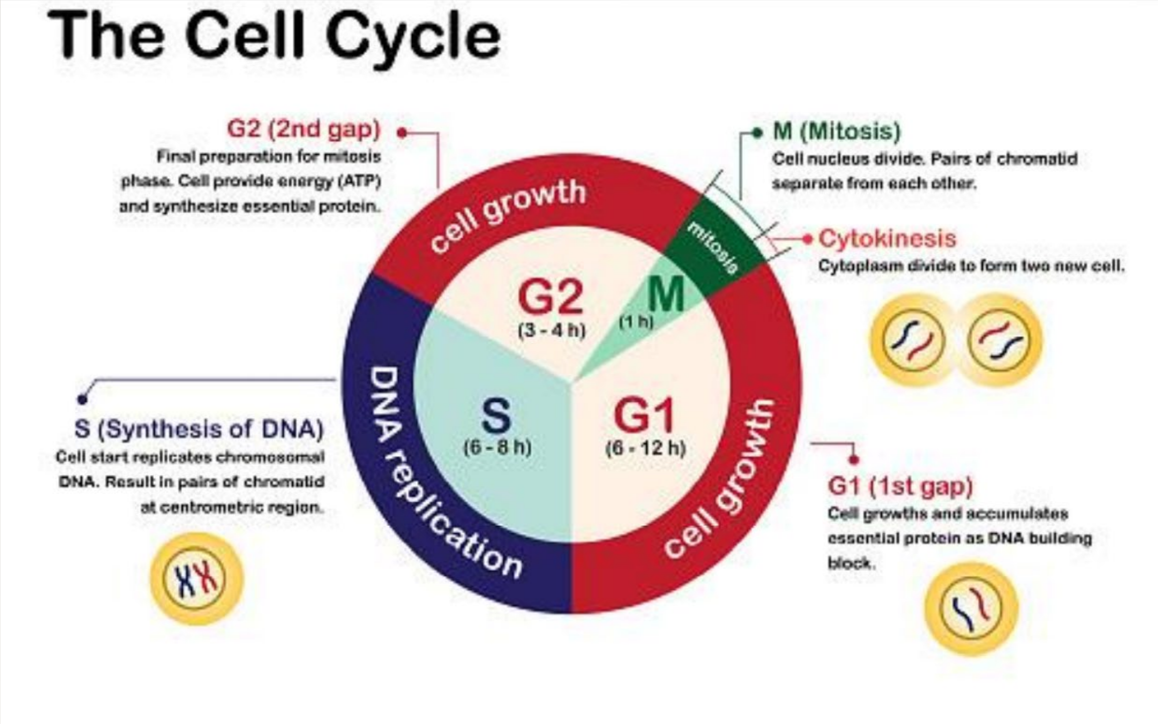


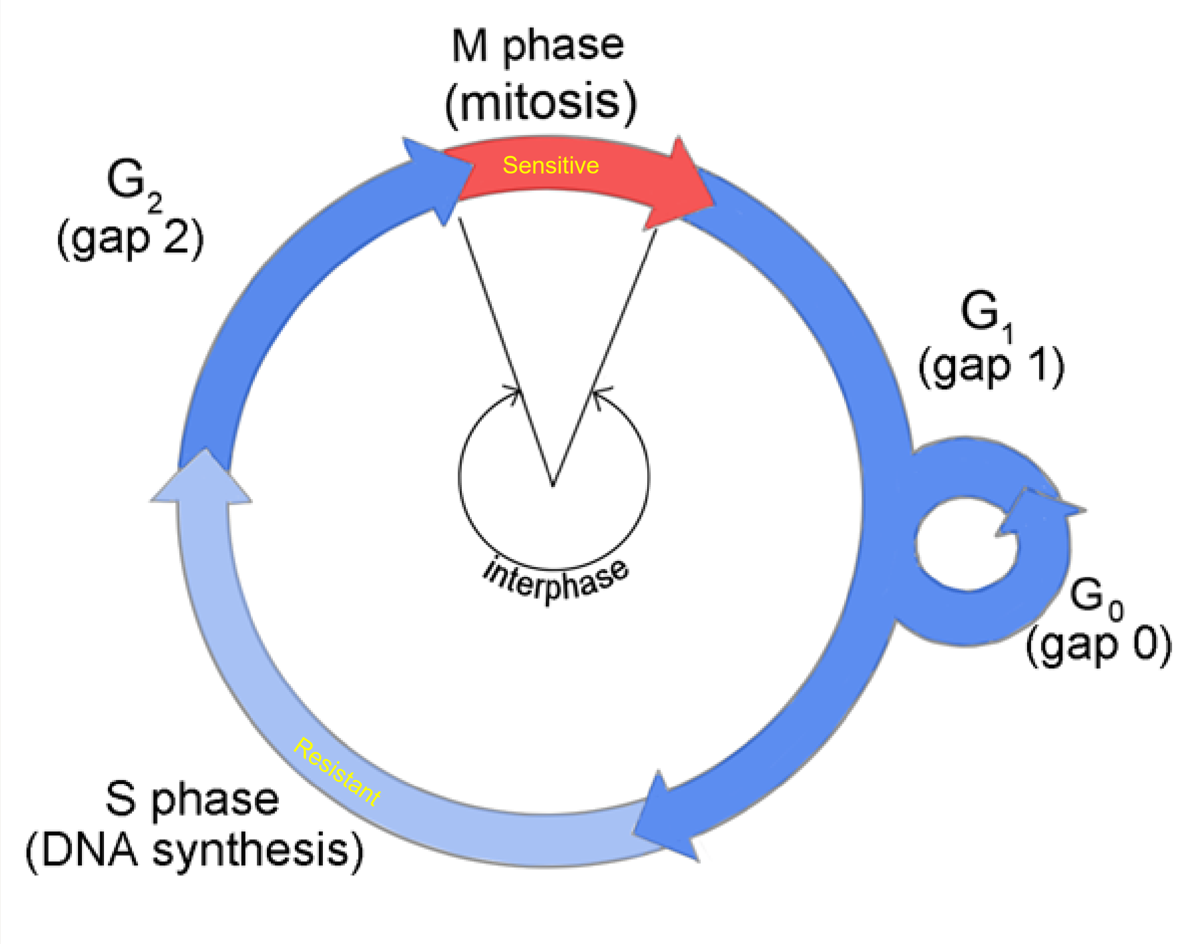
REVIEW | VOLUME 132, ISSUE 4, P583-597, FEBRUARY 22, 2008
Mechanisms of Asymmetric Stem Cell Division. Juergen A. Knoblich. Open Archive
DOI:https://doi.org/10.1016/j.cell.2008.02.007

6.1.E INTRODUCTION: Cell Cycle

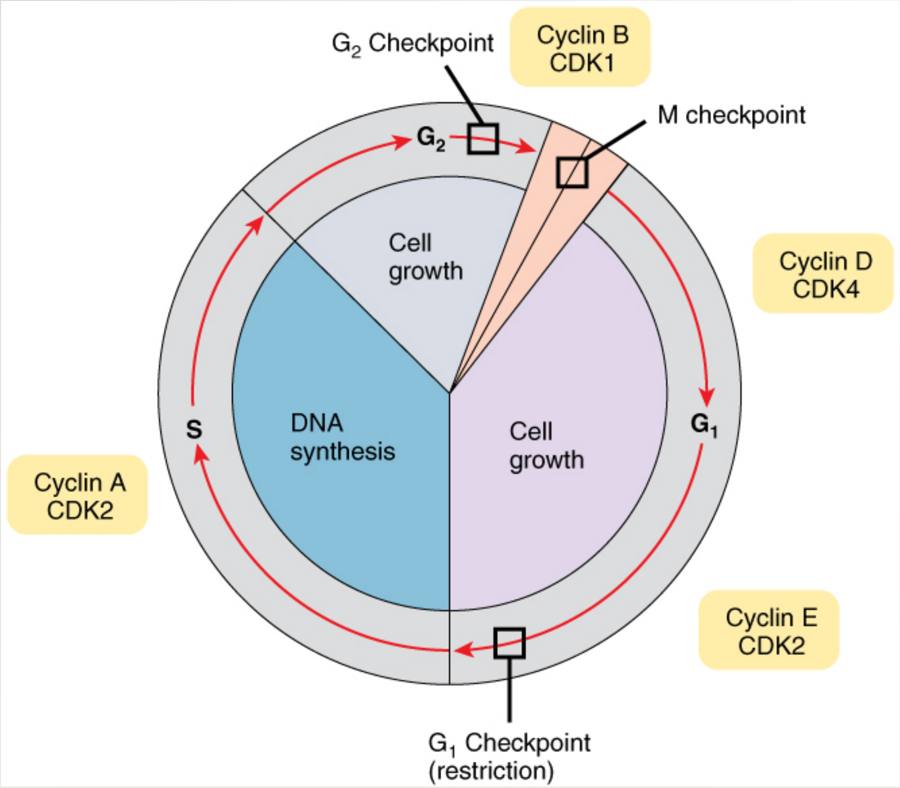
- Time between successive divisions (mitoses) is called cell cycle time.
  - Cell cycle time for stem cells in certain tissues is up to 10 days
  - Cell cycle time for mammalian cells is of the order of 10 – 20 hours and is divided in 4 phases:
    - G1 is in the range of 1 – 8 hours (30%) – **most variable**
    - G0 describes a cellular state outside of the replicative cell cycle
    - S phase is usually in the range of 6 – 8 hours (50%)
    - G2 is in the range of 2 – 4 hours (15%)
    - M phase is less than 1 hour (5 %)

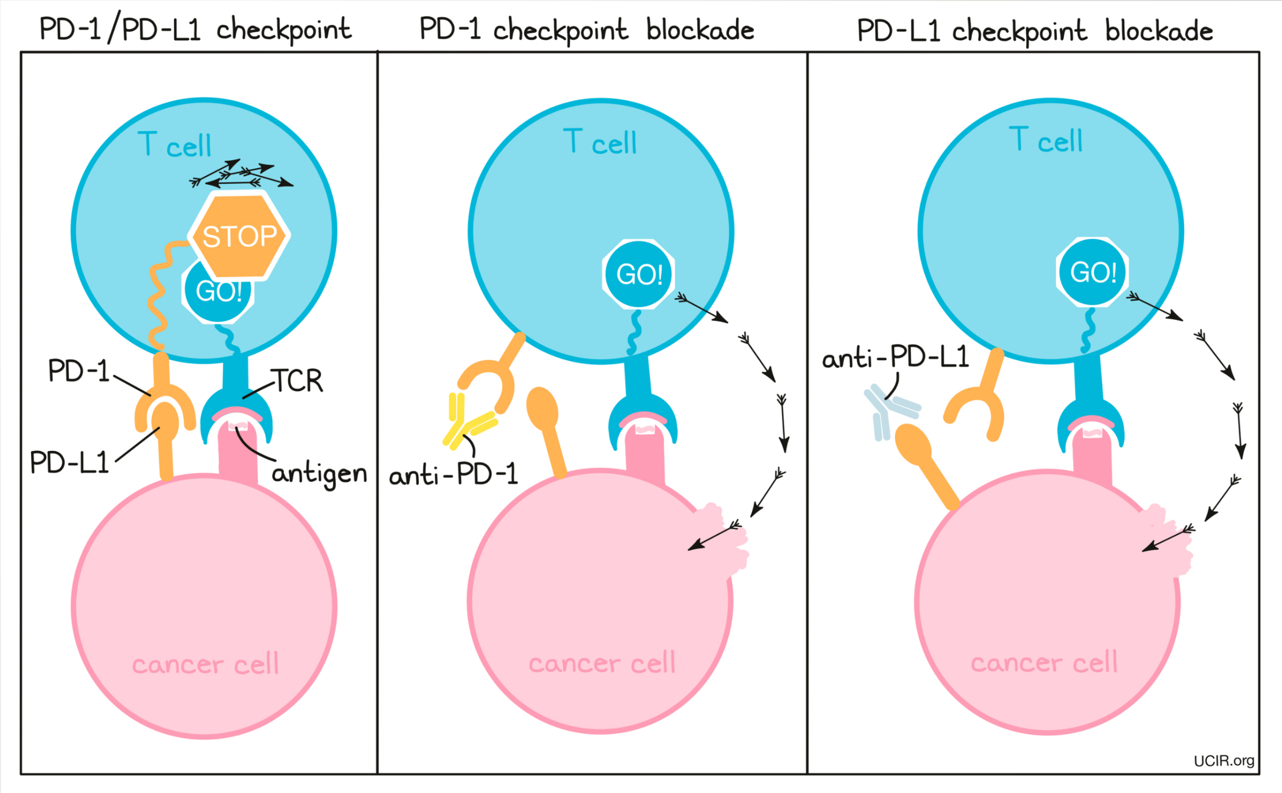
6.1.E INTRODUCTION: Cell Cycle





6.1.E INTRODUCTION:
Cell Cycle checkpoints vs immune checkpoints

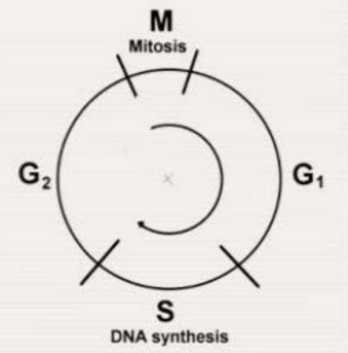


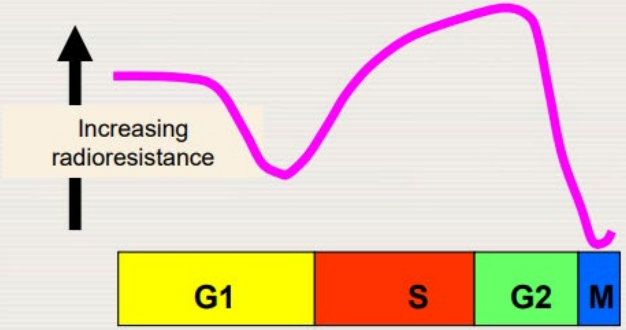


6.2 IRRADIATION OF CELLS

Radiosensitivity differs throughout the cell cycle with, in general:

- late S phase being the most radioresistant
- G_2/M being the most radiosensitive (Cells going through the division phase)
- G_1 phase taking an intermediate position



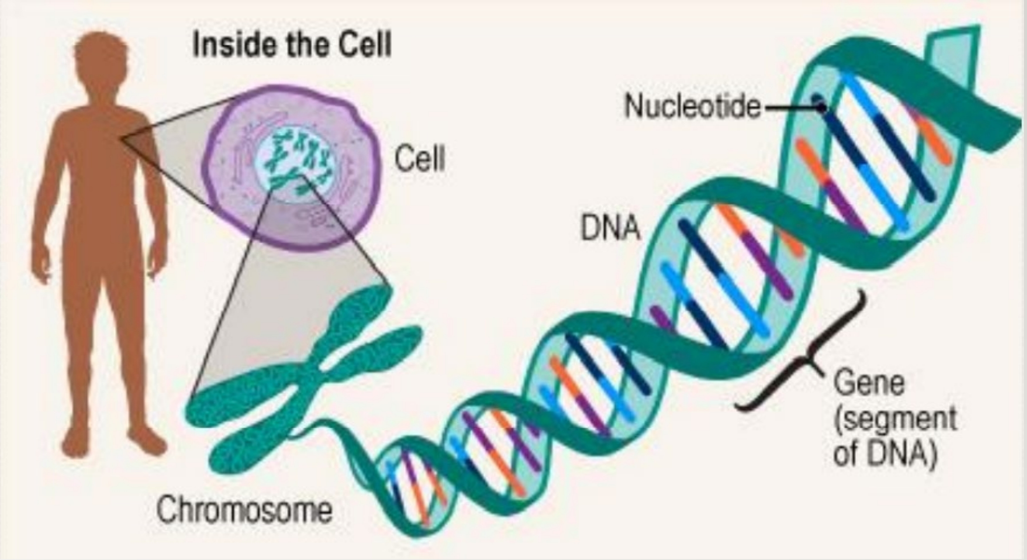


- The greater proportion of DNA enzymatic repair during late S phase may explain the resistance of late S phase cells
- Poor repair competence (reduced enzyme access due to chromatin compaction) explains the high radiosensitivity in G_2/M phase
- Resting cells in G_0, not involved in the cell cycle, are more resistant to radiation when compared to late S-phase cells

IAEA

6.1.C INTRODUCTION
Basic Concepts of Cell Biology

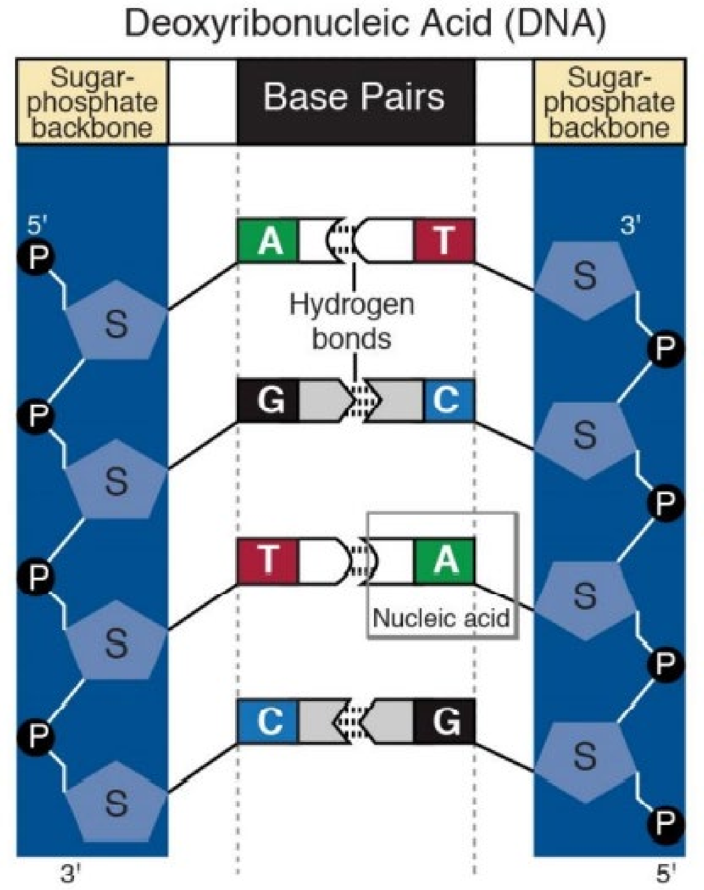
- Chromosome is a microscopic, threadlike part of a cell that carries hereditary information in the form of genes.
- Every species has a characteristic number of chromosomes; humans have 23 pairs (22 pairs are non-sex chromosomes and 1 pair is sex chromosome).
- Gene is a unit of heredity that occupies a fixed position on a chromosome.



Dogs → 78 chromosomes (39 pairs)
Cats → 38 chromosomes (19 pairs)
Drosophila → 8 chromosomes

6.1.D INTRODUCTION: Structure of DNA

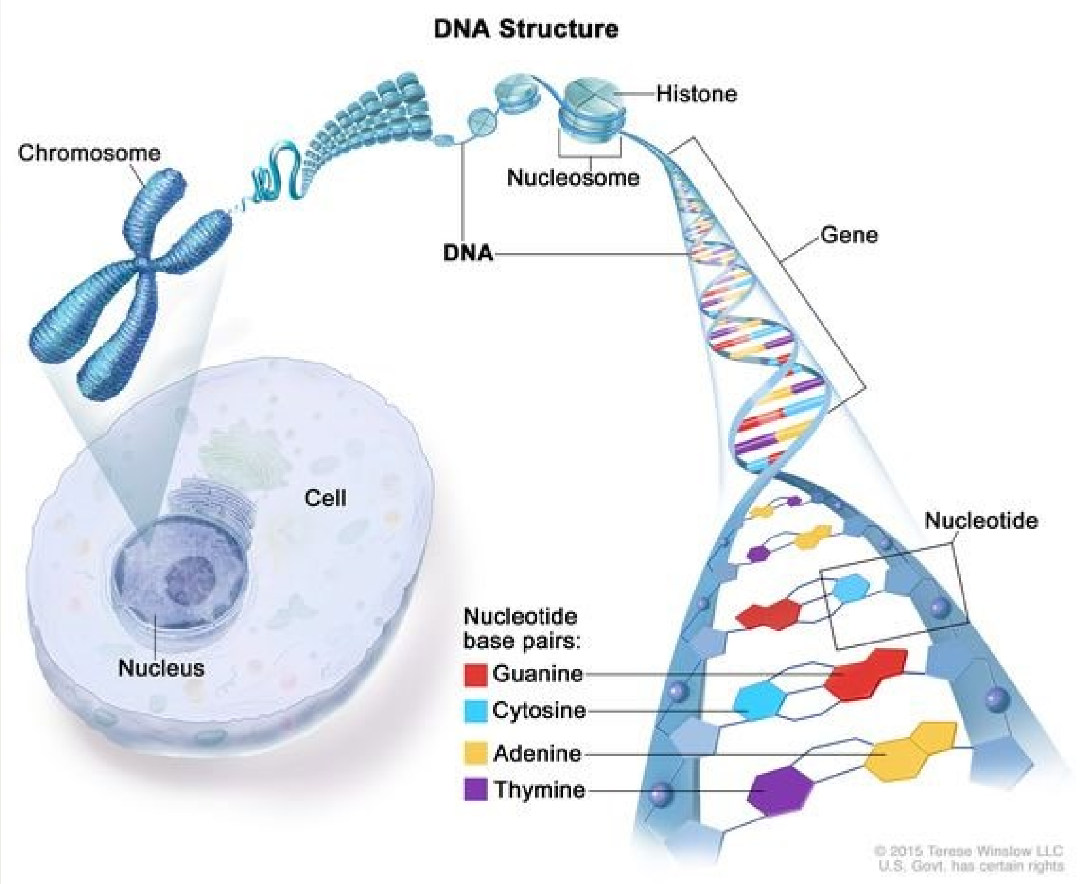
- Deoxyribonucleic acid (DNA) contains the genetic information of the cell
  - DNA is a large molecule and has a characteristic double helix structure (twisted ladder) consisting of two strands, each made up of a sequence of nucleotides
  - The backbone of the DNA strand is made of alternating sugar and phosphate groups
  - A nucleotide is a subunit of DNA, and is composed of a base linked to a sugar (deoxyribose) and a phosphate group
  - Each cell contains about 2m of DNA



Ref. Nature, vol 171, page 737, 1953
J. D. WATSON and F. H. C. CRICK

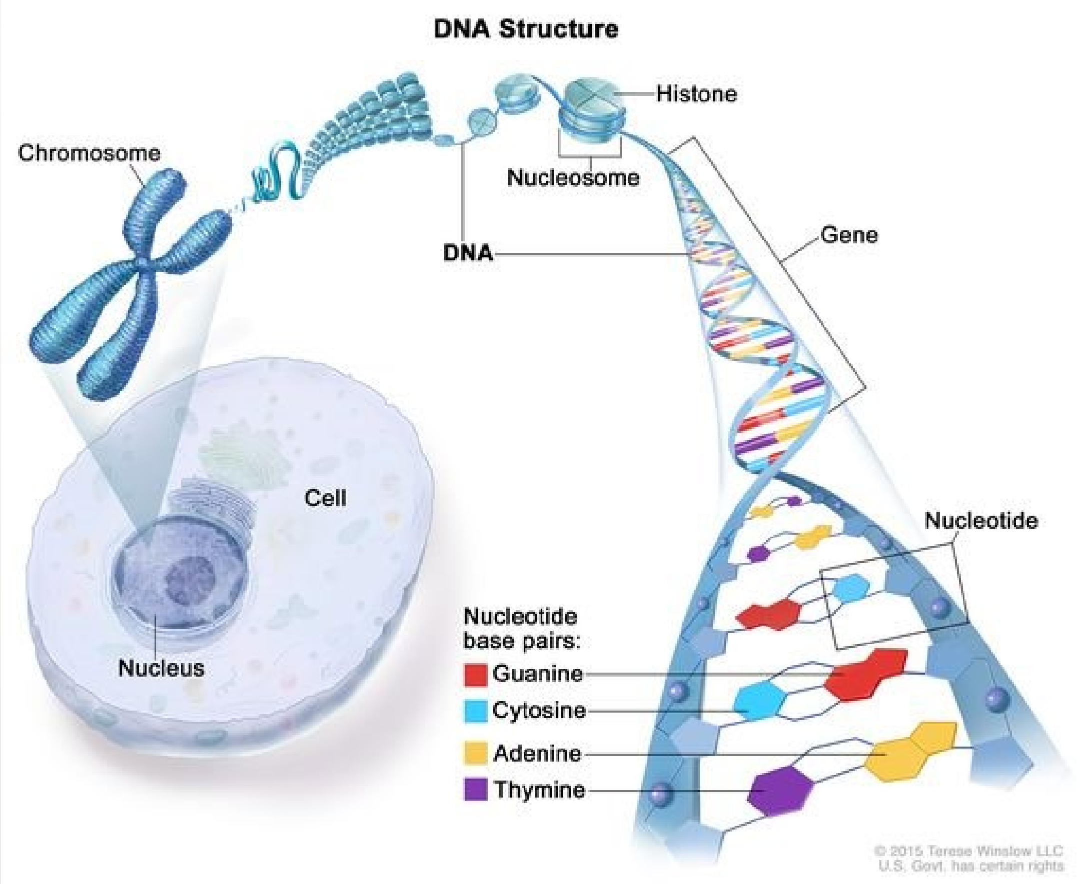
6.1.D INTRODUCTION: Structure of DNA

- Four bases of DNA
  - Purines
    - Adenine (A)
    - Guanine (G)
  - Pyrimidines
    - Cytosine (C)
    - Thymidine (T)
- The cell's genetic information is carried in a linear sequence of nucleotides that make up the organism's set of genes.

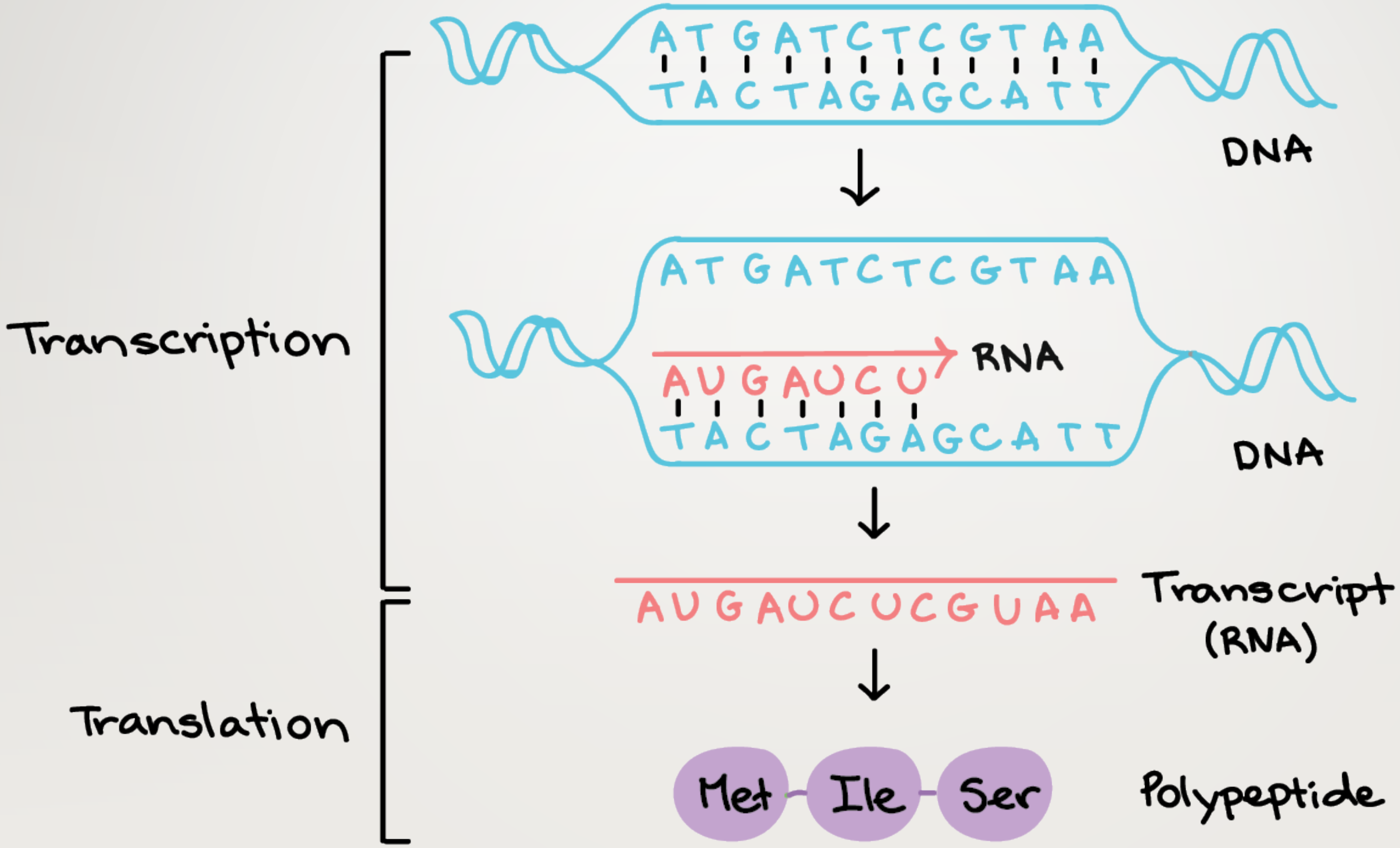


6.1.D INTRODUCTION: Structure of DNA

- Four bases of DNA
  - Purines
    - Adenine (A)
    - Guanine (G)
  - Pyrimidines
    - Cytosine (C)
    - Thymidine (T)
- The cell's genetic information is carried in a linear sequence of nucleotides that make up the organism's set of genes.



6.1.D INTRODUCTION: Structure of DNA



CONSIDER METHYLATION OF GENES AND POST-TRANSLATIONAL MODIFICATIONS

VEVOX poll

- The main constituents of a cell are (Vote for up to 3 choices)
- 1. cytoplasm
- 2. organelles such as mitochondria, ribosomes, etc…
- 3. protoplasm
- 4. nucleus
- 5. meiosis

CHAPTER 6. TABLE OF CONTENTS (classes April 3rd, 8th, 10th, 15th)

6.2.A IRRADIATION OF CELLS – Time frame of radiation effect

- When cells are exposed to ionizing radiation:
  - First, the standard physical effects between radiation and the atoms or molecules of the cells occur.
  - Possible biological damage to cell functions follows.
- Photoelectric effect vs Compton scatter

TABLE 13.1. Time Frame for Effects of Ionizing Radiation

Times	Events
Physical stage $\lesssim 10^{-15}$ s	Formation of H_2O^+, H_2O^*, and subexcitation electrons, e^-, in local track regions ($\lesssim 0.1$ μm)
Prechemical stage $\sim 10^{-15}$ s to $\sim 10^{-12}$ s	Three initial species replaced by H_3O^+, OH, e^-_{aq}, H, and H_2
Chemical stage $\sim 10^{-12}$ s to $\sim 10^{-6}$ s	The four species H_3O^+, OH, e^-_{aq}, and H diffuse and either react with one another or become widely separated. Intratrack reactions essentially complete by $\sim 10^{-6}$ s
Biological stages	
$\lesssim 10^{-3}$ s	Radical reactions with biological molecules complete
$\lesssim 1$ s	Biochemical changes
Minutes	Cell division affected
Days	Gastrointestinal and central nervous system changes
Weeks	Lung fibrosis develops
Years	Cataracts and cancer may appear; genetic effects in offspring

6.2 IRRADIATION OF CELLS:
Time Frame of Radiation Effect: PHYSICAL STAGE

- Radiation interacts with molecules and atoms: mainly water, since about 80% of a cell is composed of water to produce free radicals.
- A free radical is a molecule or atom, which is not combined to anything (ie. free) and carries an unpaired electron in its outer shell (looking for something to interact with)
- In a state associated with a high degree of chemical reactivity.
- Basic radiochemical reactions in the physical stage are:

- 1. $H_2O \xrightarrow{h\nu} H_2O^+ + e^-$
- 2. $H_2O \xrightarrow{h\nu} H_2O^*$

The initial changes produced by radiation in water are the creation of **(1)ionized** and **(2) excited** molecules.
They are produced in **<10^{-15}s** in **local regions** of the track.

Prechemical Stage

- The time between 10^{-15}s to 10^{-12}s are called the **pre-chemical stage**.
- the species produced by the radiation (H_2O^+, H_2O^* and free, sub-excitation electrons) induce chemical reactions as follows:

Process #1:

An ionized water molecule reacts with a neighboring molecule, forming a **hydronium ion** and a **hydroxyl radical**:

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

Process #2

An excited water molecule gets rid of its energy either by losing an electron, thus becoming an **ion radical** and proceeding according to the reaction or by **molecular dissociation**:

$$H_2O^* \rightarrow \begin{cases} H_2O^+ + e^- \\ H + OH \end{cases}$$

Prechemical Changes in Irradiated Water

Process #3:

- The sub-excitation free electrons migrate, losing energy by vibrational and rotational excitation of water molecules, and become thermalized by times ~10^{-12} s.
- The thermalized electrons orient the permanent moments of neighboring water molecules, forming a cluster, called a **hydrated electron**:

$$\underbrace{e^{-} \rightarrow e^{-}_{aq},}$$

end products of the pre-chemical stage

Active radiolytic species

H_3O^+, OH, e^-_{aq}, and H

Hydronium ion — *Hydroxyl* — *Hydrated electron*

Radiolysis is **the dissociation of molecules by ionizing radiation**.

Chemical Stage

- The time between 10^{-12}s to 10^{-6}s are called the **chemical stage**.
- The chemical stage is characterized by a **diffusion-controlled reactions**.
- The average distance a particle traveled $\boldsymbol{\lambda}$ is related to time τ and the diffusion constant D by

The average distance a particle traveled

diffusion coef.

$$\frac{\lambda^2}{6\tau} = D$$

time

- Two species that are closer than the sum of their reaction radii will have a chance to interact.

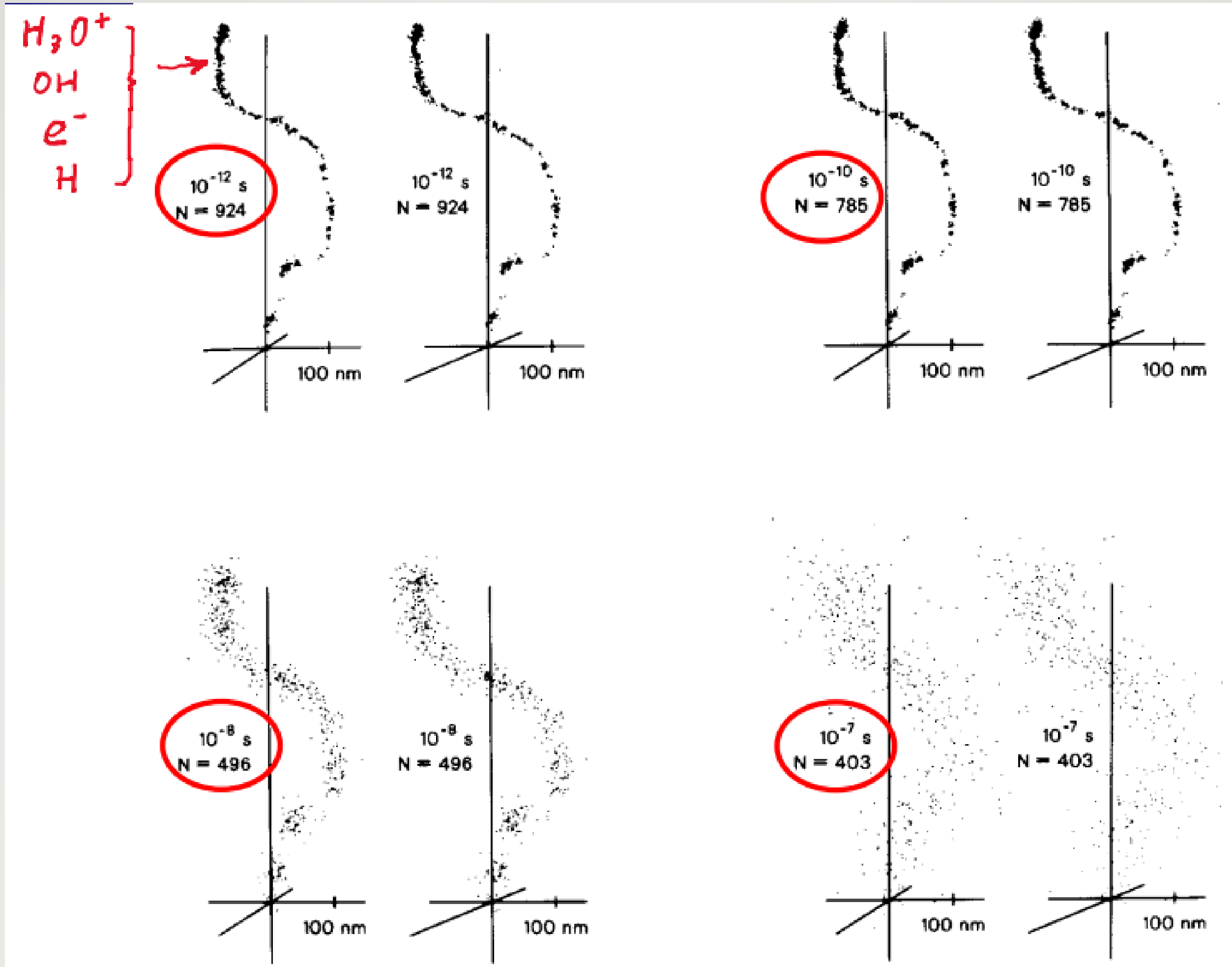


FIGURE 13.1. Chemical development of a 4-keV electron track in liquid water, calculated by Monte Carlo simulation. Each dot in these stereo views gives the location of one of the active radiolytic species, OH, H_3O^+, e^-_{aq}, or H, at the times shown. Note structure of track with spurs, or clusters of species, at early times. After 10^{-7} s, remaining species continue to diffuse further apart, with relatively few additional chemical reactions. (Courtesy Oak Ridge National Laboratory, operated by Martin Marietta Energy Systems, Inc., for the Department of Energy.)

er, pp. 402.

Turner, page 402

Example

Estimate how far a hydroxyl radical will diffuse in 10^{-12} s.

Solution

From Eq. (13.11) with $\tau = 10^{-12}$ s and from Table 13.2, we find

$$\lambda = (6\tau D)^{1/2} = (6 \times 10^{-12}\ \text{s} \times 2 \times 10^{-5}\ \text{cm}^2\ \text{s}^{-1})^{1/2}$$
$$= 1.10 \times 10^{-8}\ \text{cm} = 1.10\ \text{Å}. \qquad (13.12)$$

For comparison, the diameter of the water molecule is 2.9 Å. The answer (13.12) is compatible with our taking the time $\sim 10^{-12}$ s as marking the beginning of the chemical stage of charged-particle track development.

Table 13.2 Diffusion Constants D and Reaction Radii R for Reactive Species

Species	D (10^{-5} cm^2 s^{-1})	R (Å)
OH	2	2.4
e^-_{aq}	5	2.1
H_3O^+	8	0.30
H	8	0.42

Turner, pp. 402.

Chemical Stage

- After **~10^{-12} s**, the four chemically active species H_2O^+, OH, e^-_{aq}, and H are located near the positions of the original H_2O^+, H_2O^*, and e^- that triggered their formation.

- Three of the new reactants, OH, e^-_{aq}, and H are free radicals. They begin to migrate in thermal motion. Individual pairs of these reactants may get sufficiently close to induce chemical reactions, for example

$$OH + OH \rightarrow H_2O_2,$$

Hydrogen peroxide

$$OH + e^-_{aq} \rightarrow OH^-,$$

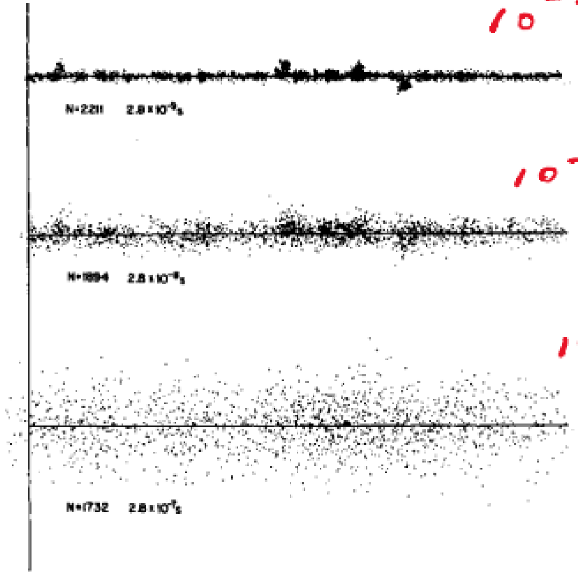
$$OH + H \rightarrow H_2O,$$

$$H_3O^+ + e^-_{aq} \rightarrow H + H_2O,$$

$$e^-_{aq} + e^-_{aq} + 2H_2O \rightarrow H_2 + 2OH^-,$$

$$e^-_{aq} + H + H_2O \rightarrow H_2 + OH^-,$$

$$H + H \rightarrow H_2.$$



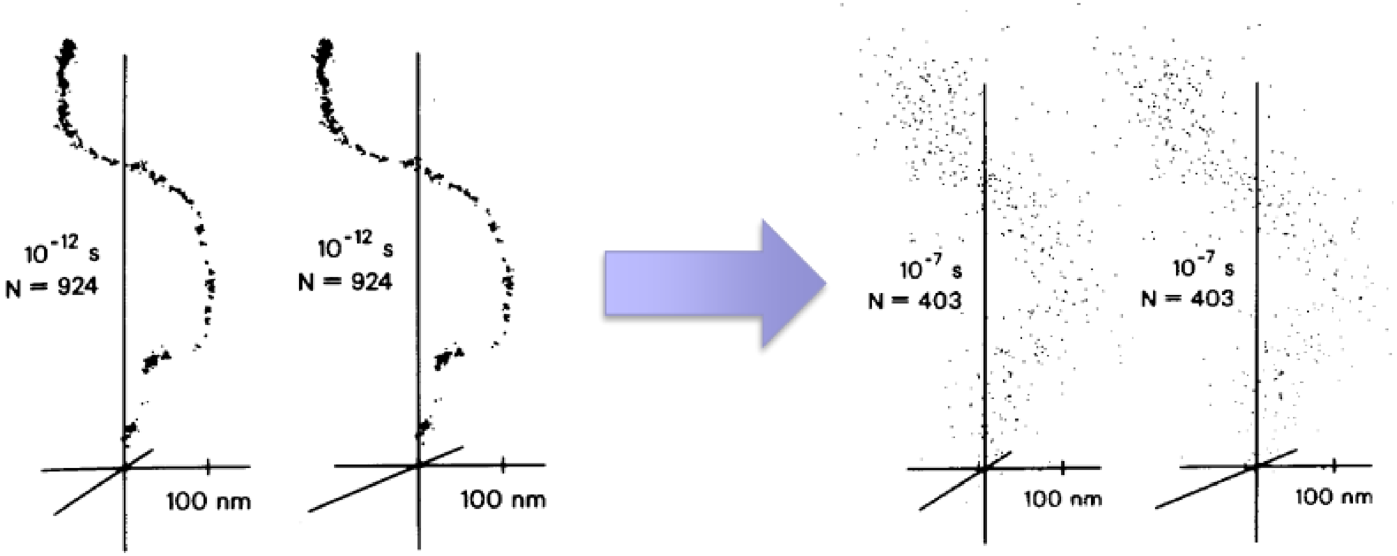
10^{-9} s

10^{-8} s

10^{-7} s

Chemical Stage

- As time passes, the reactions proceed until the remaining reactants diffused so far away from one another that **the probability of additional chemical reaction becomes very small.**
- These happen typically within **10^{-6} s**, by which the chemical development of the track in pure water is essentially over.



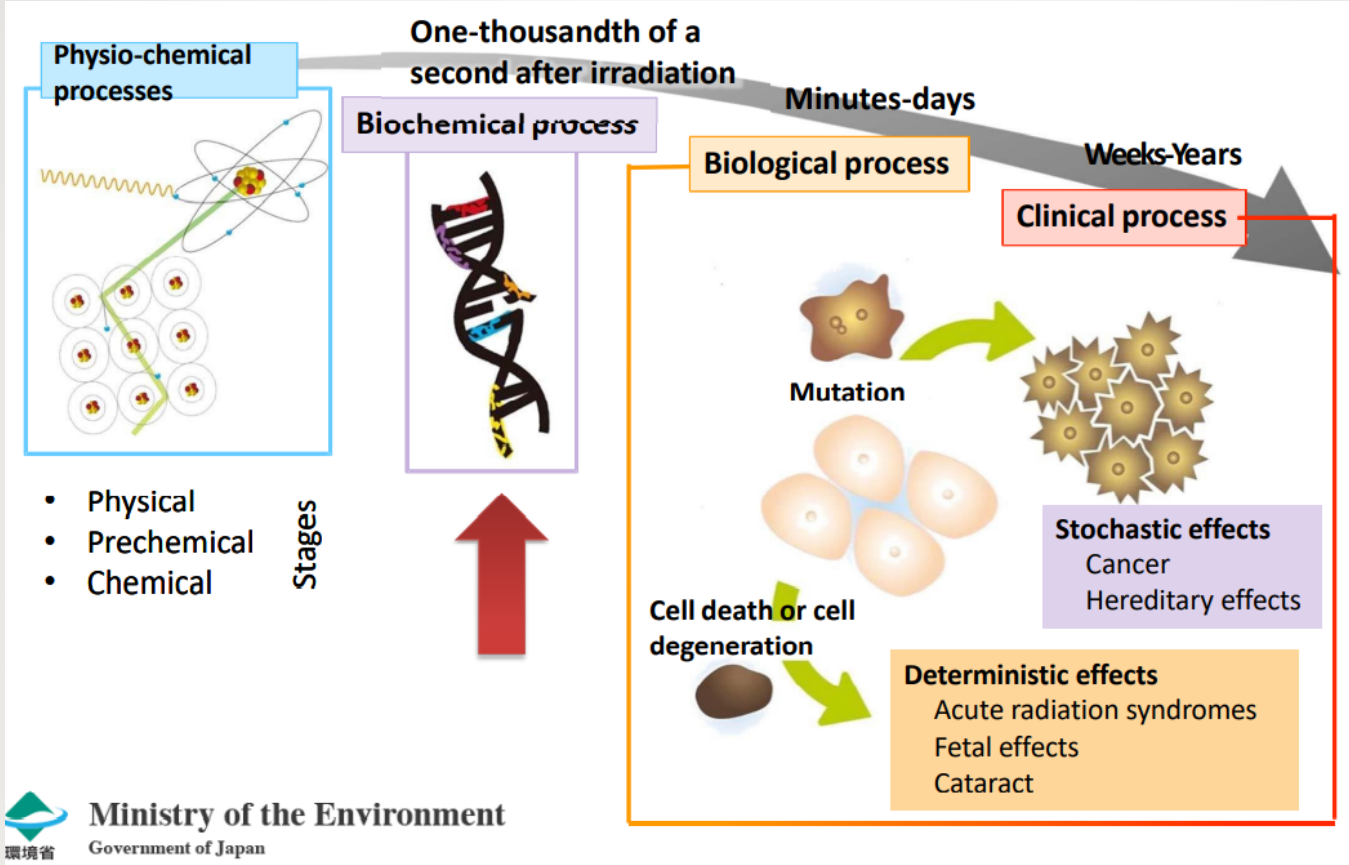
VEVOX poll

- Which of the following statements concerning free radicals is TRUE?
  - 1. Free radicals can be generated only by gamma radiation but not X-rays
  - 2. Free radicals have half-lives on the order of seconds
  - 3. Free radicals carry a net electrical charge, and therefore a low degree of chemical reactivity
  - 4. Free radicals have an unpaired electron in the outer shell

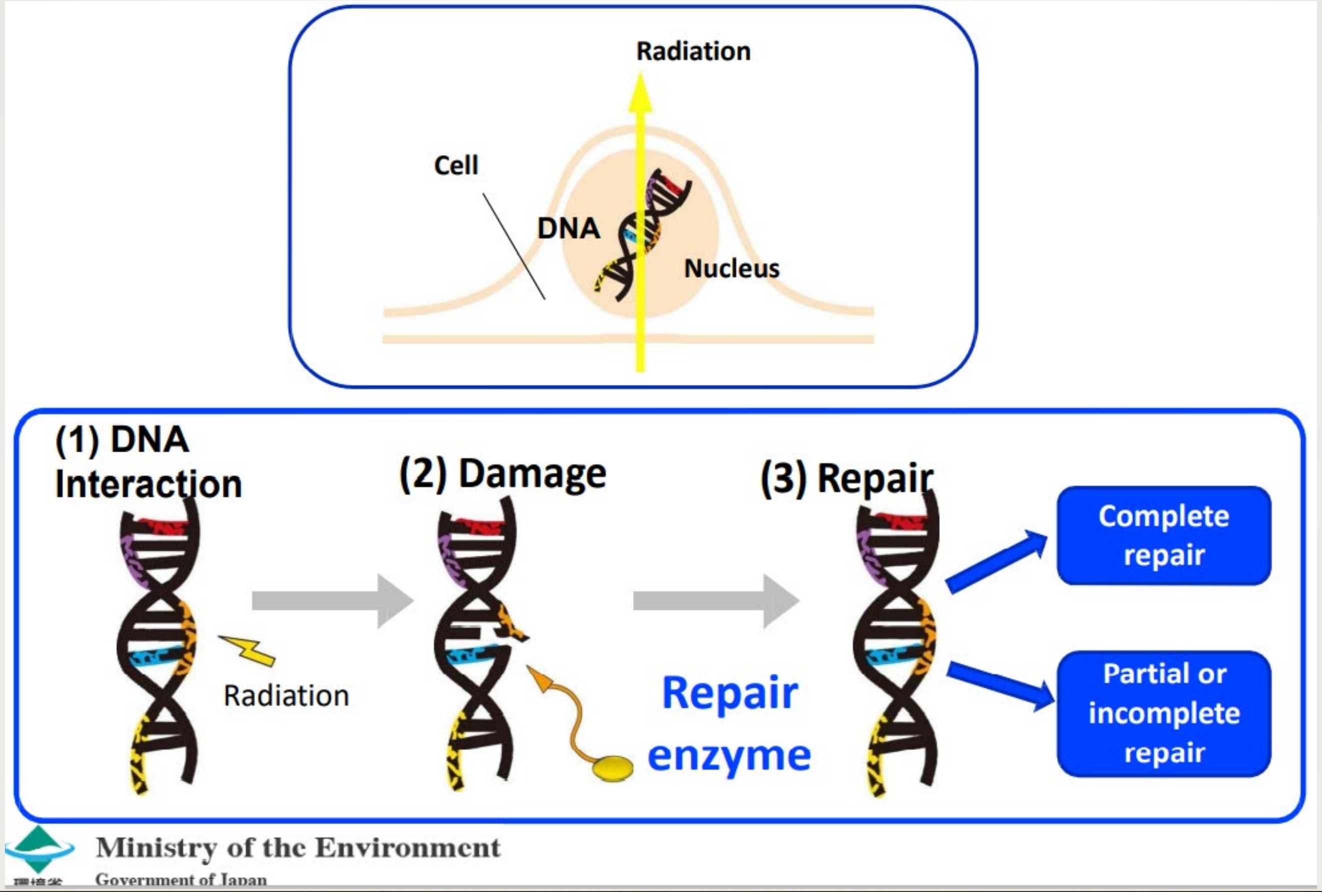
VEVOX poll

- The lifetime of radicals in target molecules is about:
- 1. $10^{(-3)}$ sec
- 2. $10^{(-6)}$ sec
- 3. $10^{(-9)}$ sec
- 4. $10^{(-12)}$ sec

6.2.A Lapse of time between exposure and effects

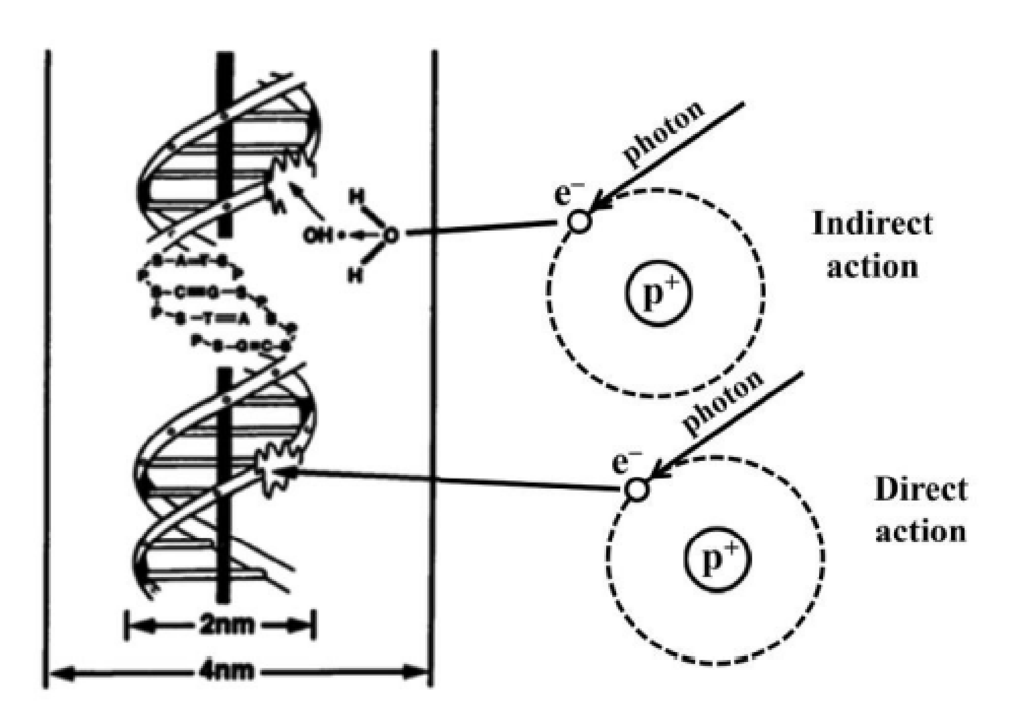


6.2.C and D Interaction, damage, and repair of DNA



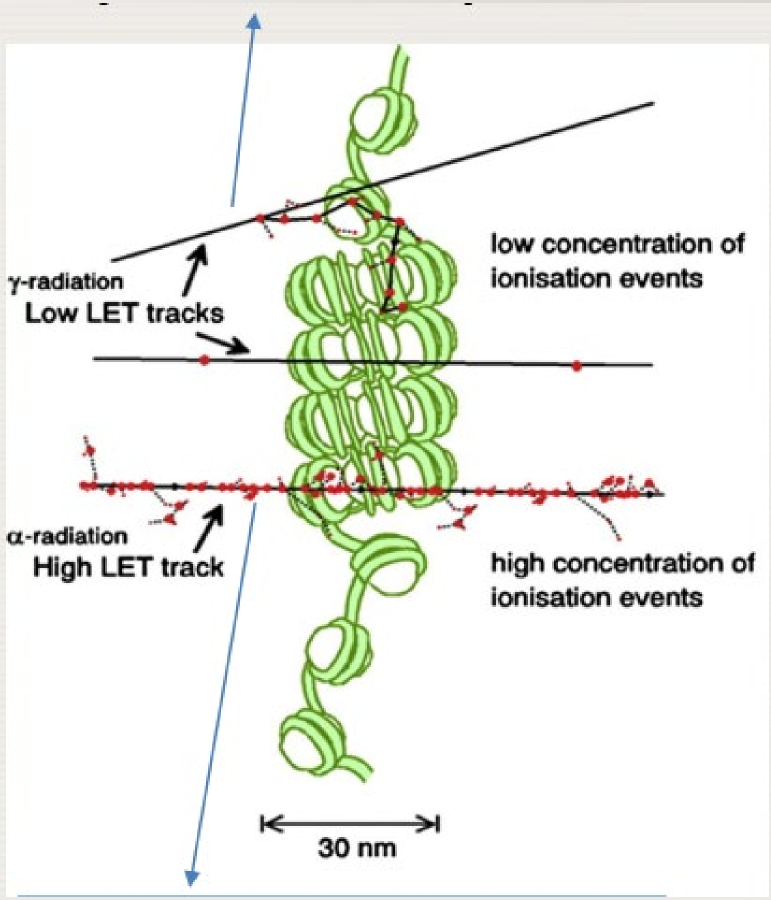
6.2.C IRRADIATION OF CELLS – interaction with DNA

- DNA is the primary target of ionizing radiation for biologic effects
  - Minor effects on membranes and organelles
  - Endothelial cells (blood vessels) can die following sphingomyelin-ceramide pathway disruption
- Mechanisms of DNA damage
  - Direct
  - Indirect



6.2.C IRRADIATION OF CELLS : Direct action

- Radiation interacts directly with the critical target in the cell.
  - ~1/3 of the damage with low LET radiation (photons and electrons) – ionization of part of the DNA
  - Direct action is the dominant process in the interaction of high LET particles such as neutrons or alpha particles with biological material.
- Low LET 1 Gy ~ 3 - 4 tracks per cell versus High LET 1 Gy ~ 1000 tracks per cell



6.2.C IRRADIATION OF CELLS: Indirect action

- Radiation interacts with other molecules and atoms (mainly water, since about 80% of a cell is composed of water) within the cell to produce free radicals, which can, through diffusion in the cell, interact and damage the critical target within the cell.
  - ~2/3 of the damage.
  - Basic radiochemical reactions that may occur in water molecules disrupted by passage of an ionizing particle are as follows:

- 1. $H_2O \xrightarrow{h\nu} H_2O^+ + e^- \rightarrow H_2O^+ + e^-_{aq}$
- 2. $H_2O^+ \rightarrow OH^\bullet + H^+$ 75% indirect damage
- 3. $H_2O \xrightarrow{h\nu} H_2O^* \rightarrow H^\bullet + OH^\bullet$

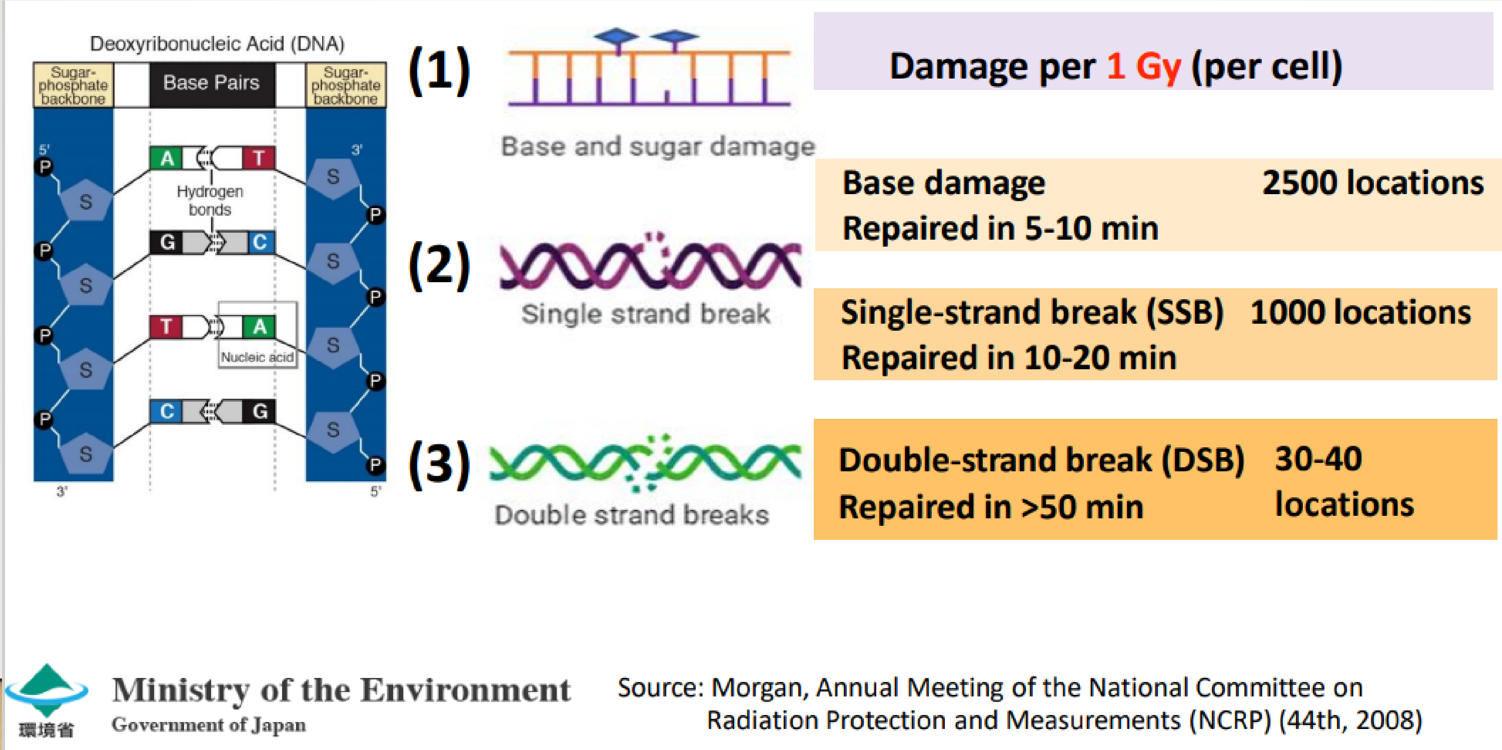
Reactive Oxygen Species (ROS) (due to an unpaired valence electron) produced in water Because short life of simple free radicals, only those formed in water column of 2-3 nm around DNA are able to participate in indirect effect

VEVOX poll

- Which of the following is a characteristic of the INDIRECT effect of ionizing radiation?
    - Scavenges diffusible free radicals
    - Produces reactive oxygen species
    - Accounts for 1/3 of the radiation damage
    - Is the dominant process for high LET radiation

6.2.C IRRADIATION OF CELLS - DNA damage

- DNA damage is the primary cause of cell death induced by radiation • Radiation exposure produces a wide range of lesions in the DNA:



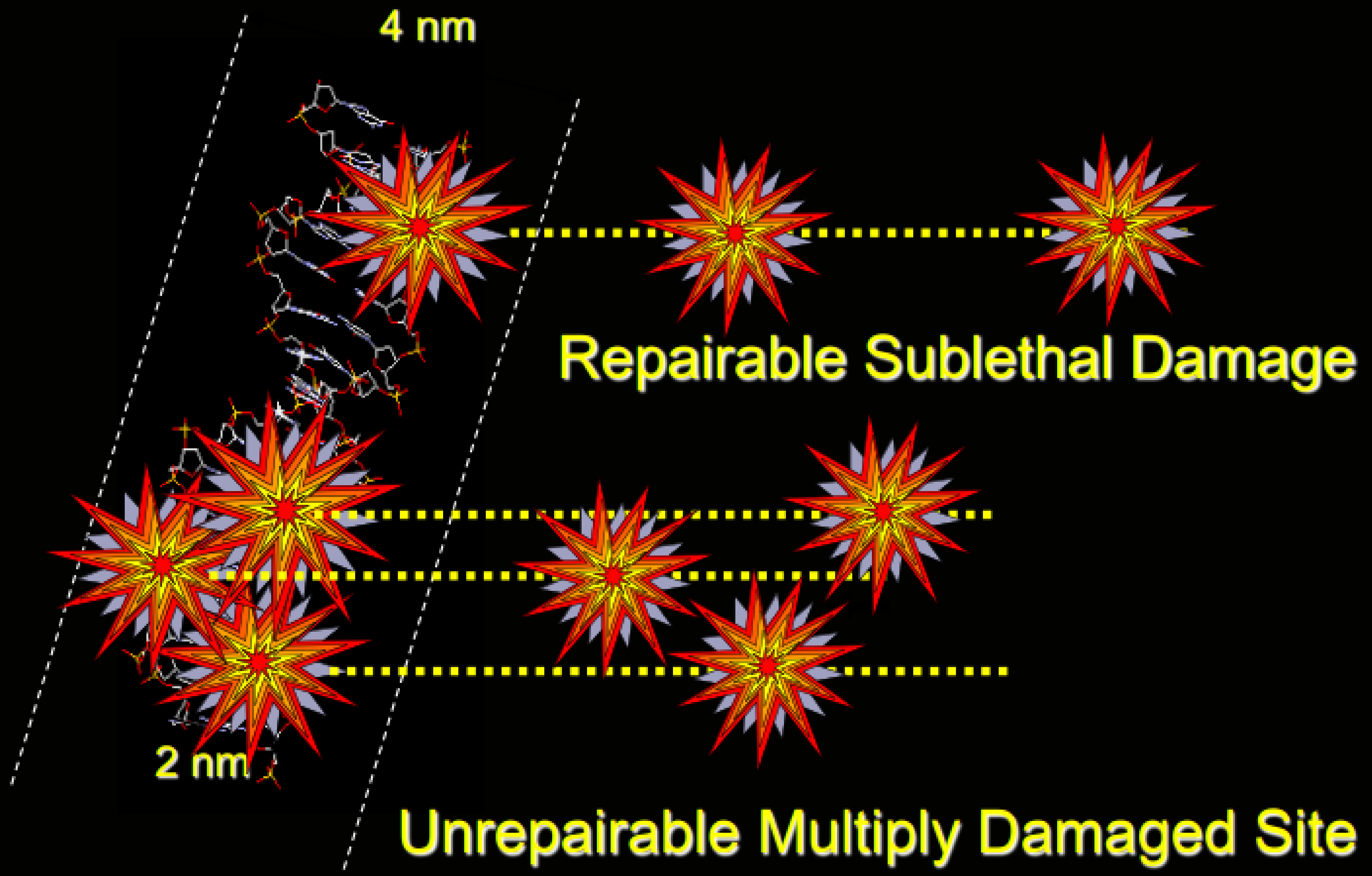
6.2.C IRRADIATION OF CELLS - DNA damage

At **lower doses and dose rates** (multiple exposures), **cellular recovery** may play an important role in the fixation of the radiation damage.

There are three broad types of cellular radiation damage:

Lethal damage	in which the **cellular DNA is irreversibly damaged** to such an extent that the cell dies or loses its proliferative capacity
Sublethal damage	in which **partially damaged DNA** is left with sufficient capacity to restore itself over a period of a few hours, provided there is **no further damage** during the repair period
Potentially lethal damage	in which repair of what would **normally be a lethal event** is made possible by manipulation of the post-irradiation cellular environment (cells are allowed to remain in the non-dividing state G_0)

Sub-lethal (or accumulated) damage results from accumulation of events that individually are incapable of killing a cell but that together can be lethal



6.2.D IRRADIATION OF CELLS: DNA repair

The number of DNA lesions generated by irradiation is large, but there are a number of mechanisms for DNA repair → the **percentage of lesions causing cell death is very small**

DNA repair mechanisms

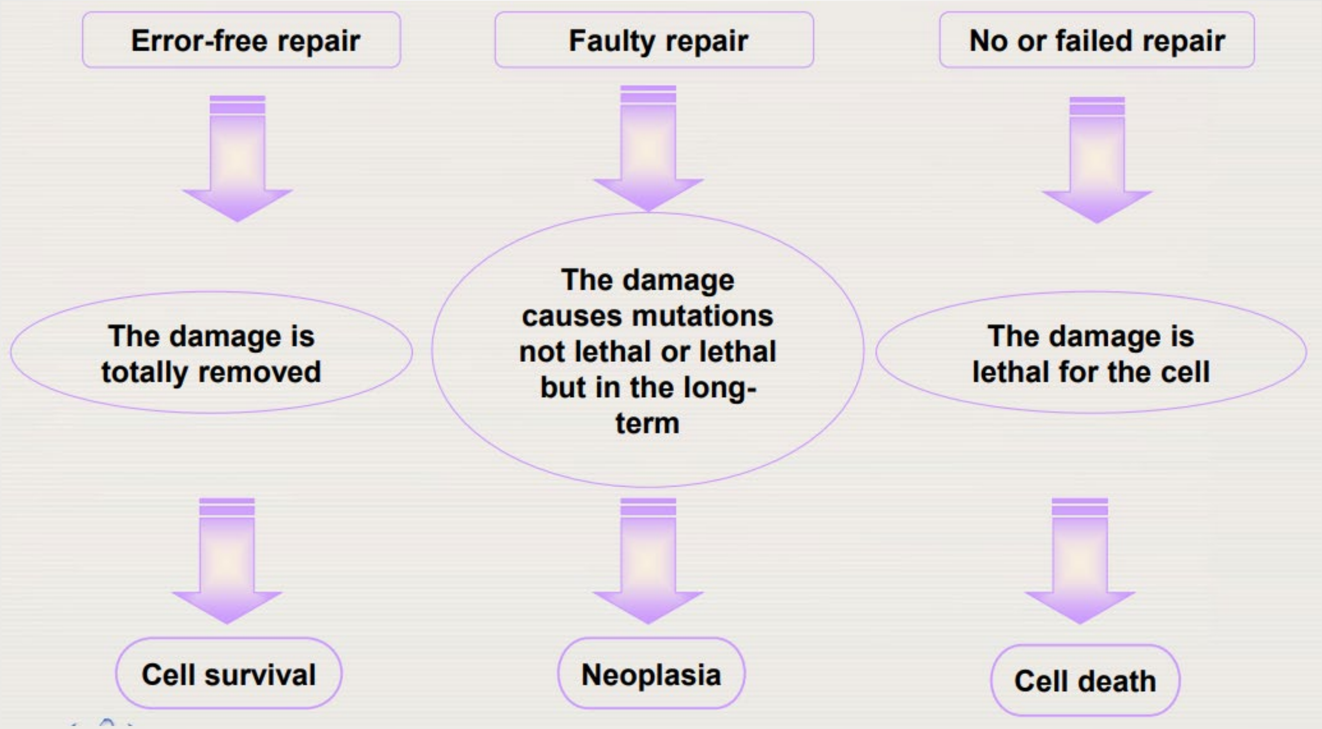
Important for the recovery of cells from radiation and other damaging agents.

There are **multiple enzymatic mechanisms** for detecting and repairing radiation induced DNA damage.

DNA repair mechanisms:

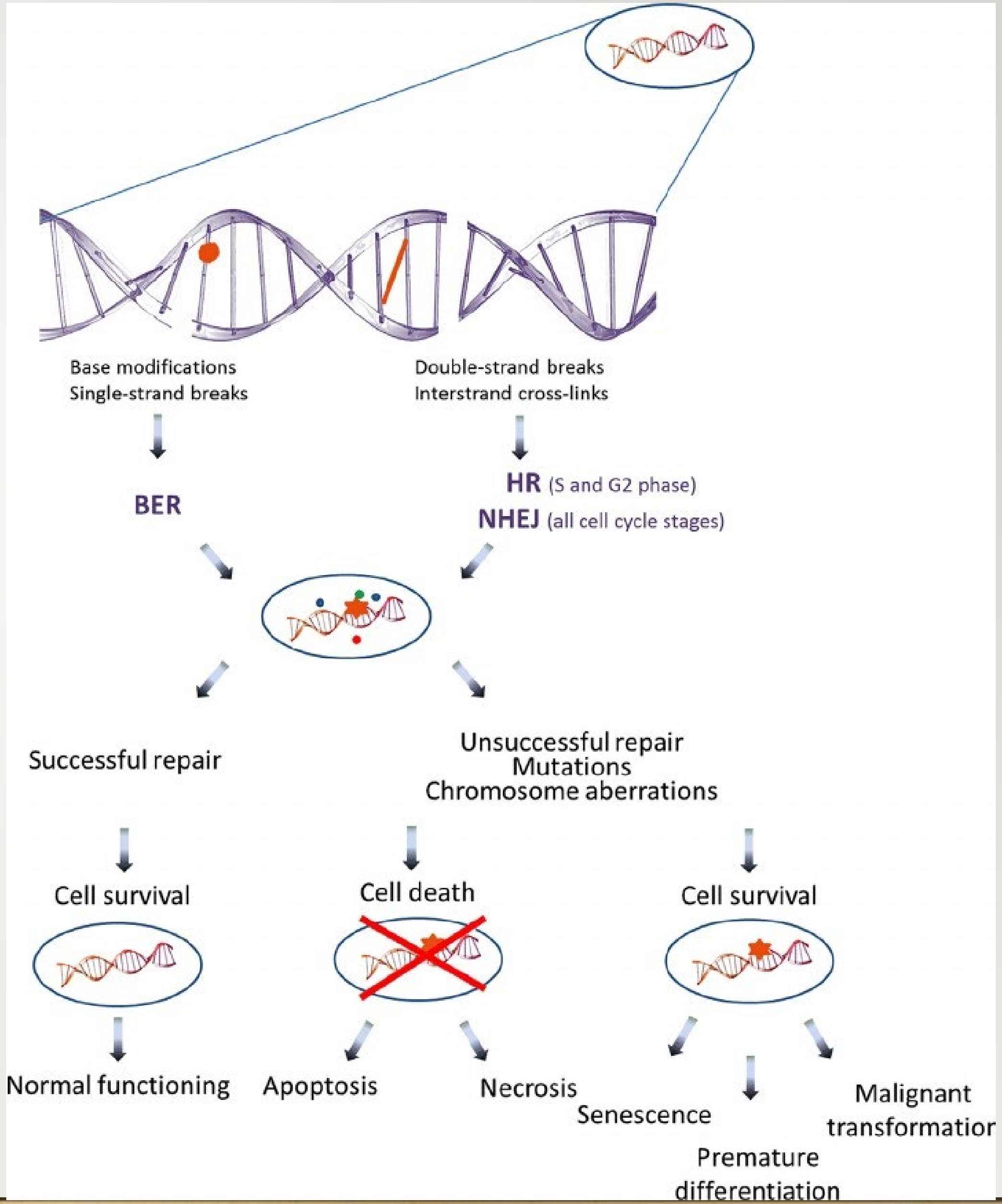
- base excision repair
- mismatch repair
- nucleotide excision repair
- Non-homologous end joining (NHEJ)
- Homologous recombination
- Double-strand repair

6.2.D IRRADIATION OF CELLS: DNA repair



6.2.D IRRADIATION OF CELLS - DNA repair

- Base excision repair
  - Defect ex. SNP, point mutation, cancer
- Nucleotide excision repair (NER)
  - Defect ex. Xeroderma pigmentosum (sun sensitivity)
- Homologous recombination (HR)
  - If in S or G2
- Non-Homologous End Joining (NHEJ)
  - Error prone, double strand breaks



6.2.E IRRADIATION OF CELLS

- ❖ Differentiating Cells: these cells are sensitive to radiation; they are relatively short-lived and include the first generation produced by division of the vegetative mitotic cells.
- ❖ Totally Differentiated Cells: these cells are relatively radioresistant; they normally have relatively long lifespans and do not undergo regular or periodic division in the adult stage, except under abnormal conditions such as following damage to or destruction of a large number of their own kind.
- ❖ Fixed Nonreplicating Cells: these cells are most radioresistant; they are highly differentiated morphologically and highly specialized in function.

6.2.E IRRADIATION OF CELLS: Possible fates

- No effect.
- Division delay: The cell is delayed in going through division.
- Apoptosis: Lymphocytes (intermitotic death)
- Cell sterilization/death (Reproductive failure: The cell dies when attempting the mitosis.)
- Mutation: The cell survives but contains a mutation (transformed genotype).
- Transformation: The mutation leads to a transformed phenotype and possibly carcinogenesis.
- Bystander effects: Irradiated cell sends signals to nearby unirradiated cells and induces genetic damage
- Adaptive responses: The irradiated cell becomes more radioresistant.

6.2.E IRRADIATION OF CELLS: Possible fate (death)

Radiation doses of the order of several Gy may lead to cell loss.
Cells are regarded as having been **'killed' by radiation** if they have **lost reproductive integrity**, according the following mechanisms:

Apoptosis	or **programmed cell death** can occur naturally or result from insult to the cell environment. It occurs in particular cell types after low doses of irradiation.	METABOLIC DEATH (mature cells)
Necrosis	is a form of cell death associated with **loss of cellular membrane** activity. Cellular necrosis generally occurs after high radiation doses.	
Mitotic catastrophe	**cells attempt to divide** without proper repair of DNA damage leading to a reproductive cell death which can occur in the first few cell divisions after irradiation, and with increasing frequency after increasing doses.	REPRODUCTIVE DEATH (stem cells)
Senescence	Senescent cells are metabolically active but **have lost the ability to divide.**	

6.2 IRRADIATION OF CELLS – cell fate

- Surviving cell that maintains its reproductive integrity and proliferates almost indefinitely into a large number of progeny is said to be clonogenic.
- In general, to destroy cell function in non-proliferating mature (static) cells (metabolic death) a typical dose of 100 Gy is required, while to destroy proliferative cells (stem cells – reproductive death) requires typically only 2 Gy.

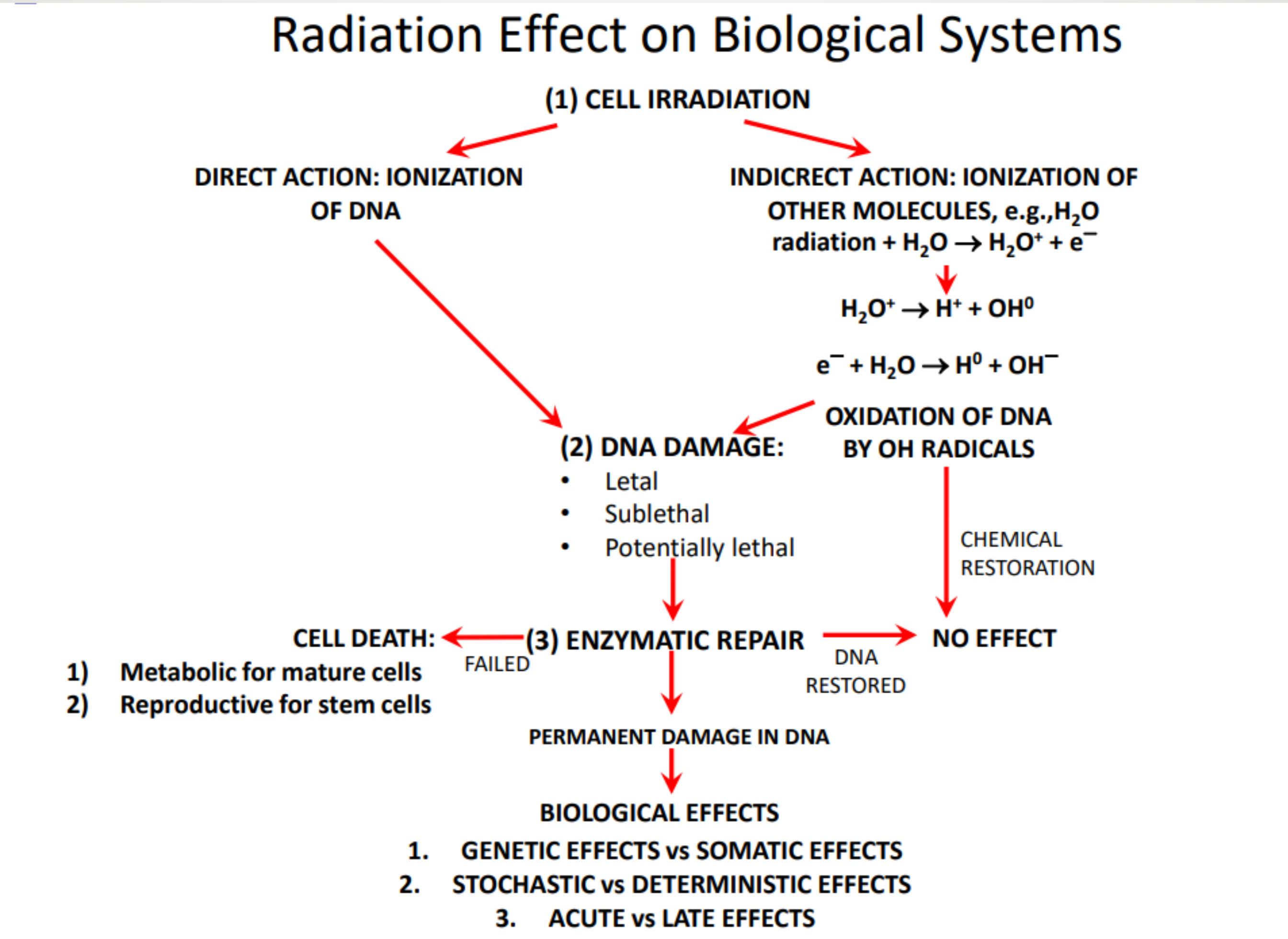
VEVOX poll

- Approximately how many DNA double strand breaks (DSB) are caused per cell per Gray?
  - 1-10
  - 30-40
  - 1000
  - 2500

VEVOX poll

- The lethal lesion caused in DNA by low LET radiation is:
  - Single strand breaks from alpha particles
  - Accumulation of irreparable damage (multiple SSB or DSB)
  - Pyrimidine dimers
  - Damage to the cell membrane

RADIATION EFFECT ON BIOLOGICAL SYSTEMS



BIBLIOGRAPHY

- ❑ Dale RG, Jones B. (Eds) Radiobiological Modelling in Radiation Oncology, The British Institute of Radiology, London (2007).
- ❑ Hall EJ, Giacca AJ. Radiobiology for the Radiologist, 6th edn, Lippincott, Williams and Wilkins, Philadelphia, PA (2006).
- ❑ ICRU - INTERNATIONAL COMMISSION ON RADIATION UNITS, Absorbeddose Specification in Nuclear Medicine, Rep. 67, Nuclear Technology Publishing, Ashford, United Kingdom (2002).
- ❑ Meredith R, Wessels B, Knox S. Risks to normal tissue from radionuclide therapy, Semin. Nucl. Med. 38 (2008) 347–357.

BIBLIOGRAPHY

- • HALL, E., GIACCIA, A.J., Radiobiology for the Radiologist, 6th edn, Lippincott Wilkins & Williams, Philadelphia, USA (2006)
- • INTERNATIONAL ATOMIC ENERGY AGENCY, Radiation Oncology Physics: A Handbook for Teachers and Students, IAEA, Vienna (2005). http://www-naweb.iaea.org/nahu/dmrp/publication.asp
- • INTERNATIONAL ATOMIC ENERGY AGENCY, Radiation Biology: A Handbook for Teachers and Students, Training Course Series, 42, IAEA, Vienna (2010). http://wwwpub.iaea.org/MTCD/publications/PDF/TCS-42_web.pdf
- • INTERNATIONAL ATOMIC ENERGY AGENCY, Radiobiology modules in the “Applied Sciences of Oncology” distance learning course. Available on CD Contact: J.Wondergem@iaea.org, or downloadable for free from the IAEA website: http://www.iaea.org/NewsCenter/News/2010/aso.html

BIBLIOGRAPHY

- • INTERNATIONAL COMMISSION ON RADIOLOGICAL PROTECTION, Pregnancy and Medical Radiation ICRP Publication 84, Pergamon Press, Oxford and New York (2000)
- • INTERNATIONAL COMMISSION ON RADIOLOGICAL PROTECTION, Recommendations of the ICRP, ICRP Publication 103, Annals of the ICRP Volume 37/2-4, Elsevier (2008). via www.sciencedirect.com
- • JOINER, M.C., VAN DER KOGEL, A.J., (Eds), Basic Clinical Radiobiology, 4th ed., Hodder Arnold, London, UK, (2009)
- • KOENIG, T.R., WOLFF, D., METTLER, F.A., WAGNER, L.K., Skin injuries from fluoroscopically guided procedures: part 1, characteristics of radiation injury, AJR Am J Roentgenol 177 1 (2001) 3-11

BIBLIOGRAPHY

- • NATIONAL RESEARCH COUNCIL OF THE NATIONAL ACADEMIES, Health risks from exposure to low levels of ionizing radiation; BEIR VII phase 2, Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation, National Academies Press, Washington, DC (2006). http://www.nap.edu/openbook.php?isbn=030909156X
- • TANNOCK, HILL, BRISTOW, HARRINGTON, (Eds), The Basic Science of Oncology, Chapters 14 & 15, 4th ed., McGraw Hill, Philadelphia, (2005)
- • WAGNER, L.K., EIFEL, P.J., GEISE, R.A., Potential biological effects following high X-ray dose interventional procedures, J Vasc Interv Radiol 5 1 (1994)