Chapter 7 – Linear Energy Transfer and Relative Biologic Effectiveness

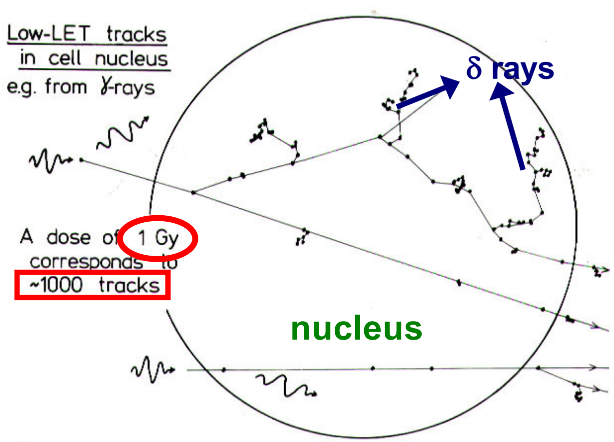
10/3/2024

Outline

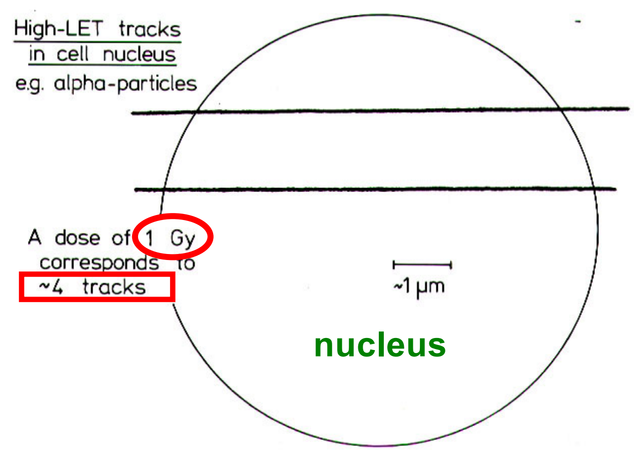
- **Linear Energy Transfer (LET)**
- Relative Biologic Effectiveness (RBE)
- RBE As a Function of LET
- The Oxygen Effect and LET
- Radiation Weighting Factor (W_R)

Energy Deposition of IR

- An important characteristic of ionizing radiation is the **localized** release of large amounts of energy
- The **spatial distribution** of ionization depends on the type of radiation

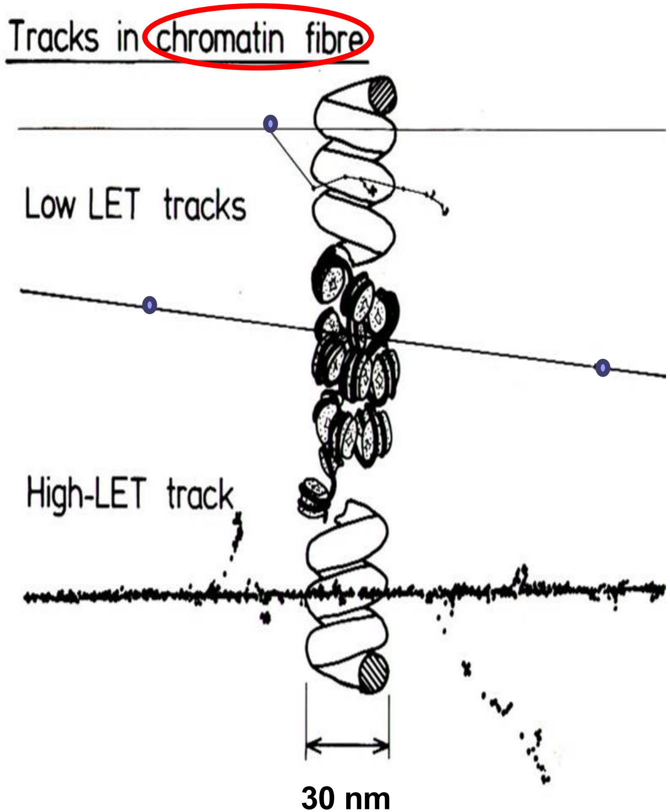


X-ray – sparsely Ionizing



α-particle – densely ionizing

Track Structure vs. DNA



Sparsely Ionizing Radiation

Less likely to cause DSB

Yield of SSB >> DSB (1000:40 for 1 Gy)

Densely Ionizing Radiation

Low probability of hitting DNA (fewer tracks per Gy)

High probability of DSB when it does hit

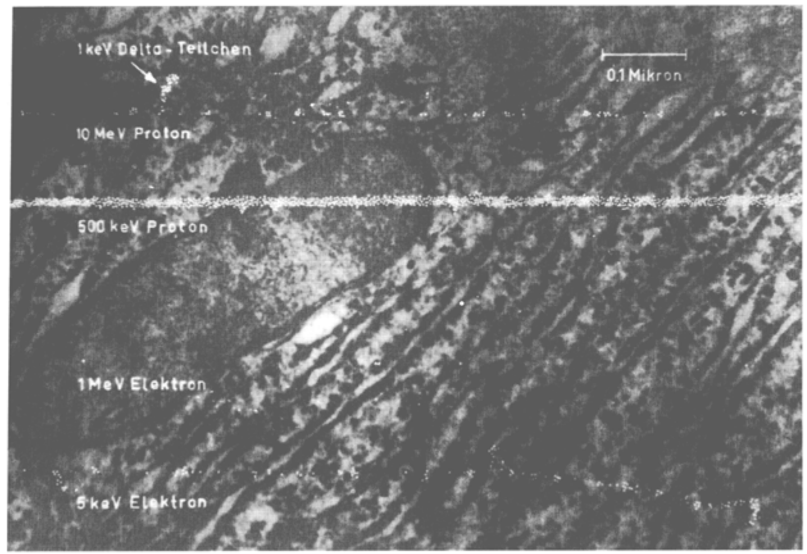
Ionization Density vs. Type of Radiation

10 MeV proton →

500 keV proton →

Co-60 γ-ray →

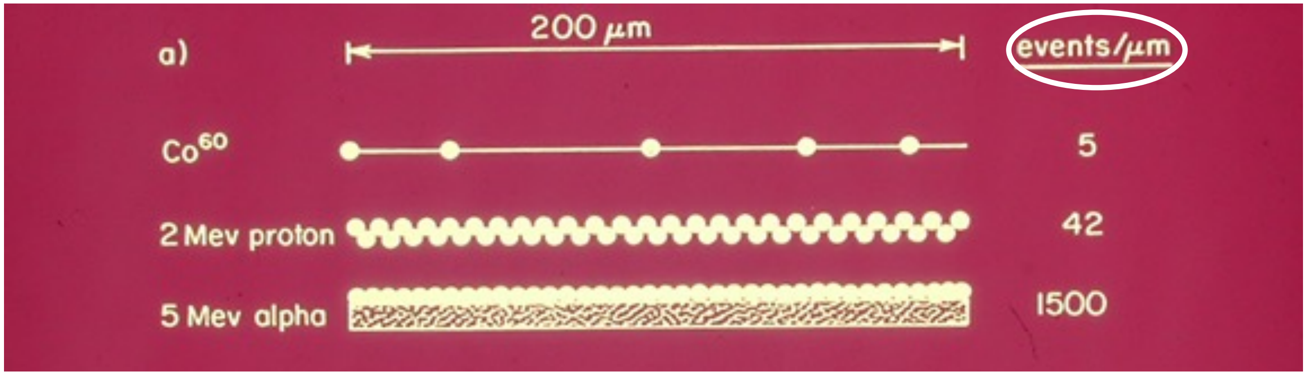
5 keV electron →

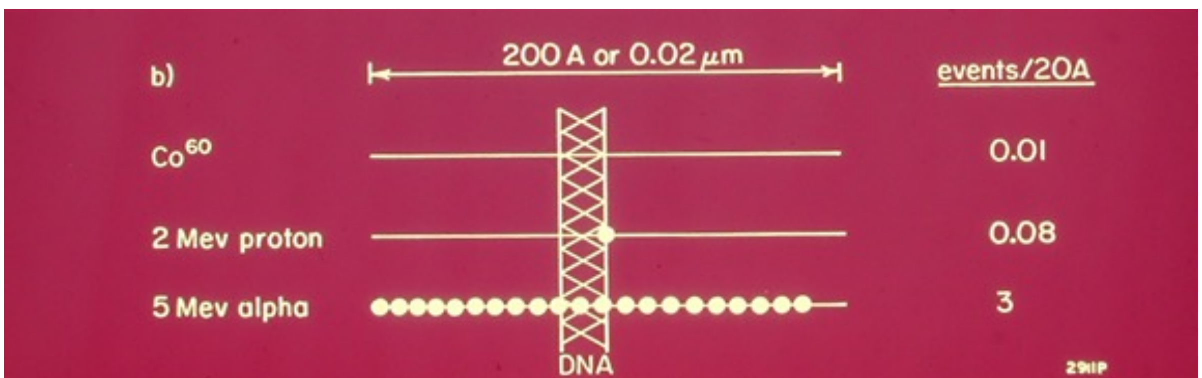


EM of human liver cell

For a given particle type, the density of ionization ↓ as the energy ↑

Density of Ionization Event





← **Dimension of DNA**

← **Much more likely to create DSB**

Definition of Linear Energy Transfer (LET)

LET (L) = *dE/dl*

dE is the ***average*** energy ***locally*** imparted to the medium by a charged particle of specified energy in traversing a distance of ***dl***

Thus, LET is the energy transferred per unit length of the track, and has unit **keV/μm**

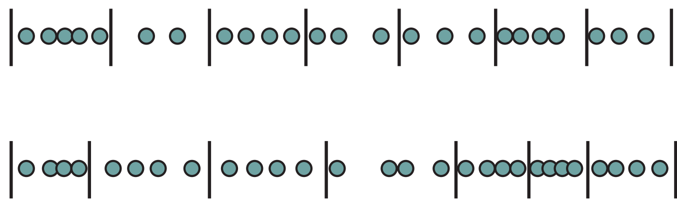
This is merely ***an average quantity*** – even for a specific type of radiation, the energy per unit length of track varies over a wide range

Track Average vs. Energy Average

LET = Average energy deposited per unit length of track (keV/μm)

Track average — Equal track length

Energy average — Equal energy increments



X-rays/gamma-rays

2 methods yield similar results

Neutron

2 methods yield different results
Example: for a 14-MeV neutron, track average = 12 keV/μm; energy average = 100 keV/μm

The biologic properties of neutrons tend to correlate best with the energy average

Typical LET Values

1.1 MeV Co-60 γ rays has lower biological effective by ~ 10%

TABLE 7.1 Typical Linear Energy Transfer Values

Radiation	Linear Energy Transfer, keV/μm		
Cobalt-60 γ-rays	—	0.2	—
250-kV x-rays	—	2.0	—
10-MeV protons	—	4.7	—
150-MeV proton	—	0.5	—
	Track average	—	Energy average
14-MeV neutrons	12	—	100
2.5-MeV α-particles	—	166	—
2-GeV Fe ions (space radiation)	—	1,000	—

High LET radiations are **qualitatively** different from low LET radiation

Note again that for a given particle type, the density of ionization ↓ as the energy ↑, and therefore the its biologic effectiveness

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- **Relative Biologic Effectiveness (RBE)**
- RBE As a Function of LET
- The Oxygen Effect and LET
- Radiation Weighting Factor (W_R)
- Summary

Relative Biologic Effectiveness (RBE)

$$RBE = \frac{\text{Dose of a standard radiation}}{\text{Dose of the test radiation}} = \frac{D_{250}}{D_r}$$

to produce ***the same biological effect*** where the "standard radiation" is usually orthovoltage x-rays (~ 250 kVp)

RBE – Example

Example: Groups of plants are exposed to x-rays or neutrons.

Biological Endpoints: death of half of the plants (also known as LD_{50}, or mean lethal dose)

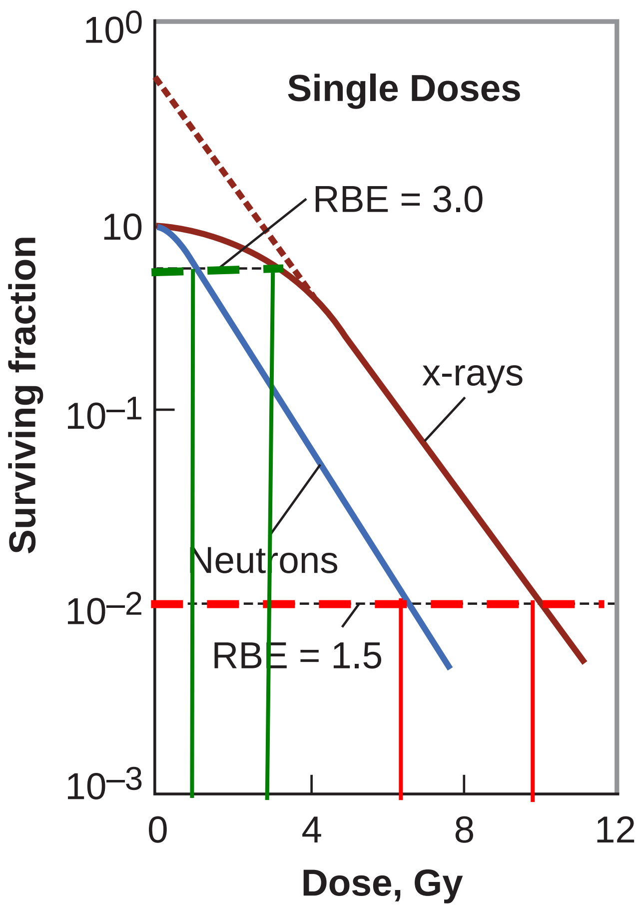
If 250 kVp is used, the dose needed to kill half of the plants = 6 Gy, i.e., D_{250} = 6 Gy

If neutron is used, the dose needed to kill half of the plants = 4 Gy, i.e., D_r = 4 Gy

Then,

$$\mathbf{RBE_{neutron} = 6\ Gy/4Gy = 1.5}$$

RBE – Single Doses

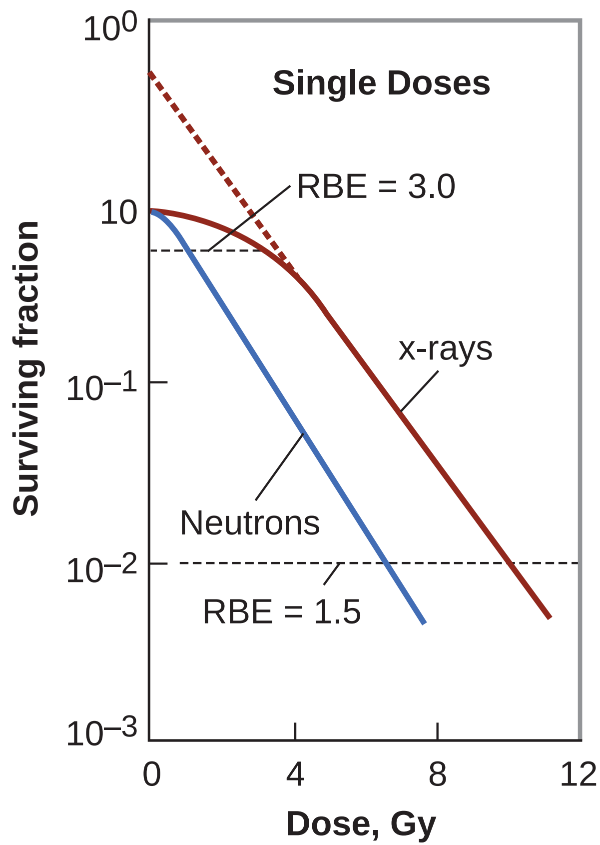


Biological endpoint: SF = 0.6
RBE = 3 Gy/1 Gy = 3.0

RBE depends on the biological endpoints chosen, and therefore the **doses**

Biological endpoint: SF = 0.01
RBE = 10 Gy /6.6 Gy = 1.5

RBE – Single Doses



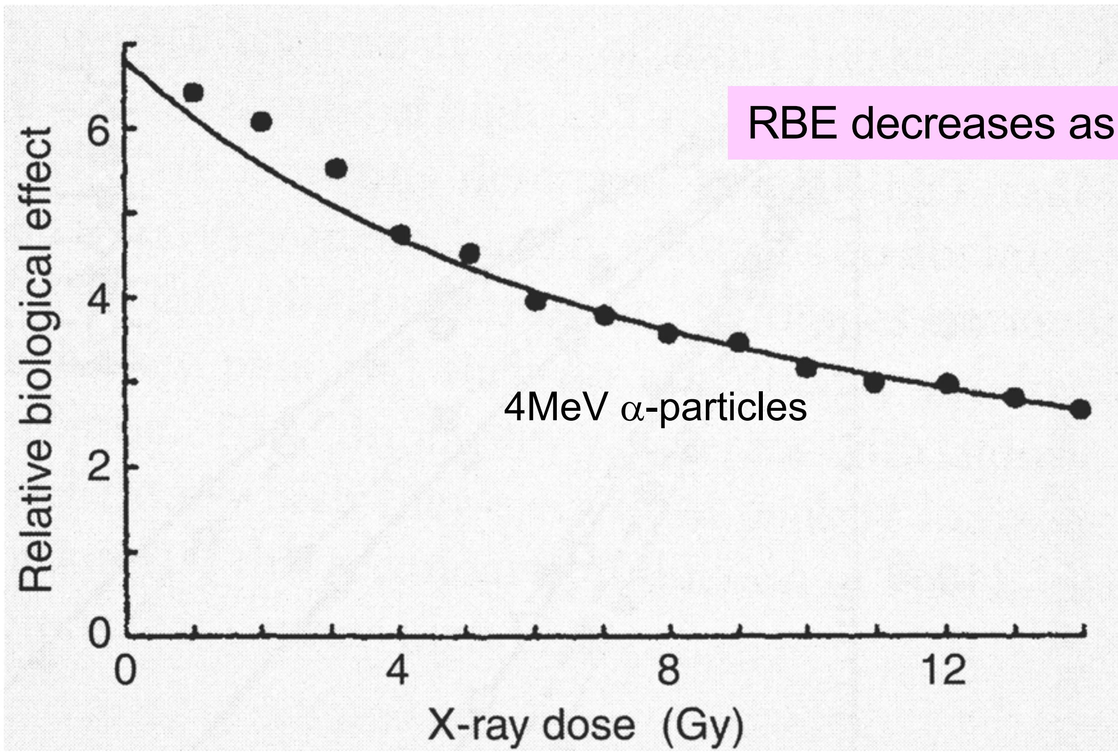
RBE is not a unique value
It varies with the biological endpoints
(and therefore the dose)

This is a result of the different shapes of the survival curves

X-rays has a large initial shoulder
Neutron has a much smaller initial shoulder

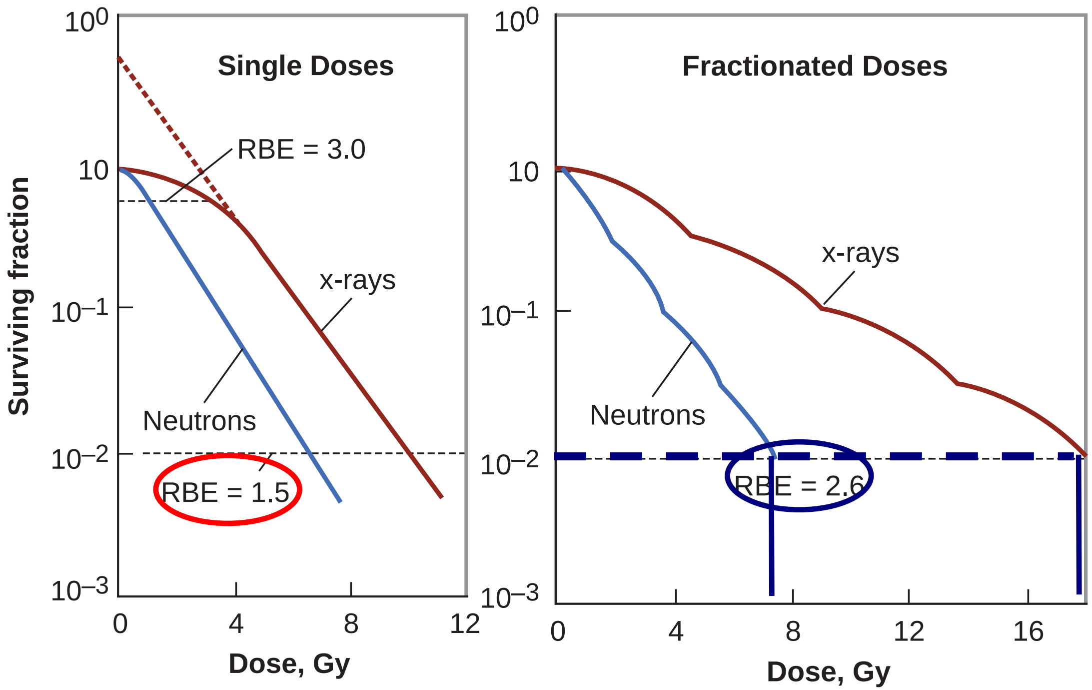
In general, RBE of neutron ↑ as dose ↓, approaching a limiting value that is the ratio of the initial slopes of the x-ray and neutron survival curves

RBE as a Function of Dose



RBE decreases as dose increases

RBE and Fractionated Dose, Dose Rates

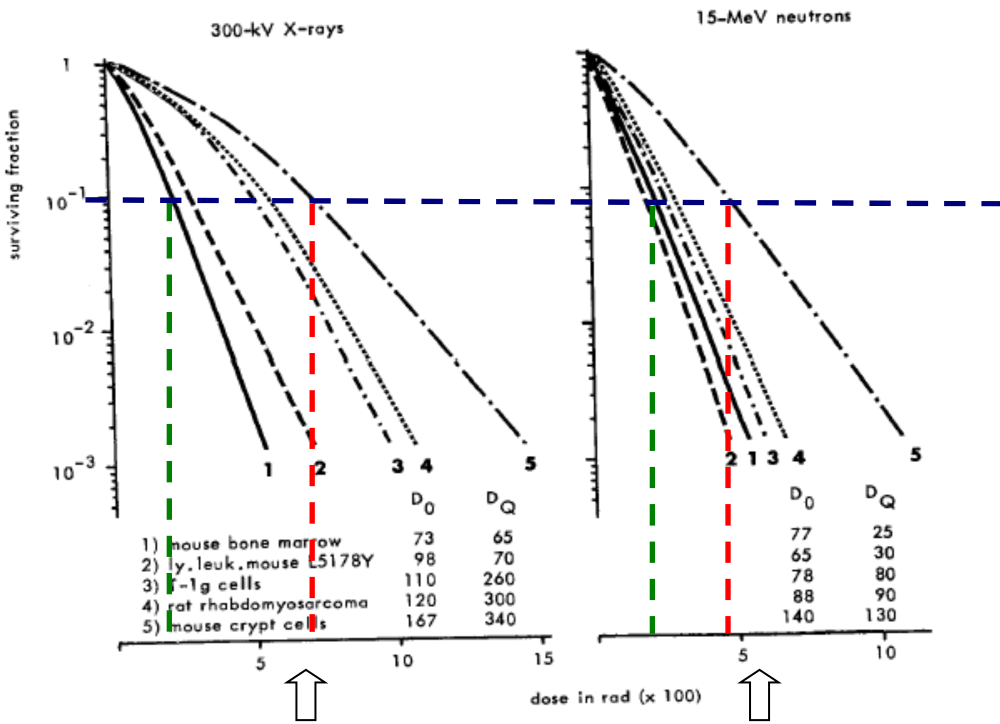


RBE is larger for a fractionated regimen than for a single exposure

This is a direct consequence of the shoulder being repeated for each dose fraction

Same is true for exposure to **continuous LDR irradiation** Recall that continuous LDR irradiation may be considered to be an infinite number of **infinitely small fractions**

RBE for Different Cells and Tissues



Biological endpoint: SF of 0.1

Mouse crypt cell
RBE = 7 Gy/4.5 Gy = 1.5

Mouse bone marrow cells
RBE = 2 Gy/2Gy = 1.0

Greater variation in width of shoulder

Less variation in width of shoulder

RBE Dependence on the Type of Cell Irradiated

- In general, cells which exhibit large shoulders in their survival curves have high neutron RBEs
- Conversely, cells with little, if any, shoulder will have low neutron RBEs
- But there are exceptions due to the different interaction mechanisms between low- and high-LET radiations

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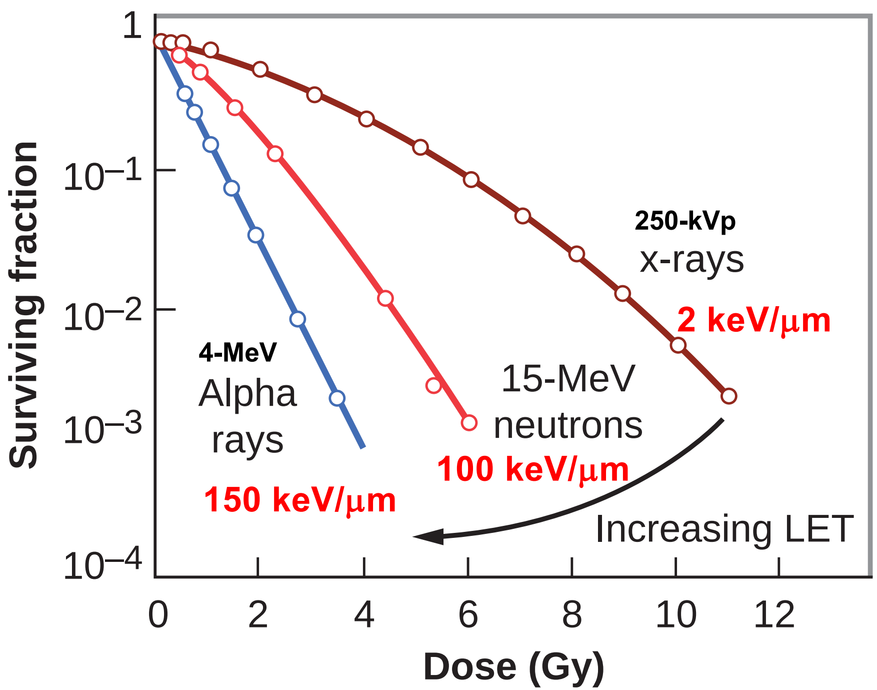
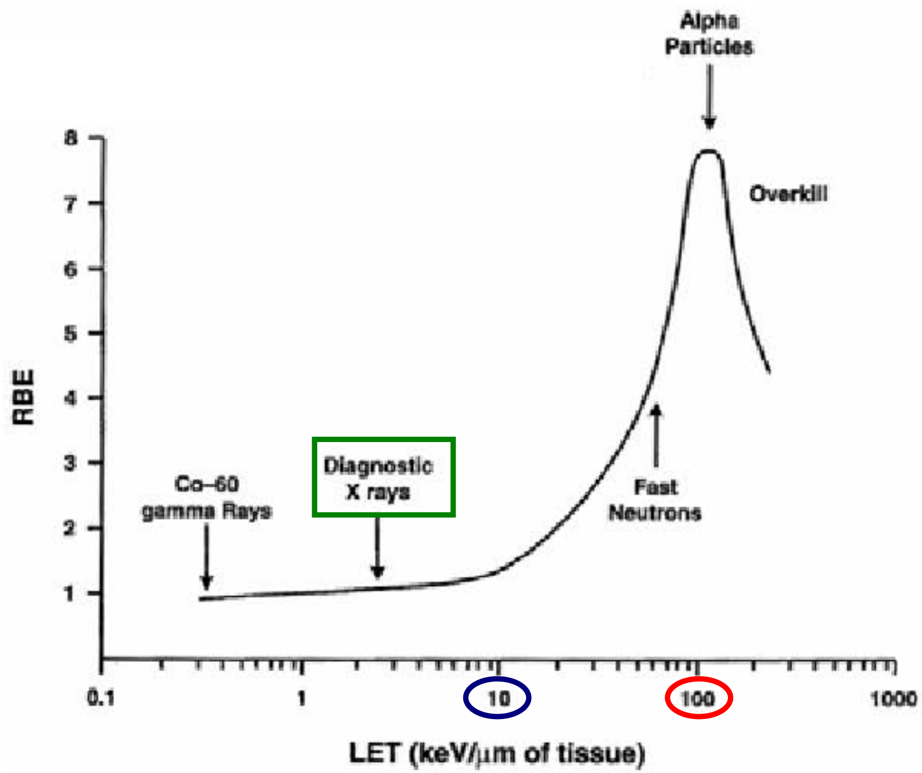
Survival Curves for X-rays, Neutrons, and α-Rays



With increasing LET
- Curve becomes steeper
- Shoulder becomes smaller

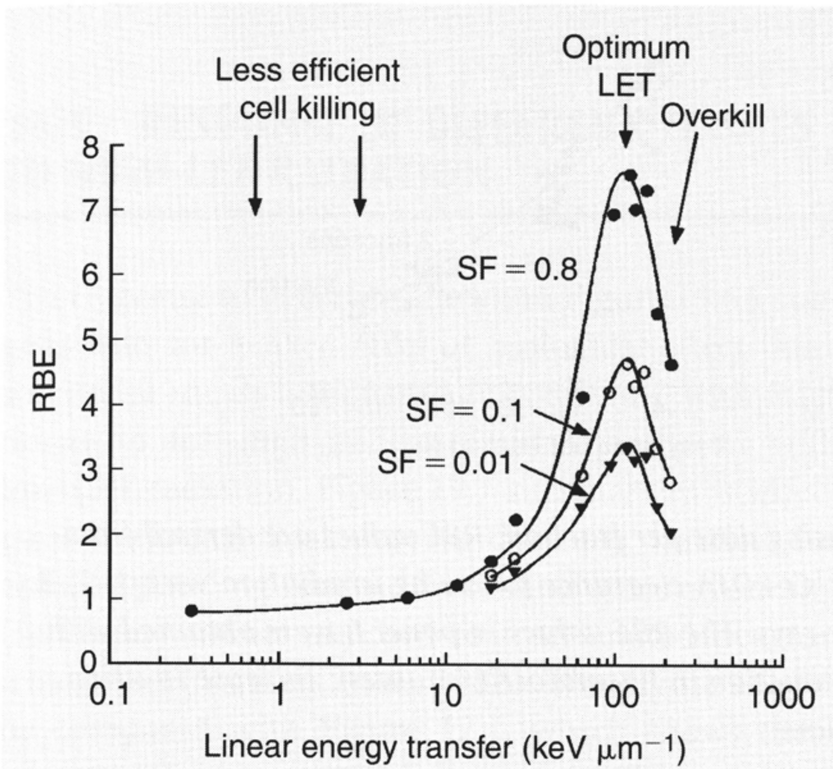
At high LET:
$SF = e^{-\alpha D}$

RBE as a Function of LET



As LET increases, RBE increases until reach a max at LET of **100 keV/μm** then it falls

RBE as a Function of LET

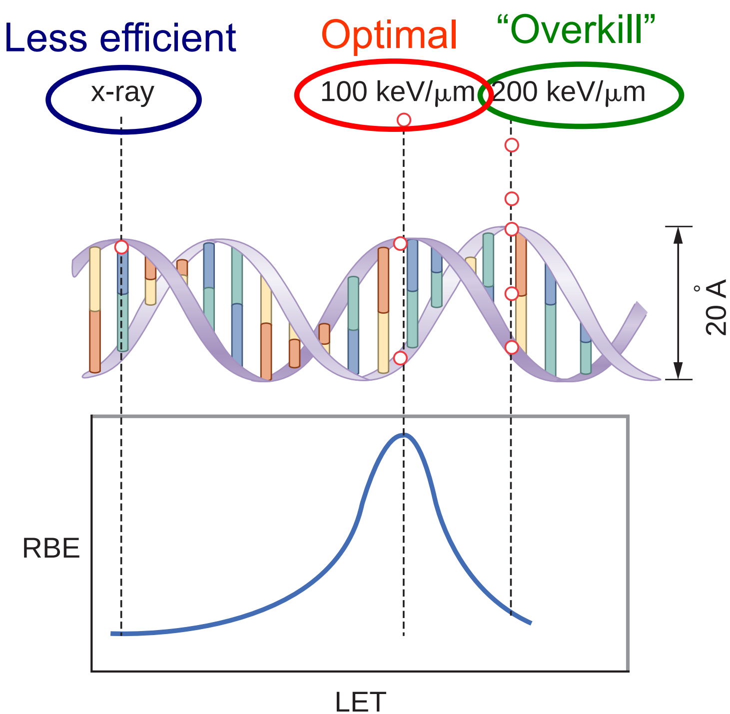


RBE varies with LET in much the same way regardless of the level of survival fraction (hence dose)

RBE reaches a peak at LET of ~ 100 keV/μm in a wide range of mammalian cells, from mouse to human

This is also the case when a different biologic endpoint, mutation, is assessed (which, like cell killing, is due to DNA damage)

The "Overkill" Effect



For more sparsely ionizing radiation, the likelihood of a single track causing a DSB is low

At LET of 100 keV/μm, the average separation b/w ionizing events coincides with the diameter of the DNA double helix (~ 2 nm), thus the highest probability of producing a DSB from a single track

For more densely ionizing radiation, though DSB is readily produced, much energy is "wasted". It is just effective per track, but less effective <u>per unit dose</u>

Radiation with optimal LET – neutrons of a few hundred keV, low energy protons, α-particles

Factors Affecting RBE

- RBE is a very complex quantity, and is dependent on many factors
  - Radiation quality (LET)
  - Radiation dose
  - Number of dose fractions
  - Dose rate
  - Biologic system or endpoint

Clinical Implication

Therapeutic gain factor = RBE (tumor)/RBE (normal tissue)
For high LET therapy to be successful, TGF must be greater than 1.0 (more on this later)

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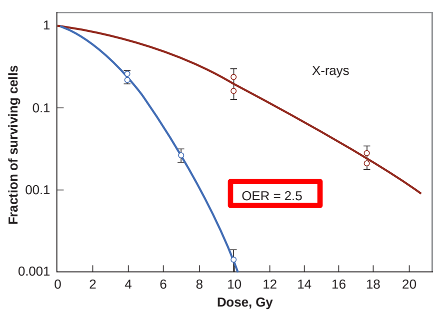
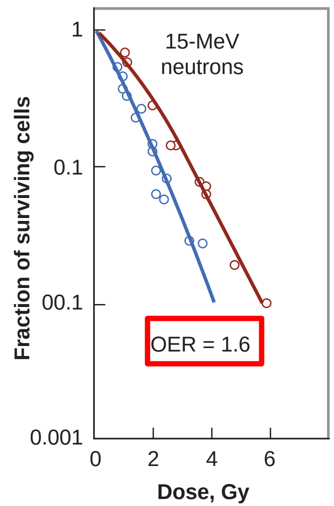
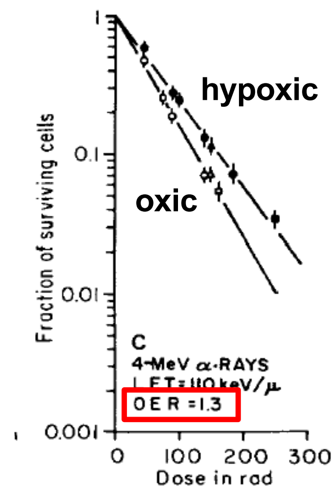
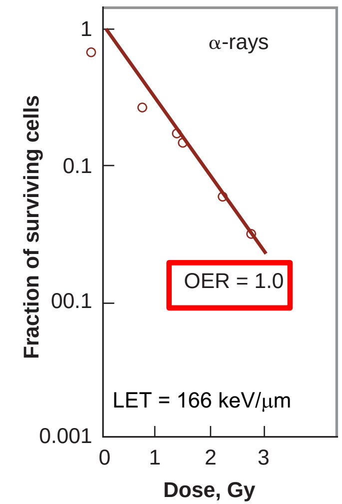
OER of High LET Radiation





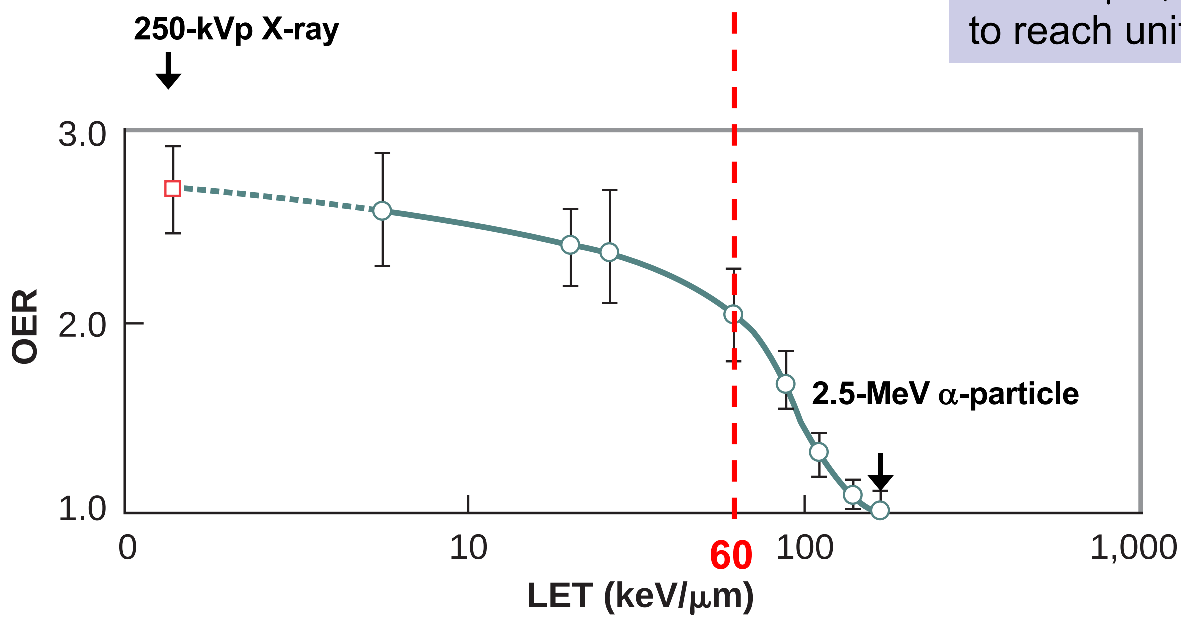




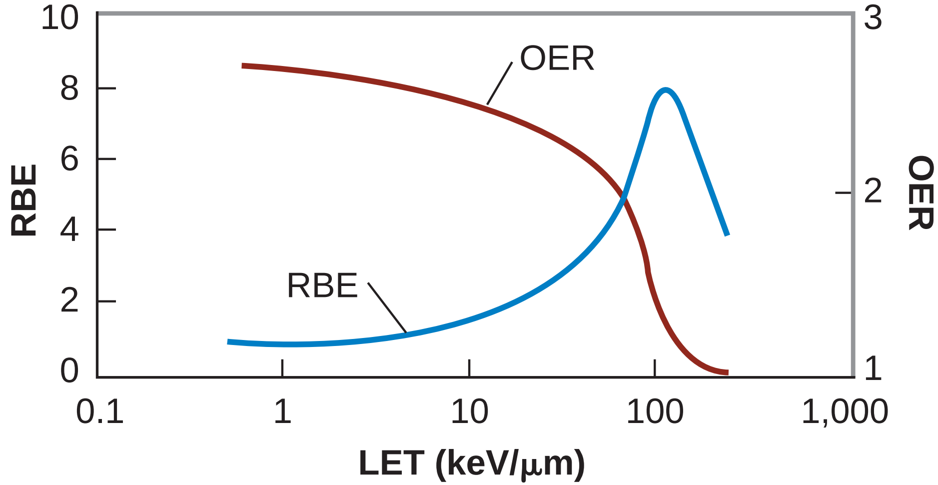
OER decreases as LET increases

OER as a Function of LET

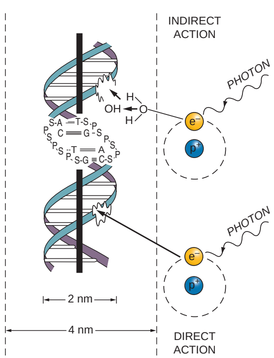
OER falls slowly until LET of 60 keV/μm, then falls rapidly to reach unity

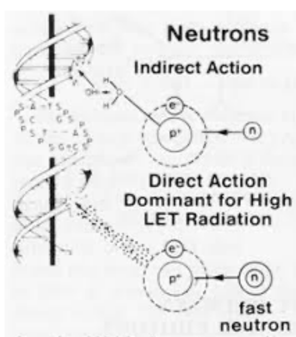


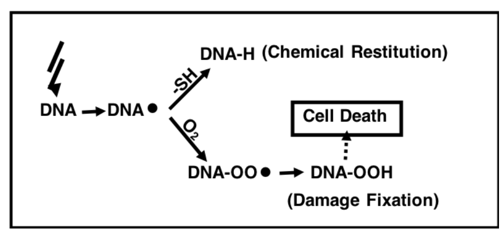
Variation of OER and RBE with LET

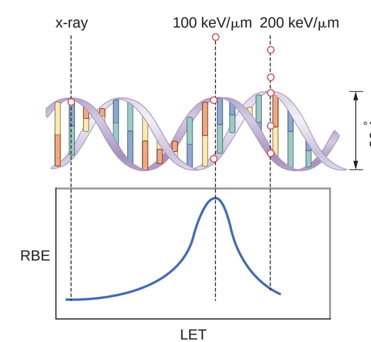


The rapid fall of OER with LET mirrors the rise of RBE









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Radiation Weighting Factor

- RBE depends on many factors
- **Radiation Weighting Factor (W_R)** was introduced as a simplified way to indicate the biological effectiveness of different radiations
- Values are chosen by International Commission on Radiological Protection (ICRP) based on
  - Experimental RBE values
  - A bias toward biologic endpoints relevant to radiation protection (e.g., carcinogenesis at low dose and low dose rate)
  - Clinical judgment

Radiation Weighting Factors

Type and Energy Range	W_R
Photons	1
Electrons	1
Protons	2
α-Particles, fission fragments, heavy nuclei	20
Neutrons	A continuous curve is recommended with a max of 20 for the most effective neutrons of about 1 MeV

2007 ICRP

Radiation Dose

- Measured
  - Either as Exposure dose in Roentgens
    - 1 R = 2.58 x 10^{-4} C/kg air : (87.33 x 10^{-4} J/kg air)
  - Or as Absorbed dose in Gray (Gy)
    - 1 Gy = 1 J/kg (=100rad). 1 cGy = 1 rad
- The same dose of different radiations has different levels of biological effect
- Therefore define (radiation equivalent dose) in **Sieverts (Sv)**
    - 1Sv = 1 Gy equivalent: 1 rem = 1 rad equivalent

Equivalent Dose

Absorbed Dose expressed in Gray (Gy)

1 Gy = 1J/kg

1 Gy = 100 rads (cGy)

Equivalent dose = absorbed dose x W_R

Equivalent Dose expressed in Sievert (Sv)

1 Sv = 100 rem (1,000 mSv)

In terms of biological effectiveness

1 Gy of neutron ≠ 1 Gy of x-ray

1 Sv of neutron = 1 Sv of x-ray

Review Questions

Question 1

The energy average LET (in KeV/μm) for 14 MeV neutrons is approximately:

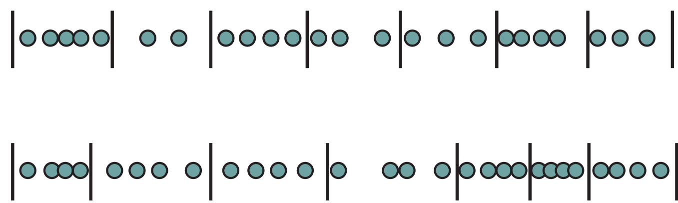
A. 1
B. 10
C. 25
D. 100
E. 250

Track Average vs. Energy Average

LET = Average energy deposited per unit length of track (keV/μm)

Track average

Energy average



Equal track length

Equal energy increments

X-rays/gamma-rays

2 methods yield similar results

Neutron

2 methods yield different results
Example: for a 14-MeV neutron, track average = 12 keV/μm; energy average = 100 keV/μm

The biologic properties of neutrons tend to correlate best with the energy average

Question 2

As the energy of a particulate type of radiation increases, the LET tends to:

A. increase
B. decrease
C. first increase and then decrease
D. first decrease and then increase
E. remain unchanged

Definition of Linear Energy Transfer (LET)

LET (L) = *dE/dl*

dE is the ***average*** energy ***locally*** imparted to the medium by a charged particle of specified energy in traversing a distance of ***dl***

Thus, LET is the energy transferred per unit length of the track, and has unit **keV/μm**

This is merely ***an average quantity*** – even for a specific type of radiation, the energy per unit length of track varies over a wide range

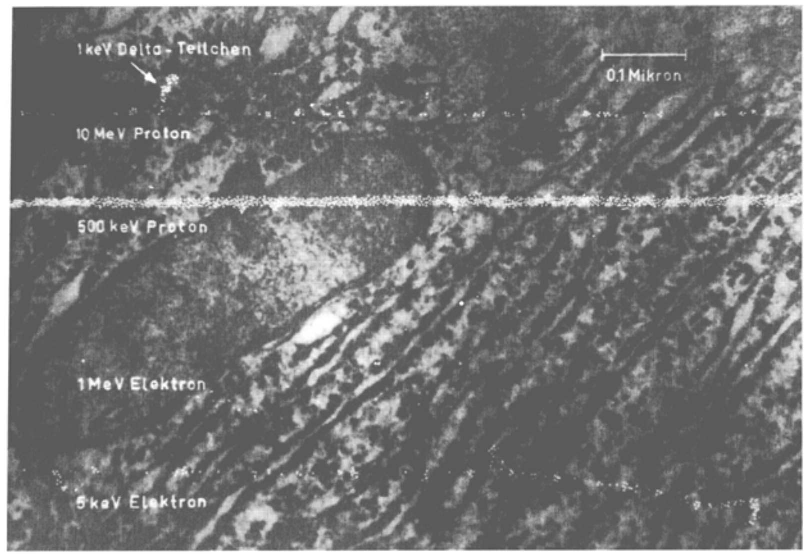
Ionization Density vs. Type of Radiation

10 MeV proton →

500 keV proton →

Co-60 γ-ray →

5 keV electron →



EM of human liver cell

For a given particle type, the density of ionization ↓ as the energy ↑

Question 3

Which of the following statements concerning RBE is CORRECT? The RBE:

A. is lower for neutrons than for protons over the therapeutic energy range
B. for high LET particles is greater for hypoxic cells than for oxygenated cells of the same type
C. for carbon ions is diminished when delivered in several fractions rather than as a single dose
D. for heavy charged particles is greatest at the beginning of the particle tracks

Question 3

Answer: B

The RBE for high LET particles is greater for hypoxic cells than for well-oxygenated cells of the same type because there is little or no oxygen effect for high LET radiation.

The RBE is greater for neutrons than it is for protons in the therapeutic energy range because the high energy protons used in radiotherapy are of a relatively low LET and therefore possess an RBE of approximately 1.1.

The RBE for carbon ions, or any other type of high LET radiation, is greater for a fractionated irradiation compared with an acute exposure because of the substantial sparing exhibited with the reference X-rays with fractionation.

The RBE for charged particles is low at the beginning of the particle track and greatest near the end of the track, in the Bragg peak region. RBE does show a fractionation dependence; it decreases with increasing fraction size.

Question 4

Concerning cellular radiation response and LET, which one of the following statements is TRUE?

A. RBE reaches a maximum for radiations with LET values in the range of ~ 25 keV/μm
B. High-LET radiations tend to produce exponential survival curves
C. High-LET radiations yield survival curves with higher D_0 values than low-LET radiations
D. Oxygen plays a greater role as a radiation sensitizer for high-LET compared with low-LET radiation
E. There is a greater variation in sensitivity through the cell cycle for high-LET compared with low-LET radiations

Question 5

The correct ranking of the following radiations in order of increasing LET is:

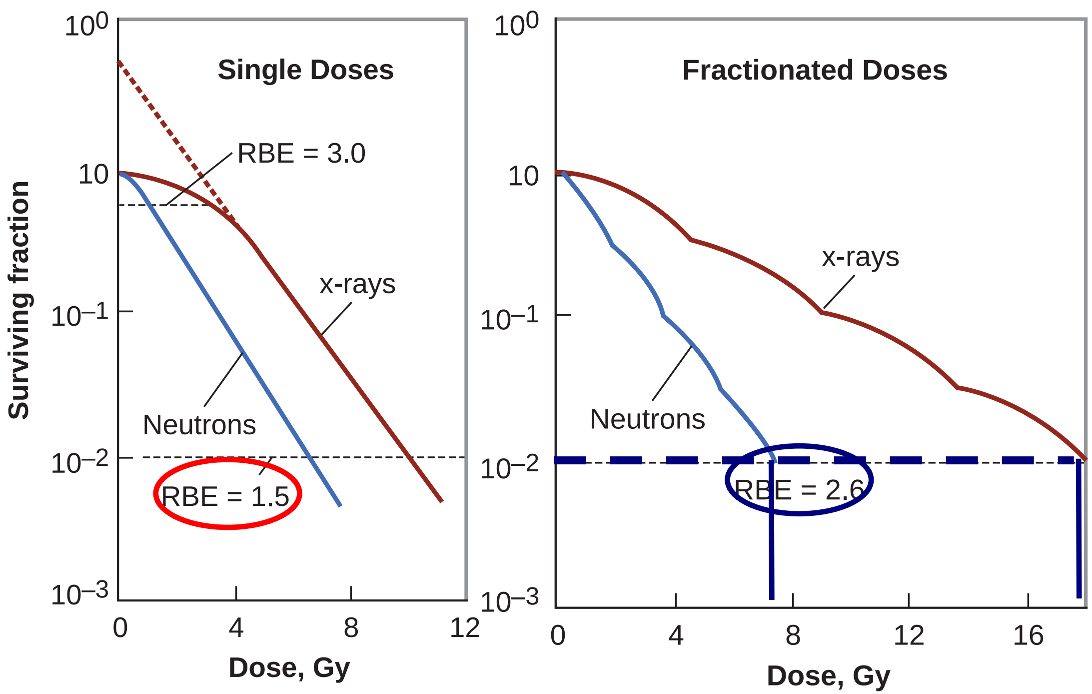
A. 50 keV X-ray, 20 MeV photons, 20 MeV alpha, 250 keV alpha
B. 20 MeV alpha, 250 keV alpha, 20 MeV photons, 50 keV X-rays
C. 250 keV alpha, 20 MeV alpha, 50 keV X-rays, 20 MeV photons
D. 20 MeV photons, 50 keV X-rays, 250 keV alpha, 20 MeV alpha
E. 20 MeV photons, 50 keV X-rays, 20 MeV alpha, 250 keV alpha

Question 6

As the time to deliver a dose of radiation increases (ex: increased number of dose fractions)

A. the RBE of neutrons increases
B. the RBE of neutrons decreases
C. LET increases
D. LET decreases

RBE and Fractionated Dose, Dose Rates



RBE is larger for a fractionated regimen than for a single exposure

This is a direct consequence of the shoulder being repeated for each dose fraction

Same is true for exposure to **continuous LDR irradiation** Recall that continuous LDR irradiation may be considered to be an infinite number of **infinitely small fractions**