Linear Energy Transfer (LET) and Relative Biological Effectiveness (RBE)

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Linear energy transfer and relative biological effectiveness

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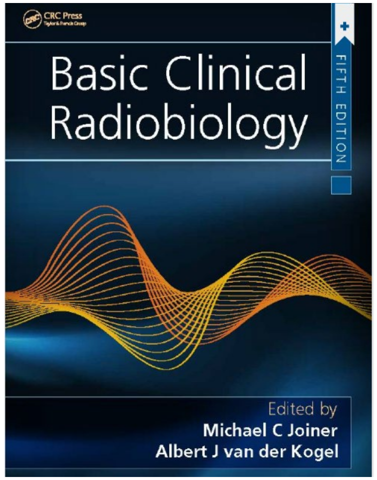

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Acknowledgments

- These slides are based on previous lectures from Dr. Richard Hill

Learning Objectives

- Clinical application of high LET radiation treatment
- Describe how energy deposition varies with charge and velocity
- Illustrate the concept of a Bragg peak
- Define LET and RBE
- Explain how LET affects the shape of the cell survival curve and effect of fractionation

Types of Radiation

Radiation	Rest Mass	Charge
Electromagnetic		
γ-rays	none	none
X-rays	none	none
Particulate		
electrons (β-rays)	0.00055 amu	-1
positrons	0.00055 amu	+1
protons (H nuclei)	1.0073 amu	+1
neutrons	1.0087 amu	none
α-particles (He nuclei)	4 amu	+2
-ve π-mesons (pions)	0.15 amu	-1
heavy ions (e.g.C, Ne, Ar)	>4 amu (depends on ion e.g. C =12)	>+ 3 (depends on ion. e.g. C = + 6)

1 amu = 1 atomic mass unit = 1.66×10^{-27} kg = 931.48 MeV.

Radiation Dose

Exposure

$$X = dQ/dm$$

where dQ is absolute value of the total charge of the ions of one sign produced in air when all the electrons liberated by photons in a volume element of air having a mass dm are completely stopped in air.

Units: 1 R = 2.58x 10-4 C /kg of air

Absorbed Dose

$$D = \frac{\mathrm{d}\bar{E}_{ab}}{\mathrm{d}m}$$

where $\mathrm{d}\bar{E}_{ab}$ is the mean energy imparted by the ionizating radiation to a mass dm of matter.

Units: 1 Gy = 1 J/kg

Energy Deposition in Tissue

- Interactions of photons and neutrons with tissue create charged particles (electrons or protons)
- Charged particles interact with other nuclei or electrons in the tissue and create a cascade of moving electrons which deposit energy each time they interact

Energy Deposited by Radiation

1) **Energy deposited by radiation**

5 Gy (lethal) = 5 J/kg = 5/4.2 cals /kg = 1.2 cals/kg

1 cal raises temperature of 1 kg of water by 10^{-3} ^{0}C

Therefore:

1) Energy in 5Gy will raise temperature of 1 kg of water by 0.0012 ^{0}C.

2) A whole body dose of 5Gy to a 70 kg person will raise temp by **0.0012^{0}C**

2) **Energy absorbed by drinking a cup of coffee**

Assume cup contains 500 cc (0.5 kg) at 51^{0}C, which drops to 37 ^{0}C in body.

Then energy absorbed is 0.5 x (51-37) x 10^{3} = 7000 cals

For a 70 kg person, temp rise is (7000/70) x 10^{-3} ^{0}C = **0.1 ^{0}C**

Conclusion: the <u>amount</u> of energy deposited is not the reason why ionizing radiation is so biologically damaging

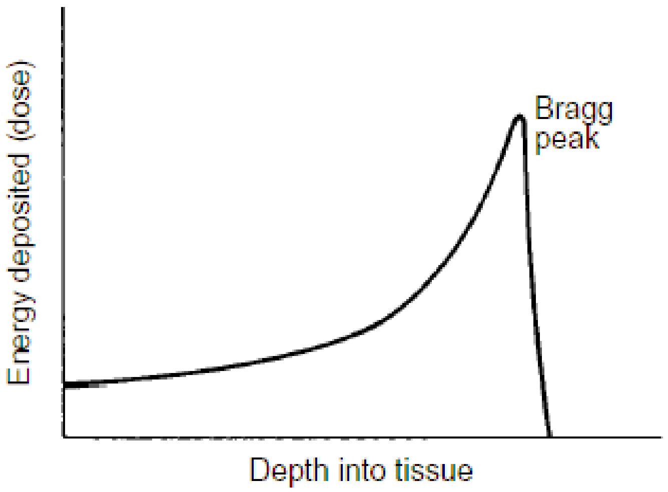
Energy Deposition of Charged Particles in Tissue

- Probability of interaction depends inversely on the velocity of the particle
- Probability of interaction depends directly on the charge z
- Velocity of a particle depends on its kinetic energy and mass

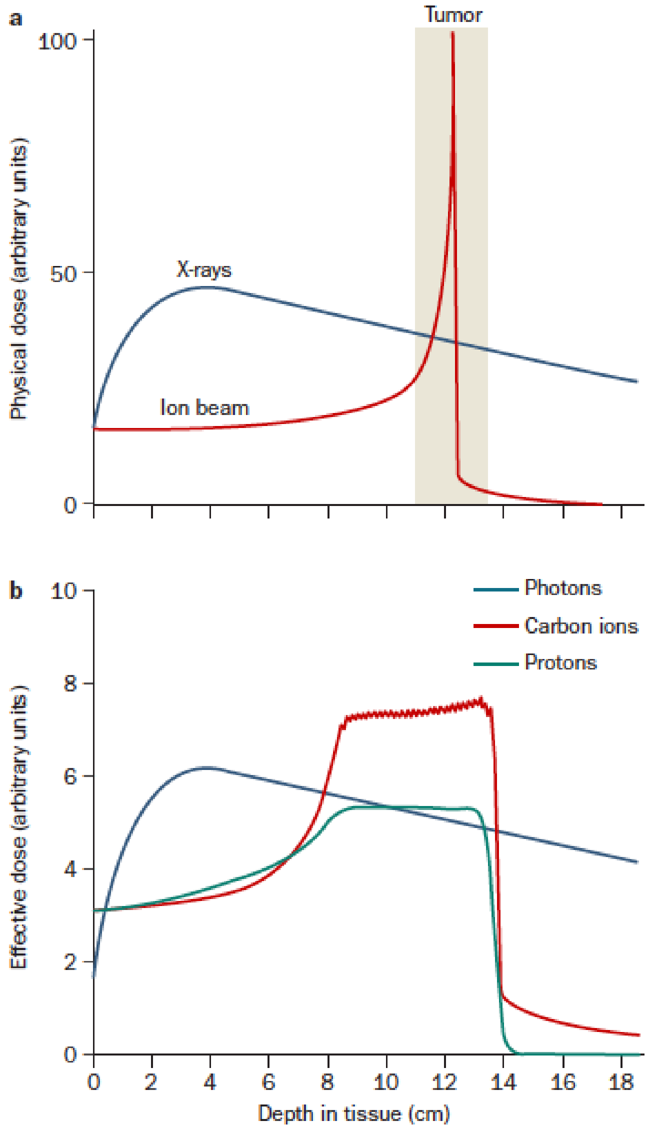
Particle	Velocity	Mass
5 MeV Electron	0.9957c	10.79 m_o
5 MeV Proton	0.1026c	1.0053 m_o
100 MeV Electron	0.999987c	192.31 m_o
100 MeV Proton	0.4283c	1.1066 m_o

Energy Deposition in Tissue

- Electrons
  - undergo many interactions with electrons in tissues
  - Incident electron is scattered, so does not travel in a straight path through tissue
  - do not exhibit a clearly visible Bragg peak
- Heavy charged particles (protons, Carbon ions etc)
  - Not deflected (as much) by interactions
  - Continue through the tissue, losing energy without much deflection of their path, until they reach their Bragg peak



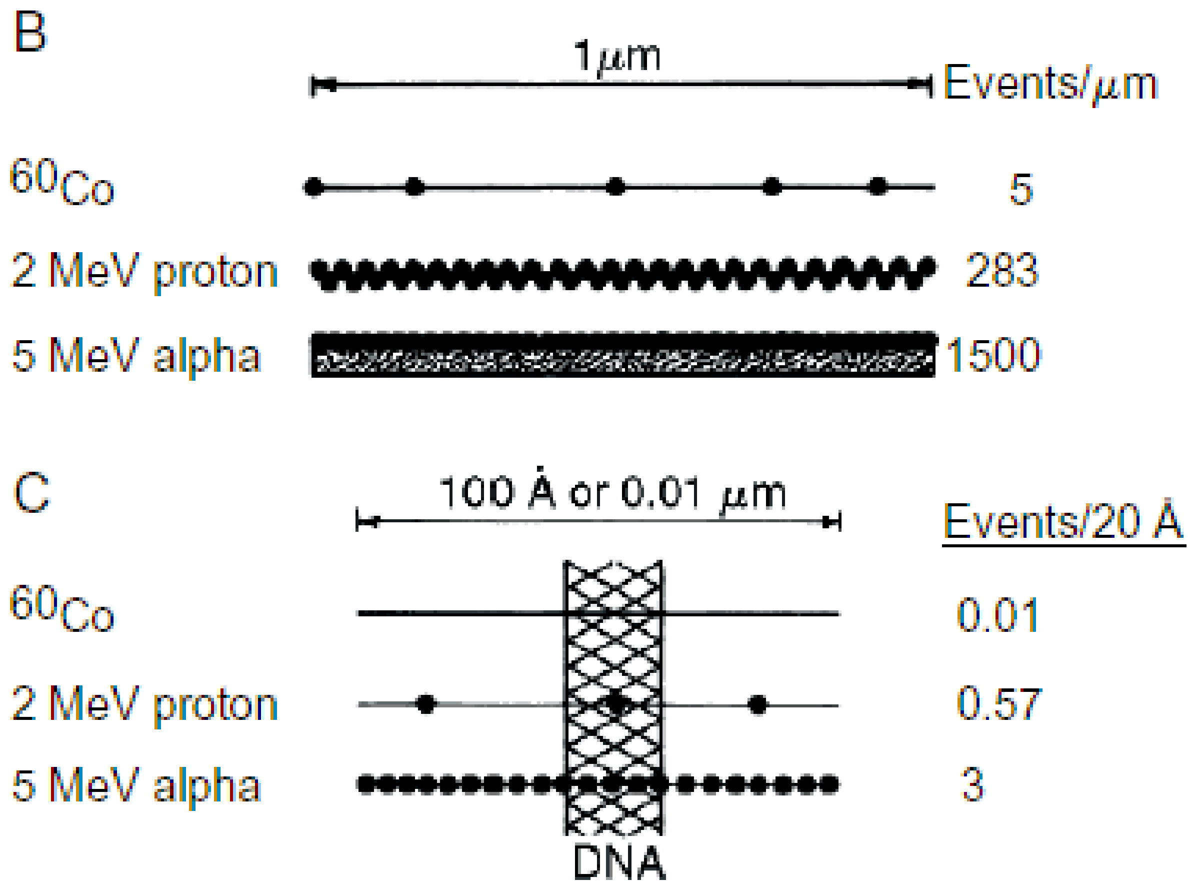
Bragg Peak



Depth dose curve for photons versus charged particles. Charged particle curves shows a pristine Bragg peak

Depth dose curve for photons versus charged particles. Charged particle curves shows a spread out Bragg peak (SOBP), which is the superposition of many Bragg peaks.

Density of Energy Loss Events



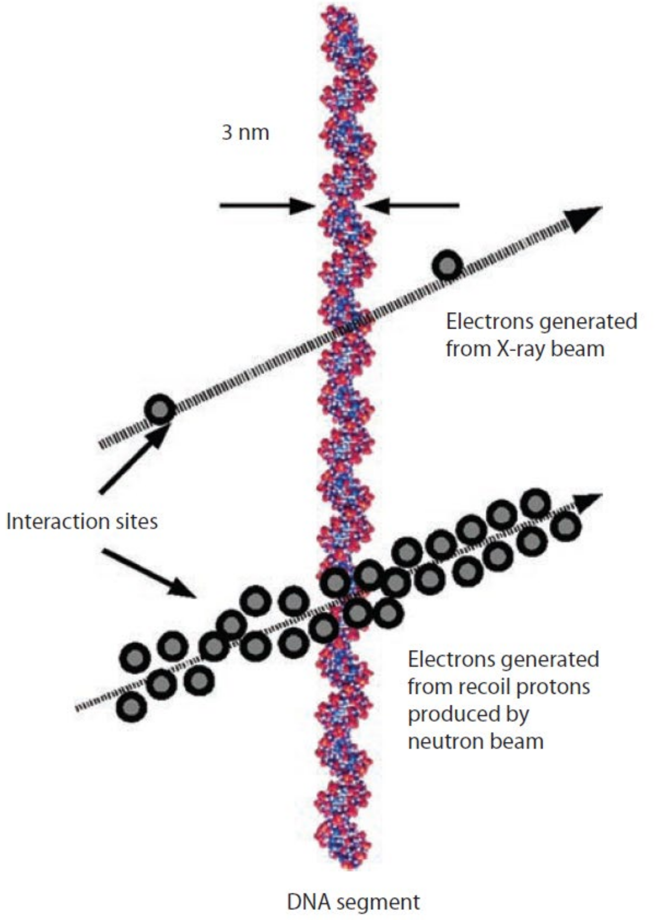


Figure 6.2 The greater DNA damage caused by the higher density of charged particles following irradiation with neutrons compared with photons.

Density of Energy Loss Events and DNA Damage

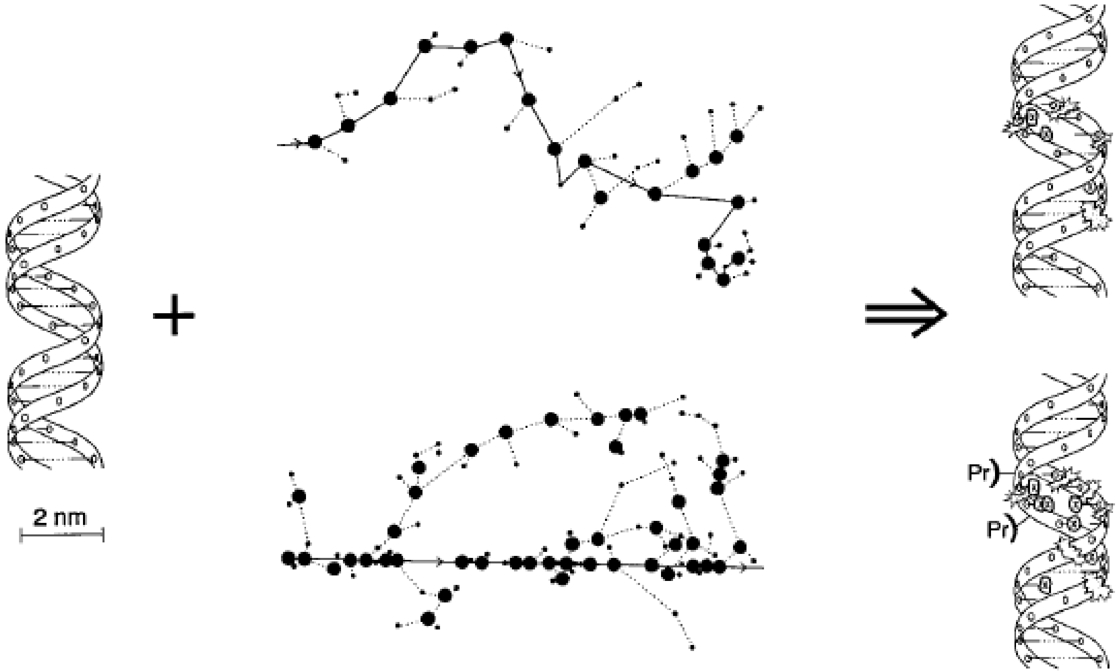


Fig. 3. Illustration of formation of complex clustered damage in DNA by direct and indirect action of radiation tracks which pass through or very close to the DNA. These short segments of Monte-Carlo simulated tracks are drawn on the same scale as the DNA and are from a low-energy electron (upper centre) and a slow α-particle (lower centre). Large dots represent ionizations and small dots excitations. (Reproduced from Goodhead, Int. J. Radiat. Biol. (1995) 65: 7-17).

Linear Energy Transfer (LET)

LET = *dE/dl*

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

Units are **keV μm^{-1}** [keV/µm]

Microdosimetry

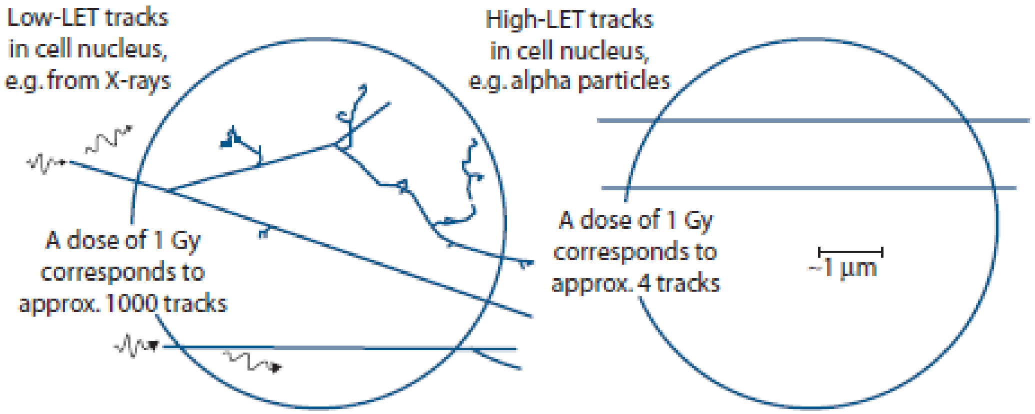


Figure 6.1 The structure of particle tracks for low-LET radiation (left) and α-particles (right). The circles indicate the typical size of mammalian cell nuclei. Note the tortuous tracks of low-energy secondary electrons, greatly magnified in this illustration. (From (5), with permission.)

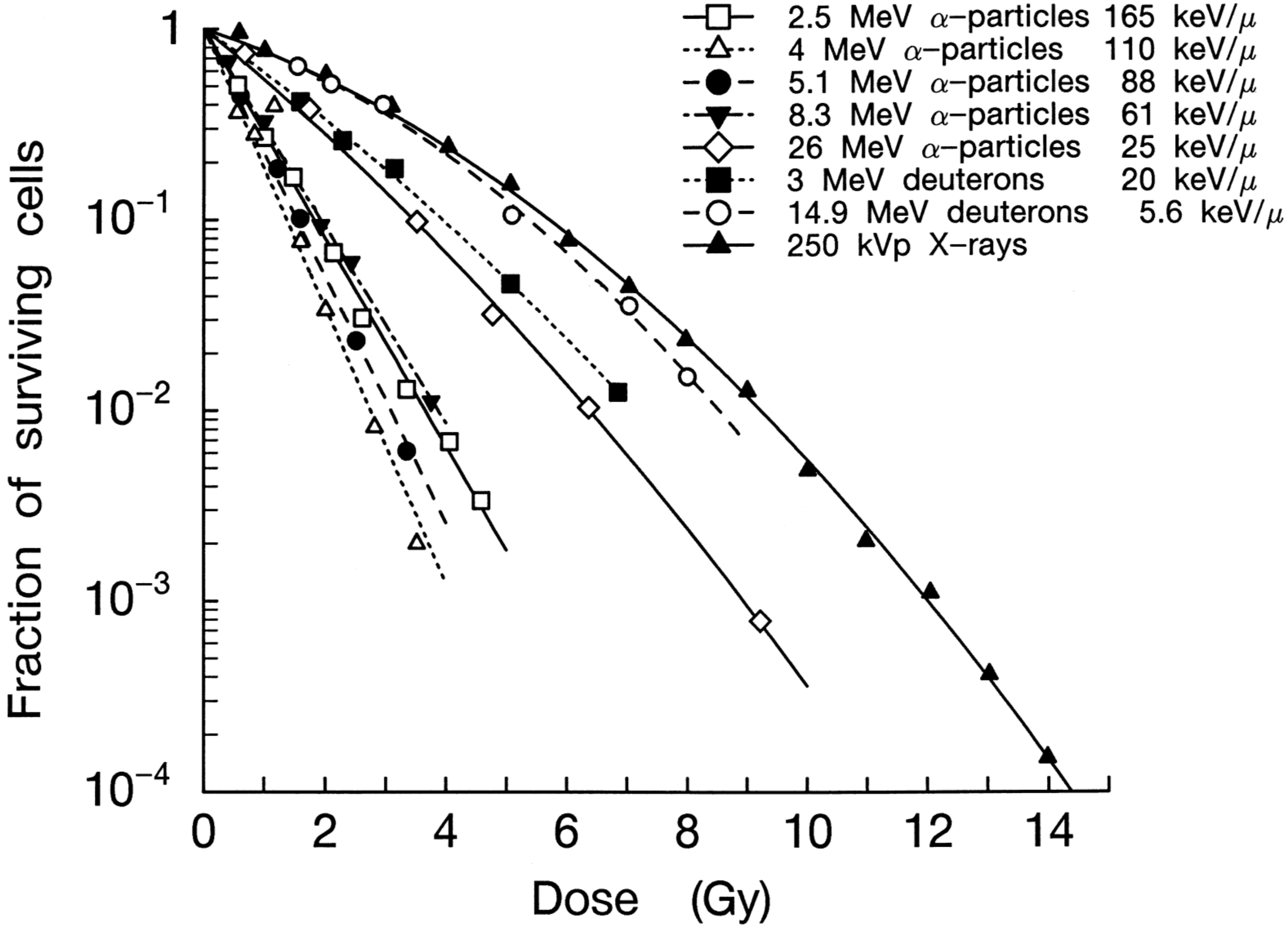
LET: Linear Energy Transfer

A measure of the average ionization density.

Typical LET Values

Radiation		LET (keV/μm)	
Cobalt-60		0.2	
250 kVp x-rays		2.0	
10 MeV protons		4.7	
150 MeV protons		0.5	
	Track Average		**Energy Average**
14 MeV neutrons	12		100
2.5 MeV α-particles		166	
2 GeV Fe ions		1,000	

Cell Survival for Different Types of Radiation



Survival of human kidney cells exposed *in vitro* to radiation of differing LET

Relative Biological Effectiveness (RBE)

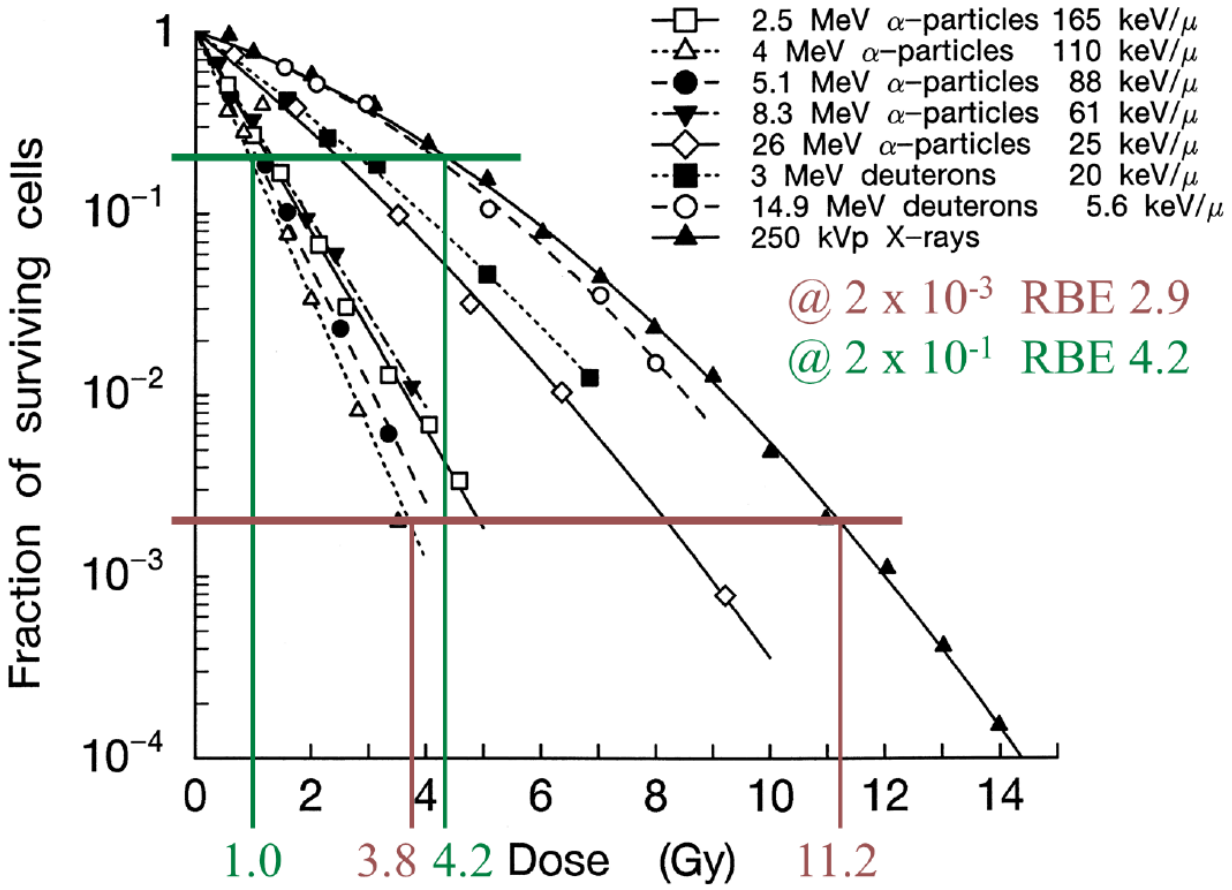
RBE is defined as:

$$\frac{Dose\ of\ Reference\ Radiation}{Dose\ of\ Test\ Radiation}$$ to produce the same biological effect

Reference Radiation: Historically 250 kVp x-rays or Co-60

RBE of Co-60 relative to 250 kVp x-rays is ~0.9

RBE Varies With Effect



RBE vs LET

Low LET Radiation

- i.e., MV photons or 250 kVp x-rays
- Inefficient cell killing

High LET Radiation

- i.e., 2 GeV Fe ions
- More dose is deposited than is needed to kill cells
- Also inefficient cell killing (per unit dose)

Optimal LET

- i.e., 4 MeV α-particles
- Produces just enough DNA DSB to kill the cell

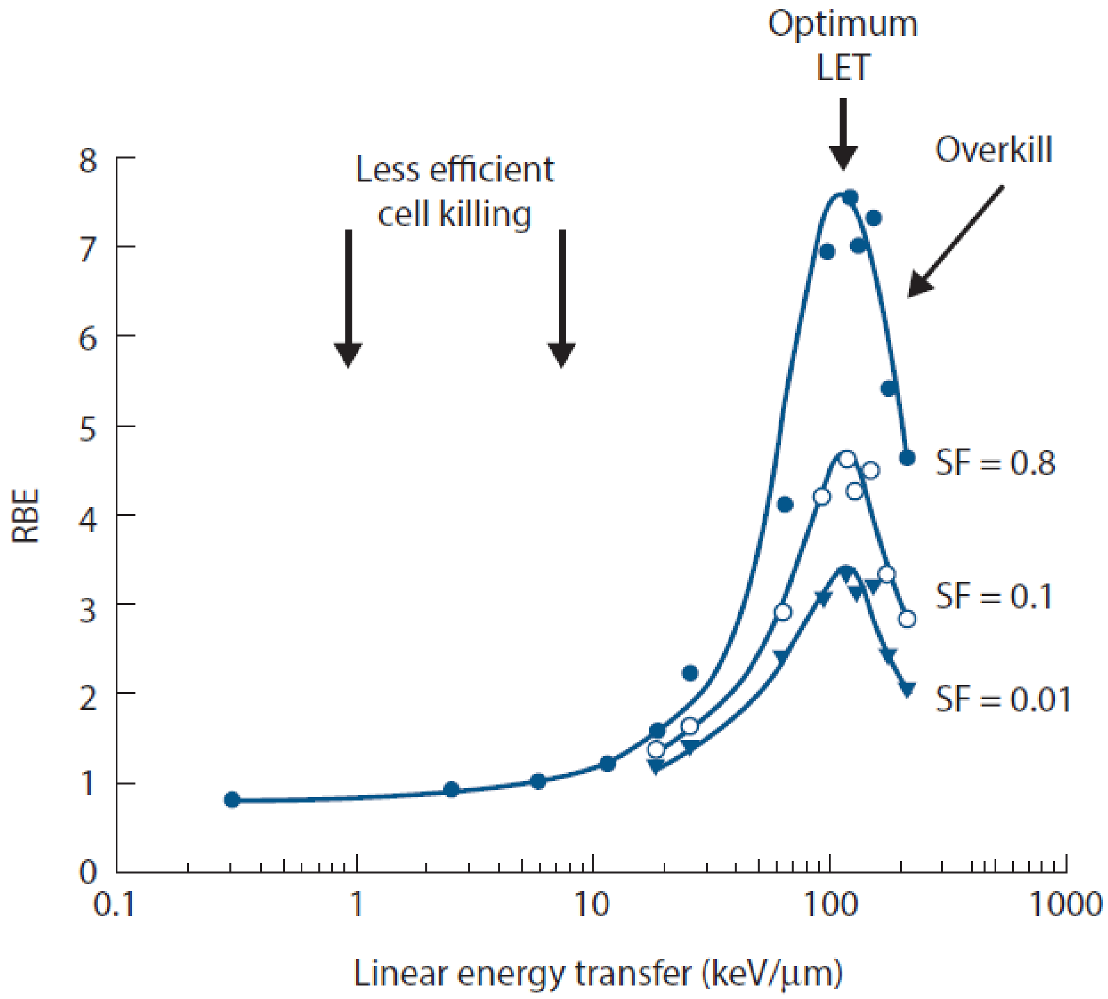


Figure 6.5 Dependence of RBE on LET and the phenomenon of overkill by very high LET radiations. RBE has been calculated from Figure 6.3 at cell surviving fraction (SF) levels of 0.8, 0.1 and 0.01. (From (1), with permission.)

RBE vs LET for Carbon Ions

Weyrather et al IJRB 1999

- Radioresistant and radiosensitive cells
- Shift of the RBE peak to LET values between 150-200 keV/µm
- Increase in RBE correlated with repair capacity
- Greatest benefit of high LET radiation would be in radioresistant tumors with a high repair capacity

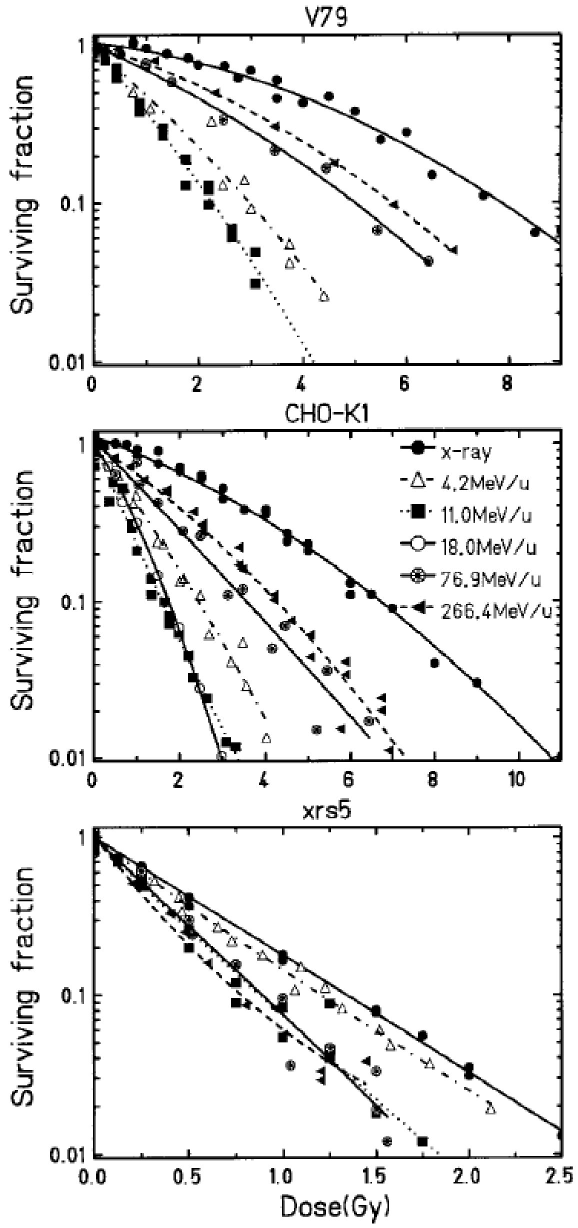


Figure 3. Survival as function of dose for x-rays and carbon ions at five representative energies.

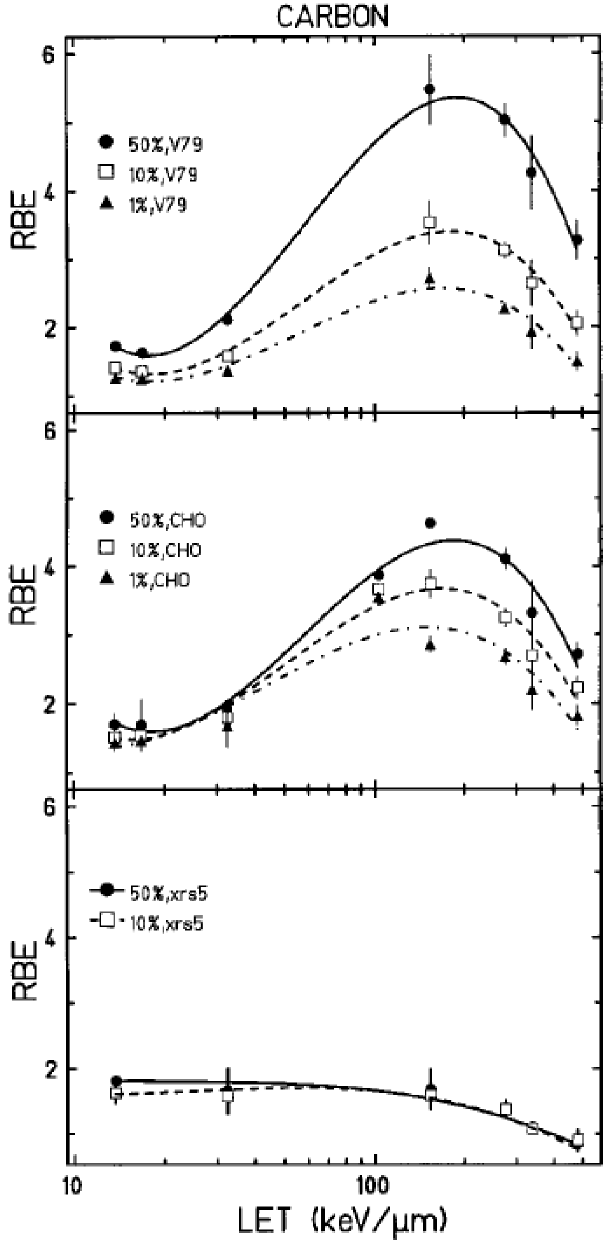
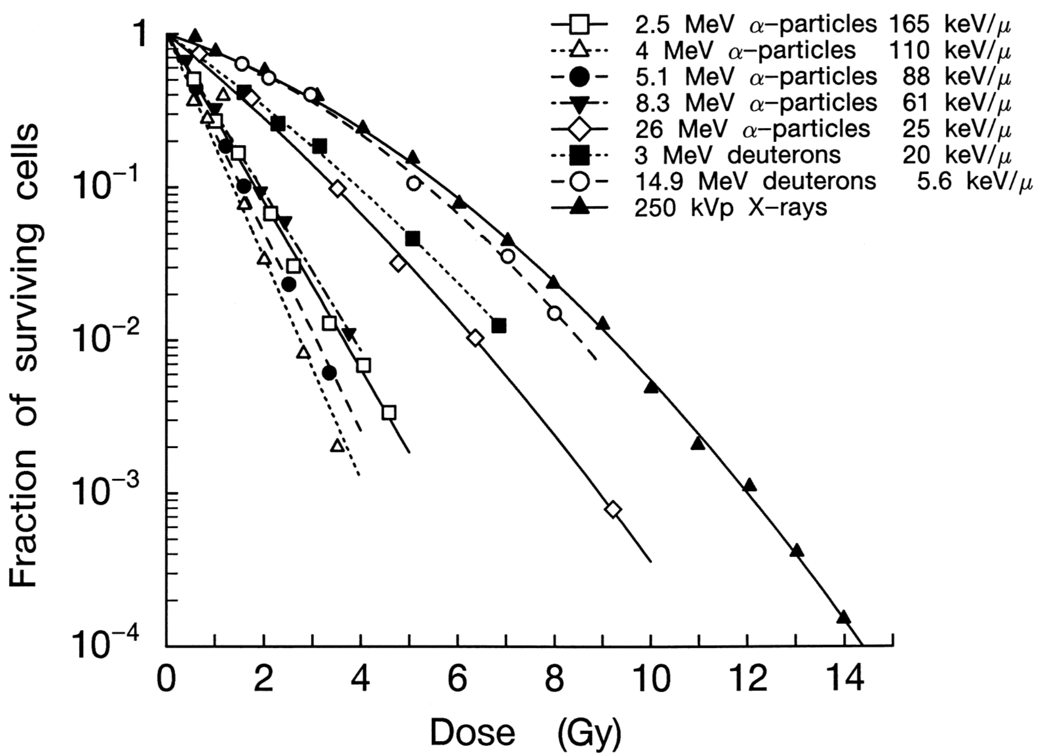


Figure 4. RBE at a survival level of 50%, 10% and 1% for V79, CHO-K1 and xrs5 cells.

Dependence of RBE on Cell Type

- Cells which have large shoulders in their x-ray survival curves will have high RBEs
- Cells with little/no shoulder will have low RBEs
- There are exceptions to this, due to different interactions between low- and high-LET radiations, e.g. cell cycle effect



reference radiation is more curved (has a shoulder) at lower doses

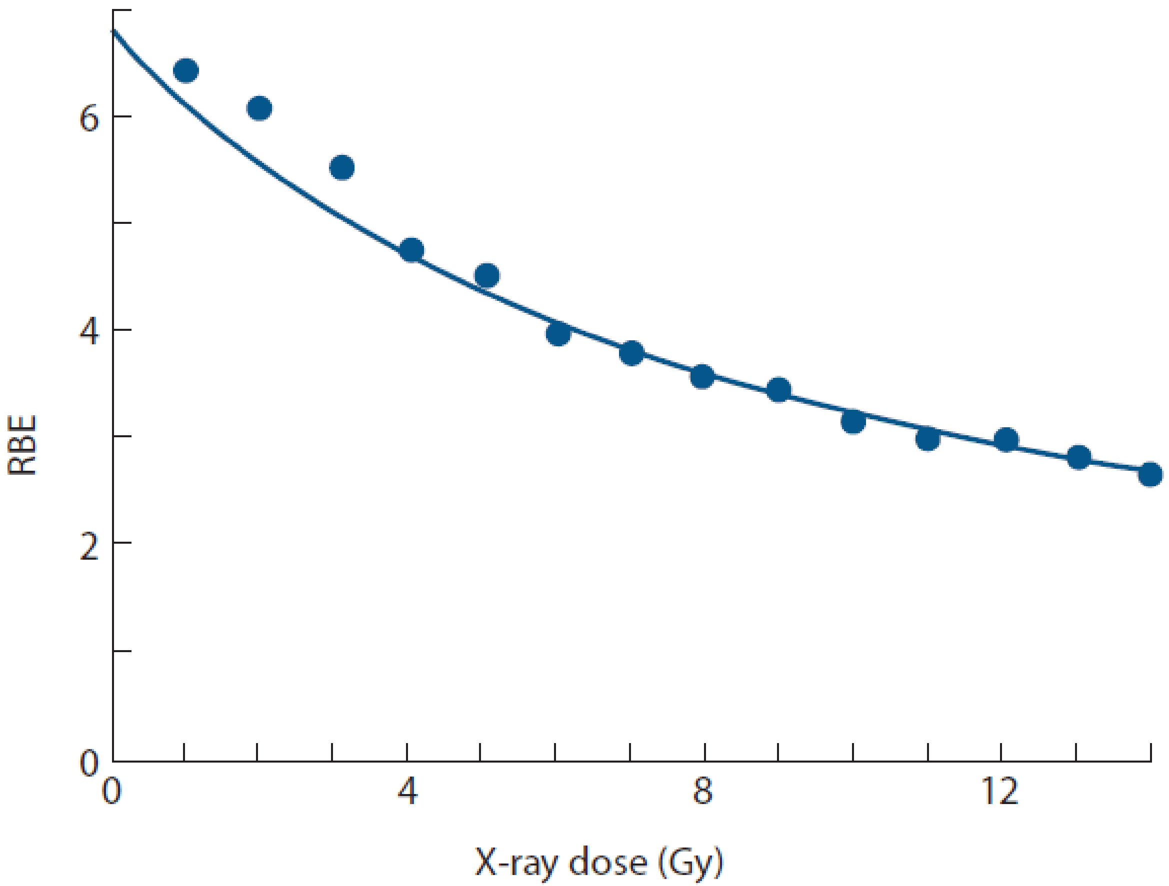
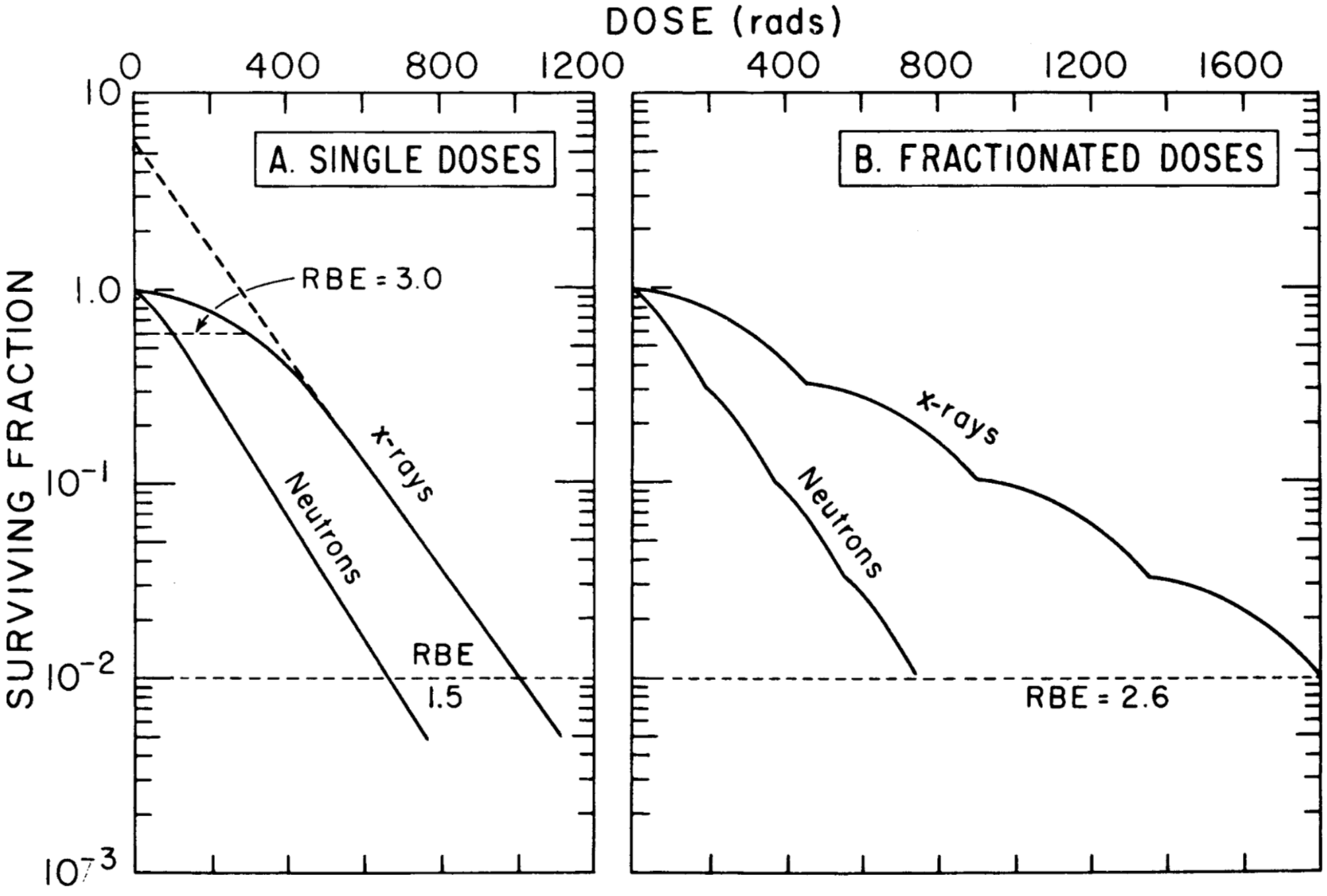


Figure 6.7 RBE of 4 MeV α-particles increases with decreasing dose for cell lines irradiated *in vitro*. RBE values were calculated from the cell survival data shown in Figure 6.4. The full line is calculated as described in the text.

Effect of Dose and Dose per fraction on RBE

At low doses (and low doses per fraction), the RBE will be higher since the dose in the numerator of the RBE equation will be relatively higher at low doses than that in the denominator because of repair at low doses with the low-LET standard radiation



$$\text{RBE} = \frac{\textit{Dose of Reference Radiation}}{\textit{Dose of Test Radiation}}$$

to produce the same biological effect

RBE and Fraction size

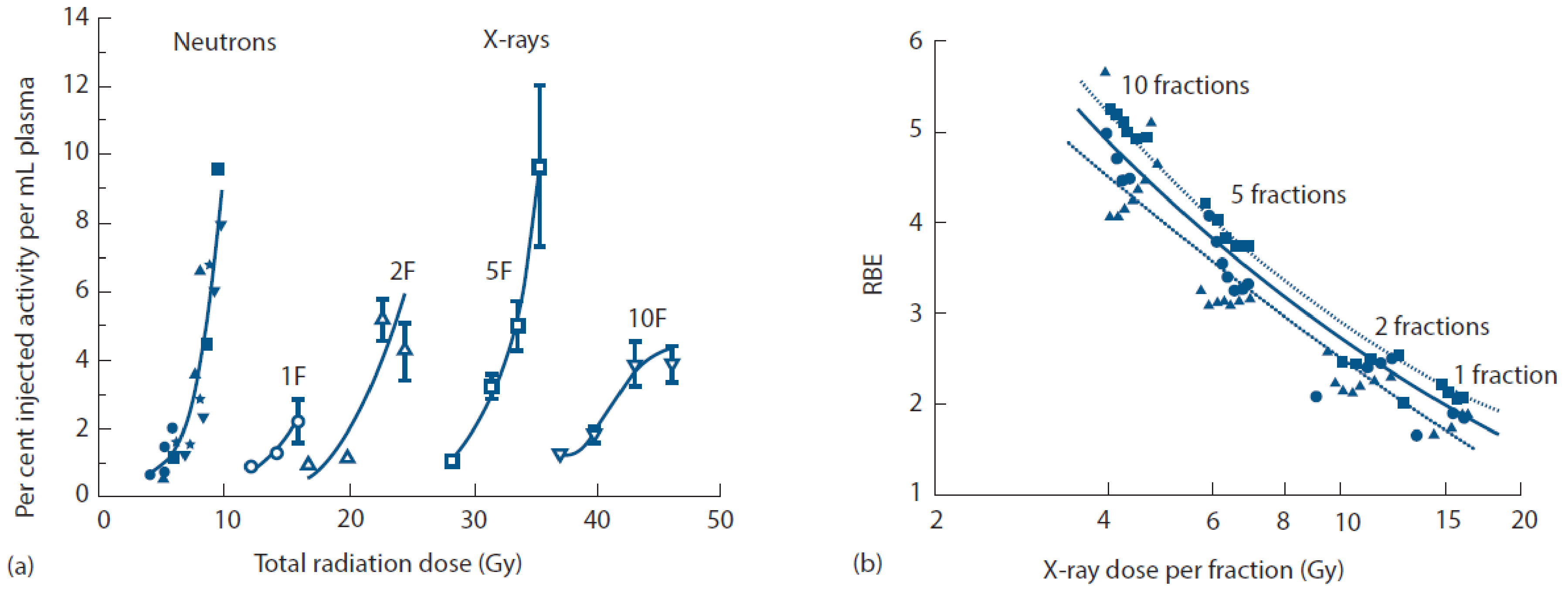
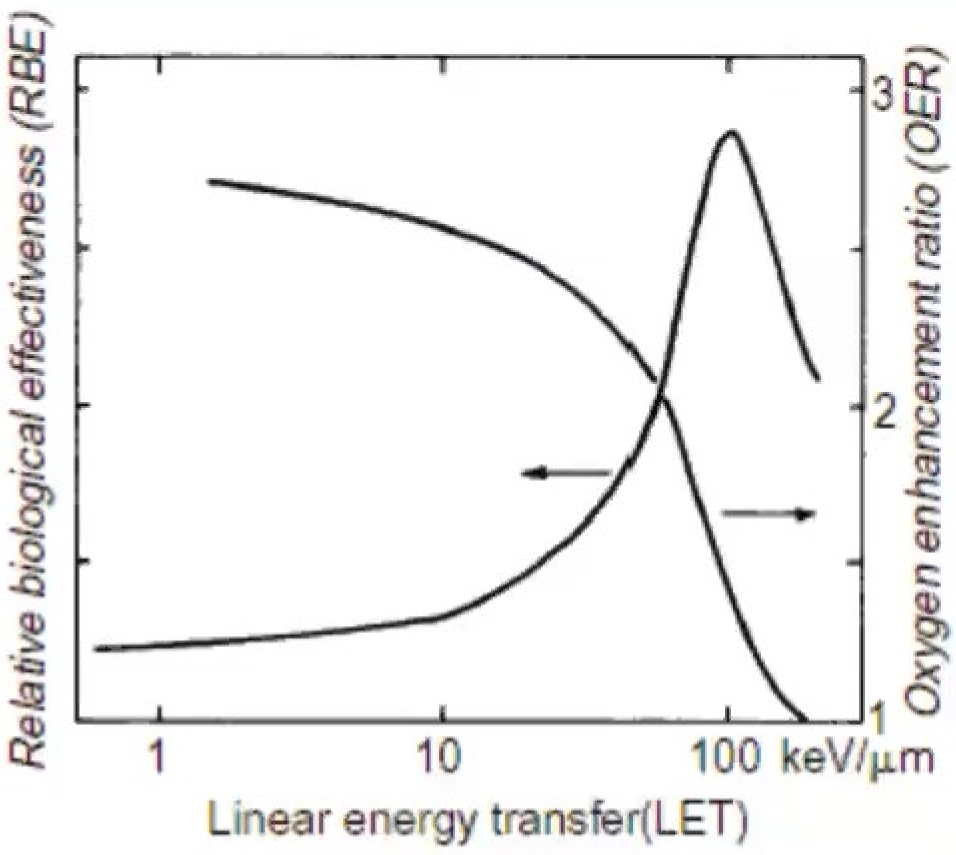


Figure 6.8 The RBE for kidney damage increases with decreasing dose per fraction. RBE values are derived from graphs similar to panel (a), which shows dose-effect curves for ^{51}Cr-EDTA clearance following irradiation with 1, 2, 3, 5 and 10 fractions of neutrons or 1, 2, 5 and 10 fractions of X-rays. The RBE values in panel (b) were obtained with various renal-damage endpoints: isotope clearance (circles), reduction in haematocrit (squares); increase in urine output (triangles). (From (7), with permission.)

Factors which Influence the RBE

- Radiation quality (LET)
- Radiation dose (dose per fraction)
- Dose rate
- Biology system or endpoint
- Conditions (e.g., oxygenation)

Dependence of RBE and OER on LET



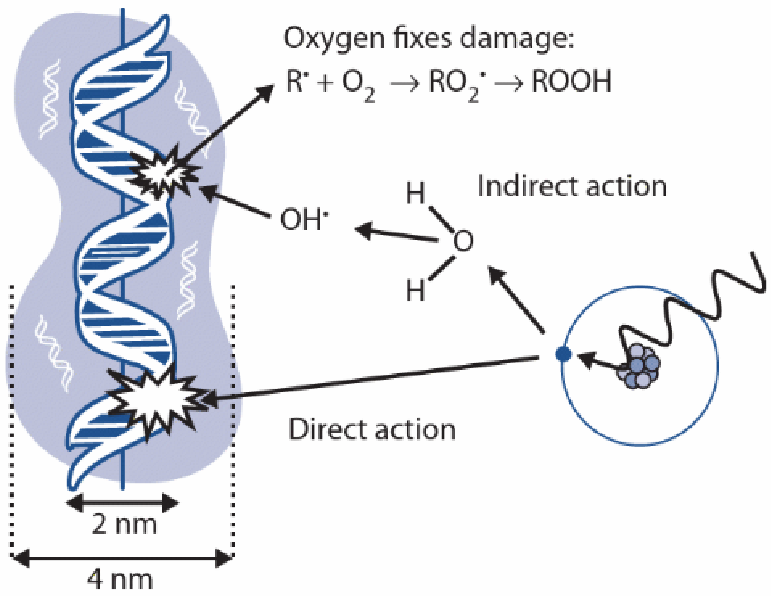


Figure 17.2 The oxygen fixation hypothesis. Free radicals produced in DNA by either a direct or indirect action of radiation can be restored to their original state under hypoxia but fixed in the presence of oxygen. (Adapted from (12).)

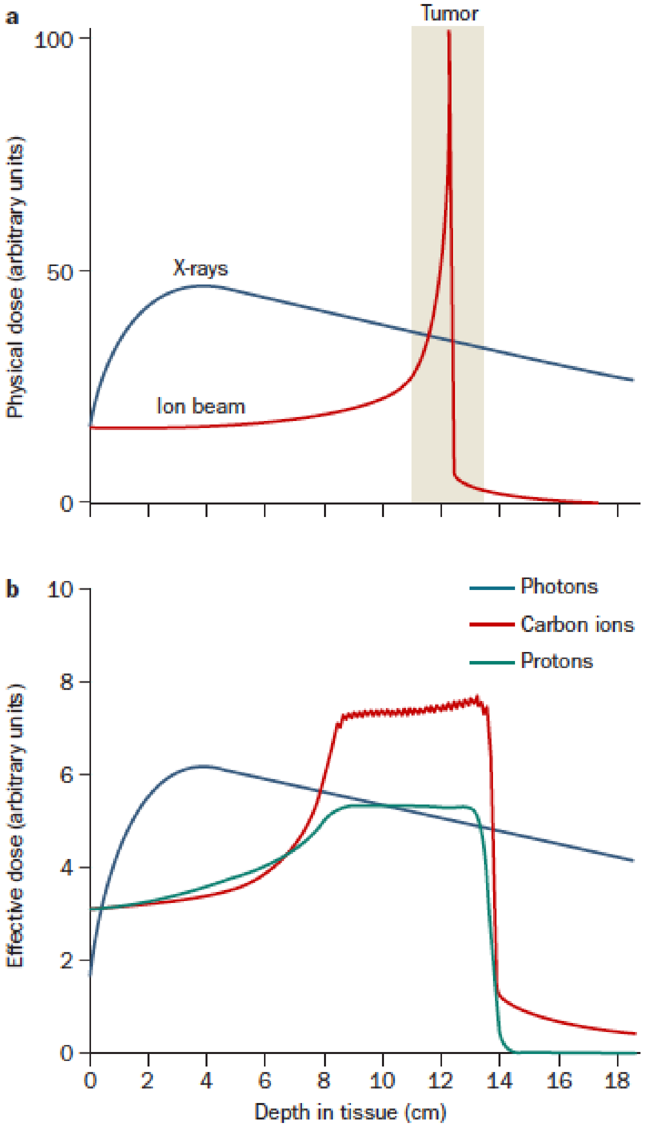
Clinical Application of Proton and Carbon Ions

Proton therapy:

- LET is low for most of the particle path
- LET increases in Bragg peak
- RBE taken to be a constant 1.1

Carbon ion therapy:

- Treatment planning uses RBE-weighted dose
- Different RBE models used by different clinics



Paganetti, H; **Relative biological effectiveness (RBE) values for proton beam therapy. Variations as a function of biological endpoint, dose, and linear energy transfer** Phys Med Biol. 2014 Nov 21;59(22):R419-72. doi: 10.1088/0031-9155/59/22/R419. Epub 2014 Oct 31.PMID: 2536

Tinganelli, W; Durante, M; **Carbon ion radiotherapy**. *Cancers* **2020**, *12*(10), 3022; https://doi.org/10.3390/cancers12103022

Summary: LET

- LET is the average energy transferred per unit path length of the track of a charged particle (track- averaged LET)
- X rays and γ rays are usually referred to as low LET, although this is actually the LET of the charged particles released when they interact
- Typical values of LET are

  ~0.3 keV/μm for high-energy X and γ rays

  ~2 keV/μm for X rays (~250 kVp)

  >100 keV/μm for heavy charged particles

Summary: RBE

- RBE is the ratio of the dose of a reference radiation to the dose of the radiation of interest to produce the same biological effect
- The reference radiation is usually 250 kVp X rays or Co-60
- RBE increases with increase in LET up to a maximum at ~100 keV/μm, and thereafter decreases due to the "overkill" effect
- RBE increases as the dose per fraction (or dose rate) decreases or the LET increases
- RBE depends on
  - *radiation quality (LET)*
  - *radiation dose (dose/fraction)*
  - *dose rate*
  - *biological system or endpoint*