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LET, RBE, OER and α/β Calculations

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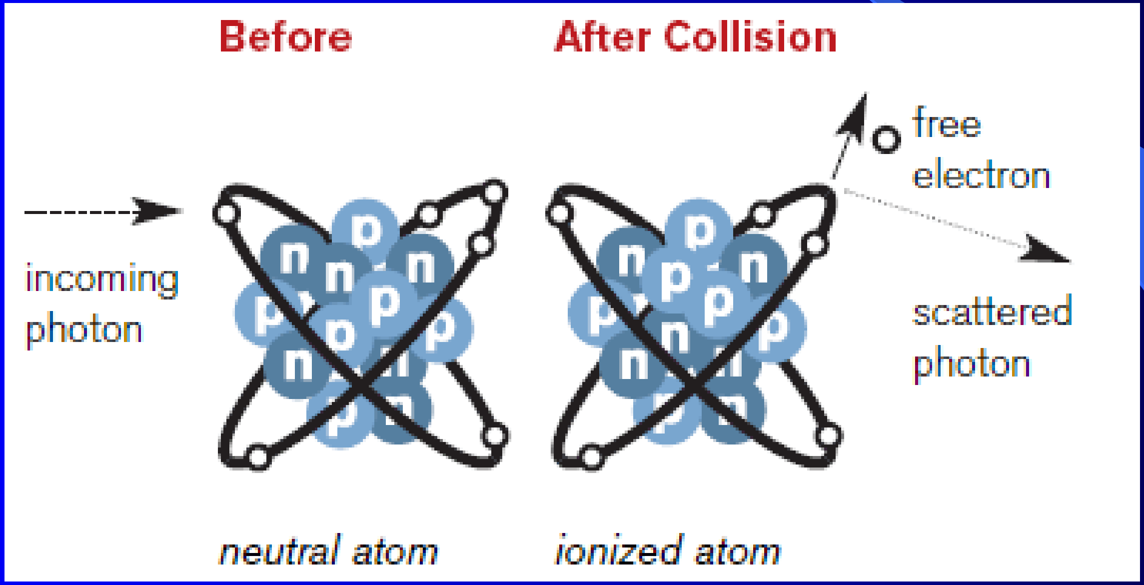
Financial Interest Disclosure

Paid Consultant to:
PINNACLE BIOLOGICS
Inventor of Phosphorothioate Mediated Antimutagenesis, Antimetastases, and MnSOD-Gene Expression Technologies
Equity Holder:
PINNACLE ONCOLOGY LLC
Development of Novel Clinical Applications for Amifostine

Response to Ionizing Radiation Depends on Radiation Quality

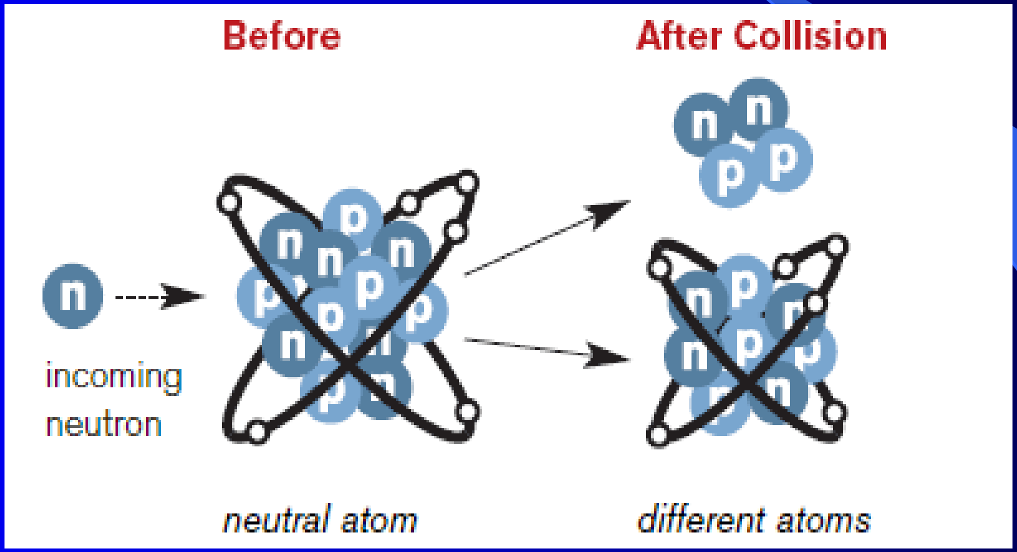
- LET, linear energy transfer = average energy imparted to a medium by a charged particle per unit track length (keV/μm)
- Low LET: sparsely ionizing (x-rays, γ-rays)
- High LET: densely ionizing (α-particles, heavy charged ions)

Low Linear Energy Transfer



- Protons and photons are low LET radiations
- Have similar biological effectiveness of ~ 1
- Different depth-dose distributions

High Linear Energy Transfer

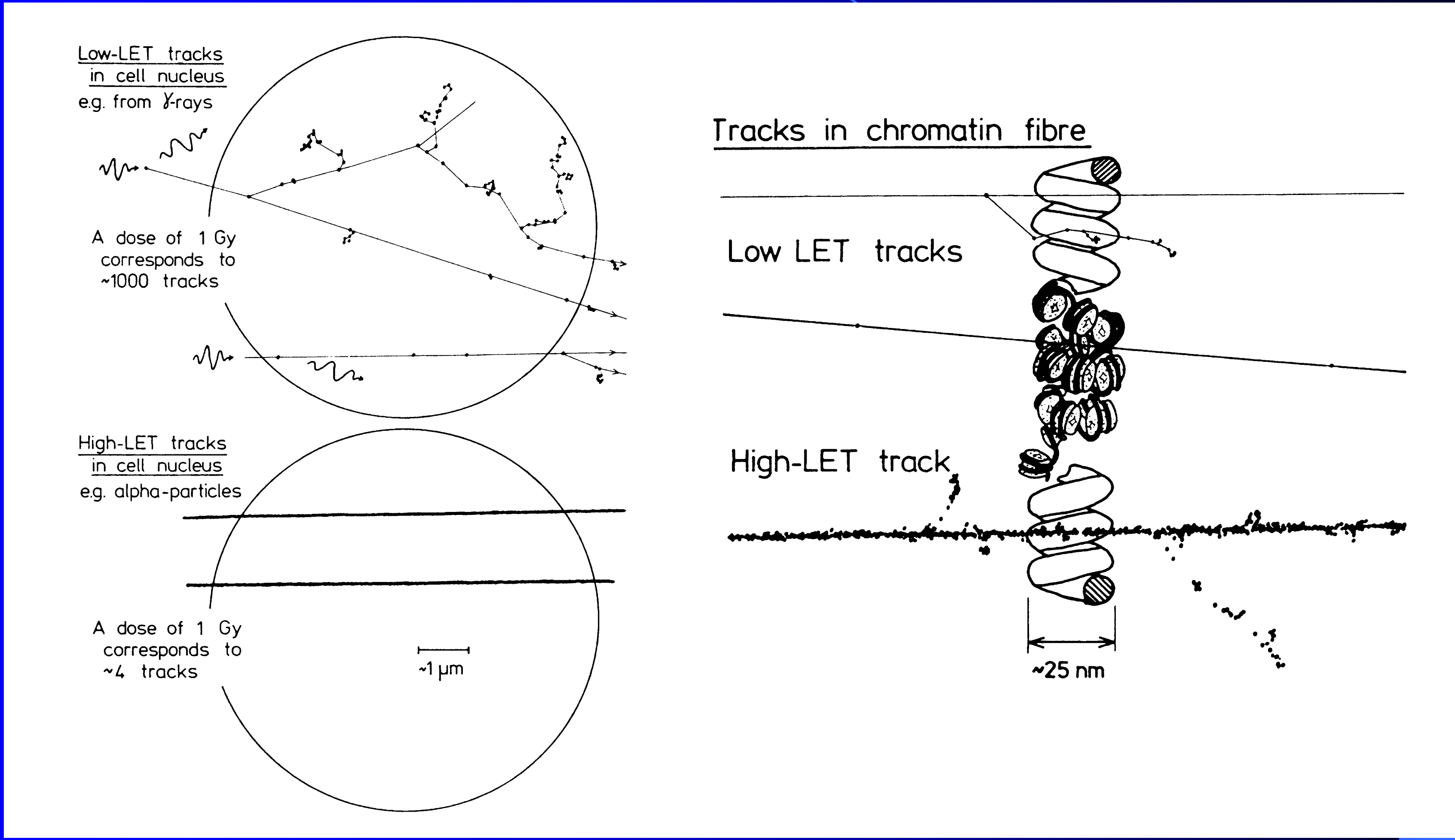


- Neutrons and ions (C, Ne) are high LET radiations
- Have high relative biological effectiveness (RBE)
- Different mechanisms of interaction with the matter
- Different depth dose distributions for neutrons and ions

Typical LET Values

Radiation	LET (keV/μm)
Cobalt-60 γ-rays	0.2
250 kVp X-rays	2.0
10 MeV protons	4.7
150 MeV protons	0.5
14 MeV neutrons	12 (track average) 100 (energy average)
290 MeV Carbon ions	12
2.5 MeV α-particles	166
2 GeV Iron ions	1,000

Clustered Lesions: Complexity Increases with LET

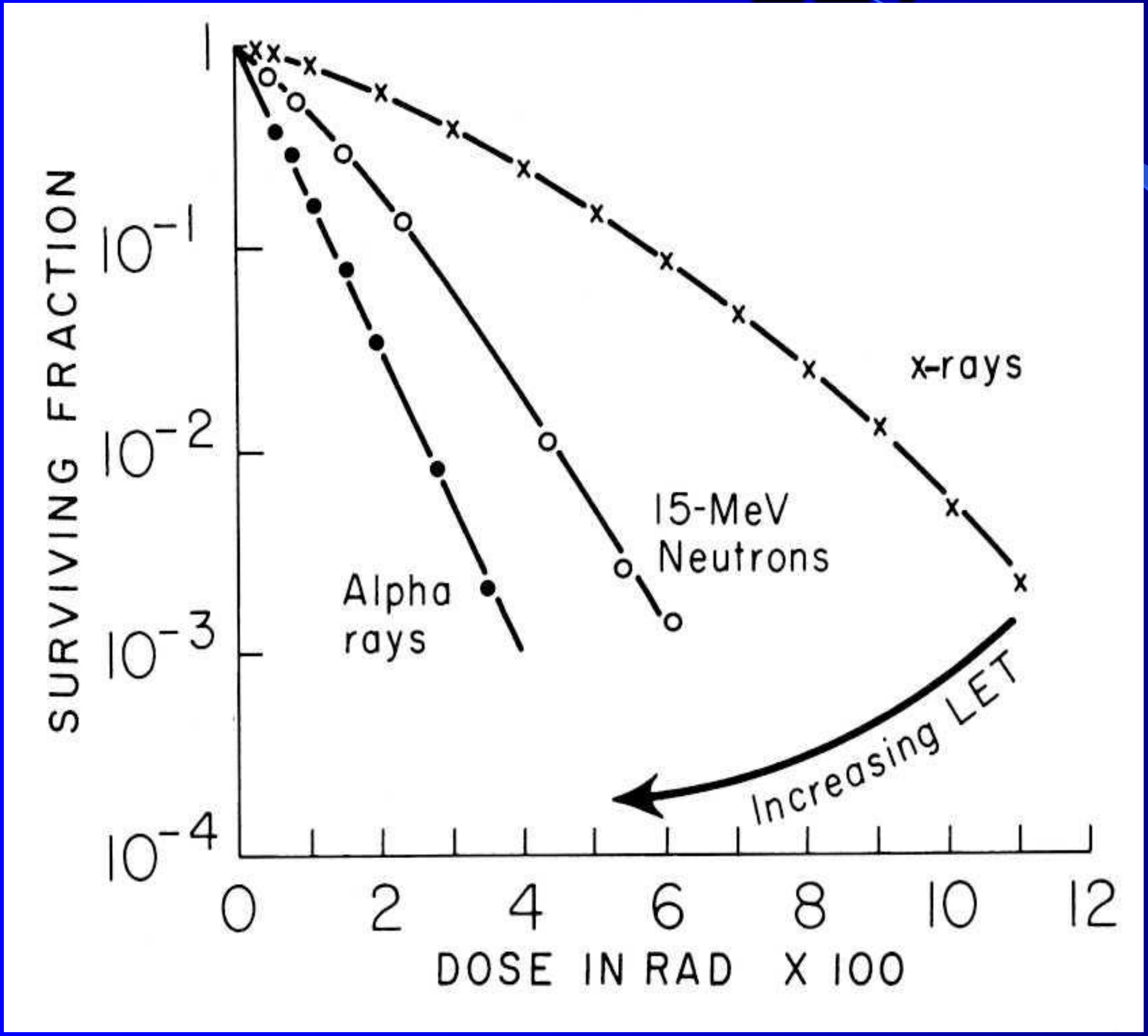


(from Goodhead 1994)

Biological Consequences of Clustered Lesions (MDS)

- Harder to repair accurately than single lesions
- Unrepaired
  - Block DNA replication
  - Loss of genetic integrity
- Mispaired
  - May lead to DSBs
  - Deletions could be produced
- Repair could be completed accurately

Cell Response Depends on LET

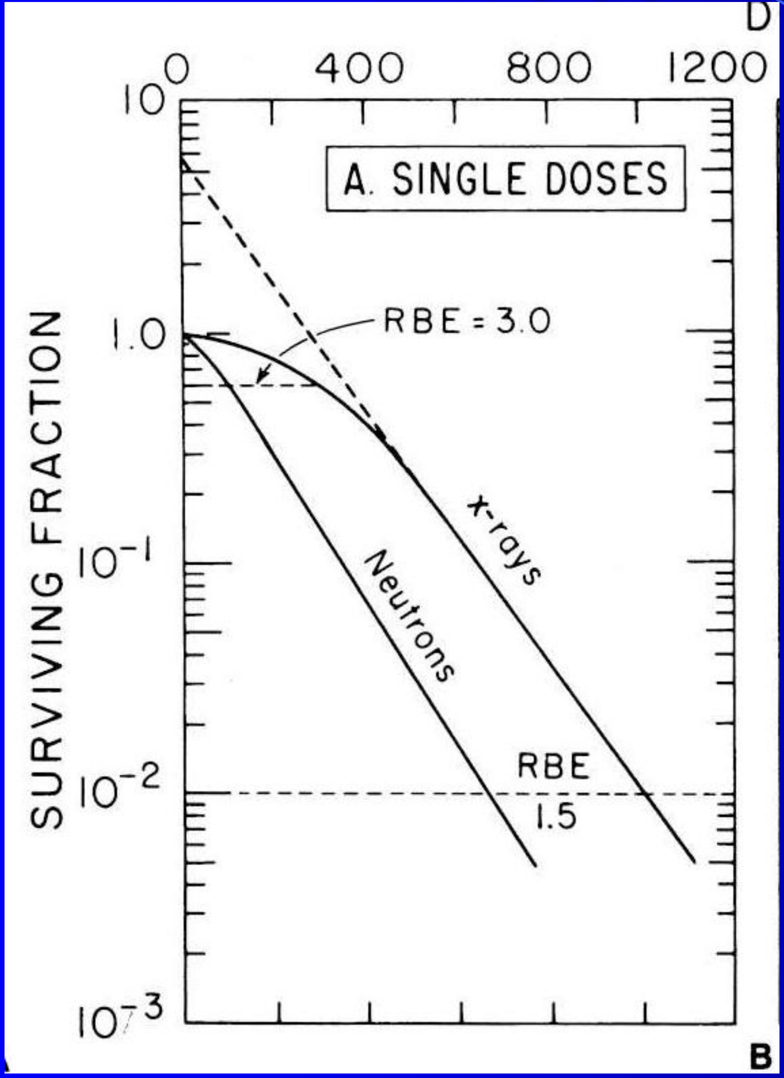


With increasing LET:
- **curves become steeper**
- **shoulder becomes smaller**

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

(From Hall 2000)

Relative Biological Effectiveness



$$\text{RBE} = \frac{\text{Dose(reference)}}{\text{Dose(test)}}$$

RBE is larger at higher survival

RBE Increases with LET to a Peak, then Decreases

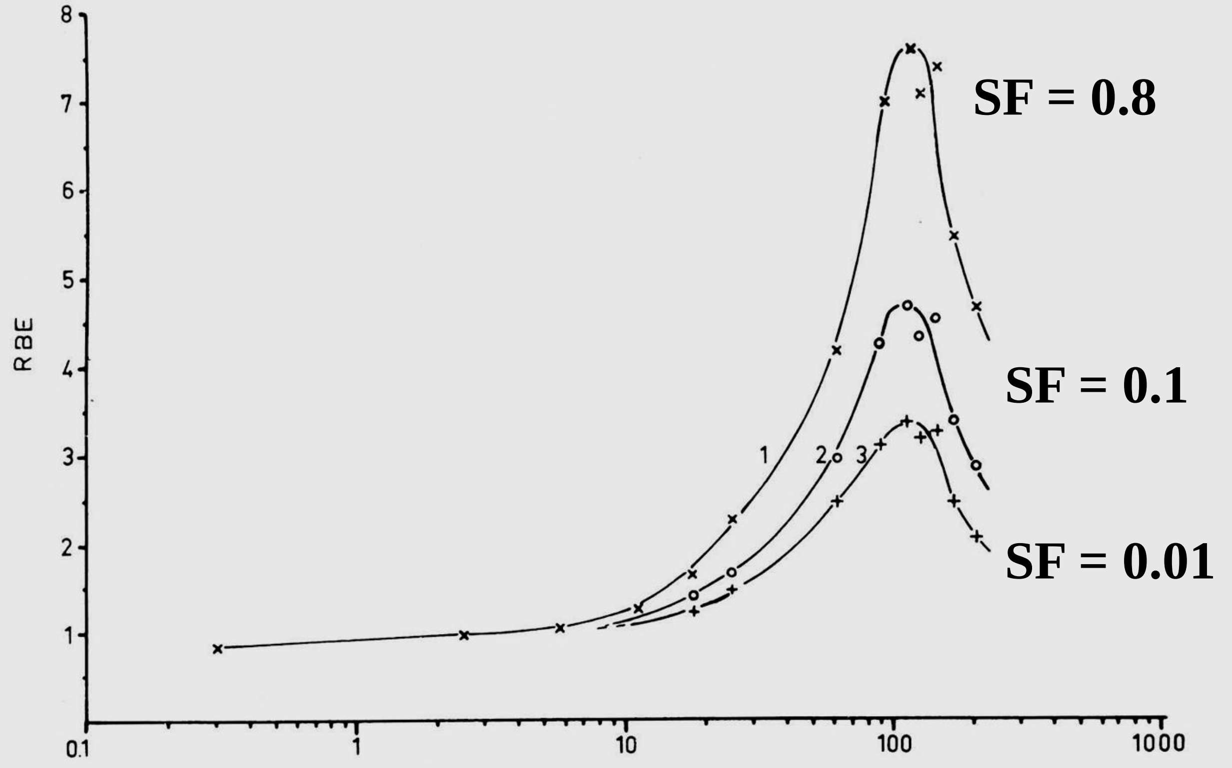
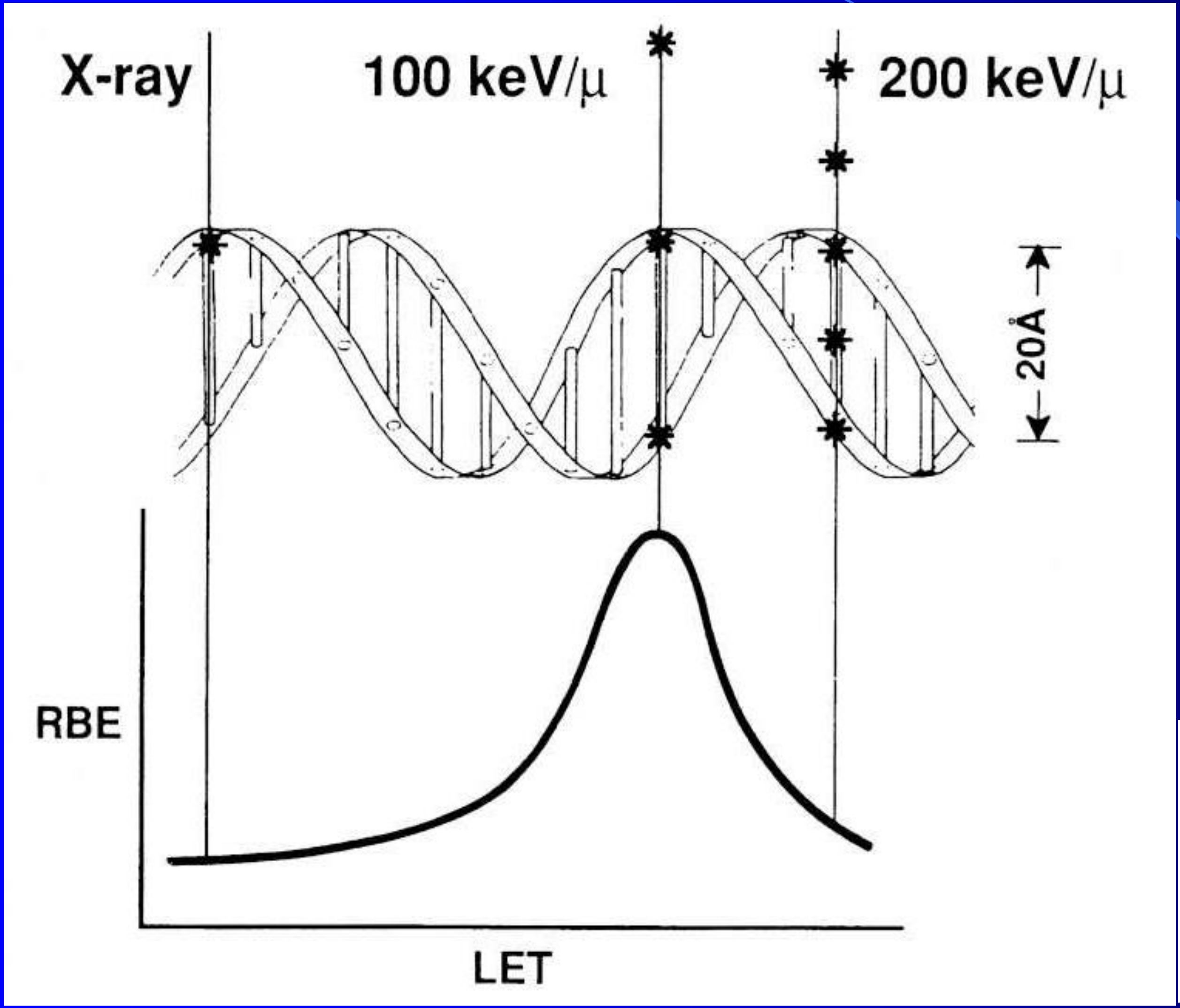


Figure 7.6. Variation of relative biologic effectiveness (RBE) with linear energy transfer (LET) for survival of mammalian cells of human origin. The RBE rises to a maximum at an LET of about 100 keV/μm and subsequently falls for higher values of LET. Curves 1, 2, and 3 refer to cell-survival levels of 0.8, 0.1, and 0.01, respectively, illustrating that the absolute value of the RBE is not unique but depends on the level of biologic damage and, therefore, on the dose level. (From Barendsen GW: Curr Top Radiat Res Q 4:293–356, 1968, with permission.)

(from Hall 2000)

“Overkill” occurs at high LET values



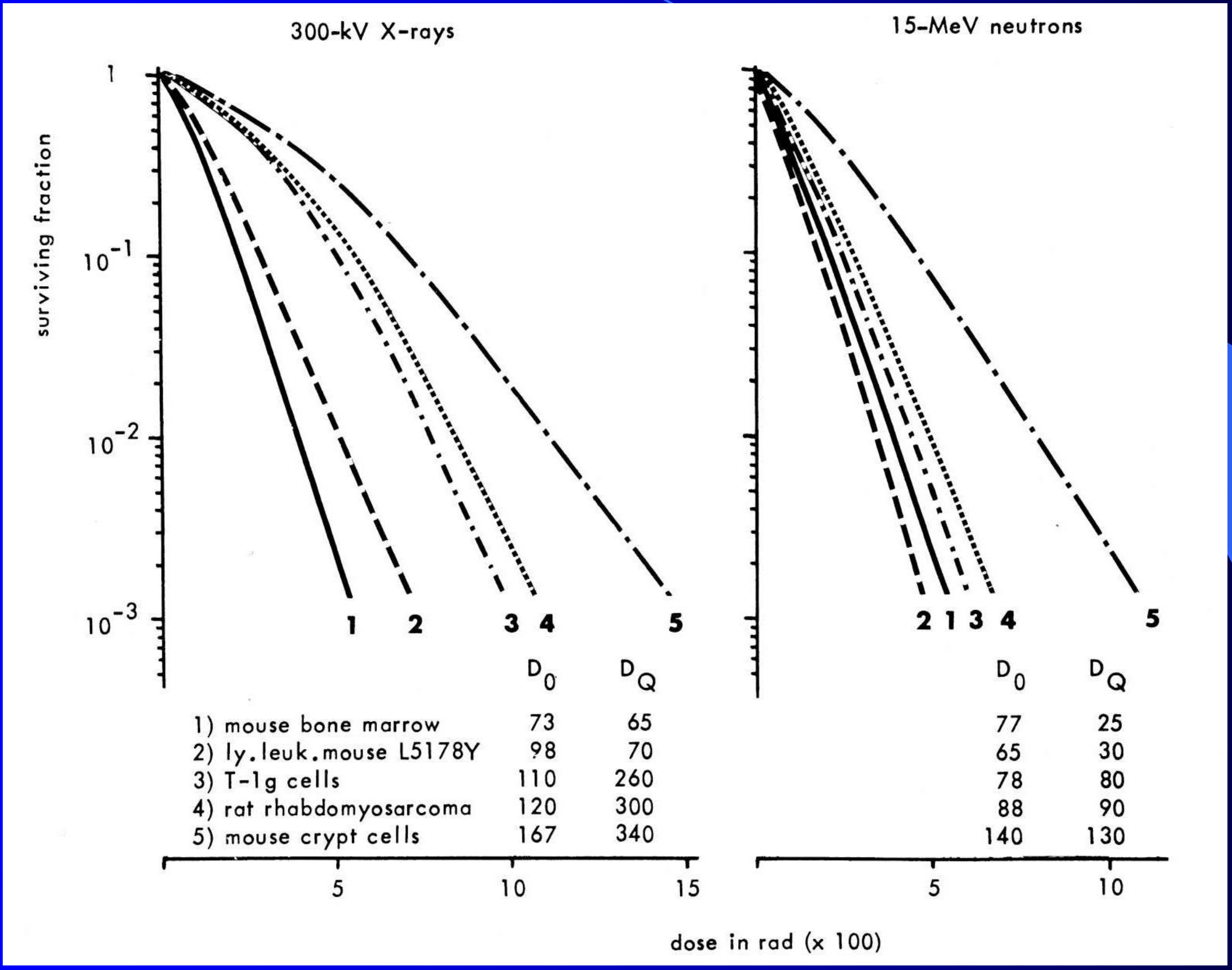
(from Hall 2000)

Figure 7.7. Diagram illustrating why radiation with a linear energy transfer of 100 keV/μm has the greatest relative biologic effectiveness for cell killing, mutagenesis, or oncogenic transformation. For this transfer, the average separation between ionizing events coincides with the diameter of the DNA double helix (*i.e.*, about 20 Å or 2 nm). Radiation of this quality is most likely to produce a double-strand break from one track for a given absorbed dose.

Factors that Influence RBE Values

- LET
- Level of survival
- Test system (cell type)
- Fractionation

RBE Depends on Test System



	X-rays D_0	X-rays D_Q	Neutrons D_0	Neutrons D_Q
1) mouse bone marrow	73	65	77	25
2) ly.leuk.mouse L5178Y	98	70	65	30
3) T-1g cells	110	260	78	80
4) rat rhabdomyosarcoma	120	300	88	90
5) mouse crypt cells	167	340	140	130

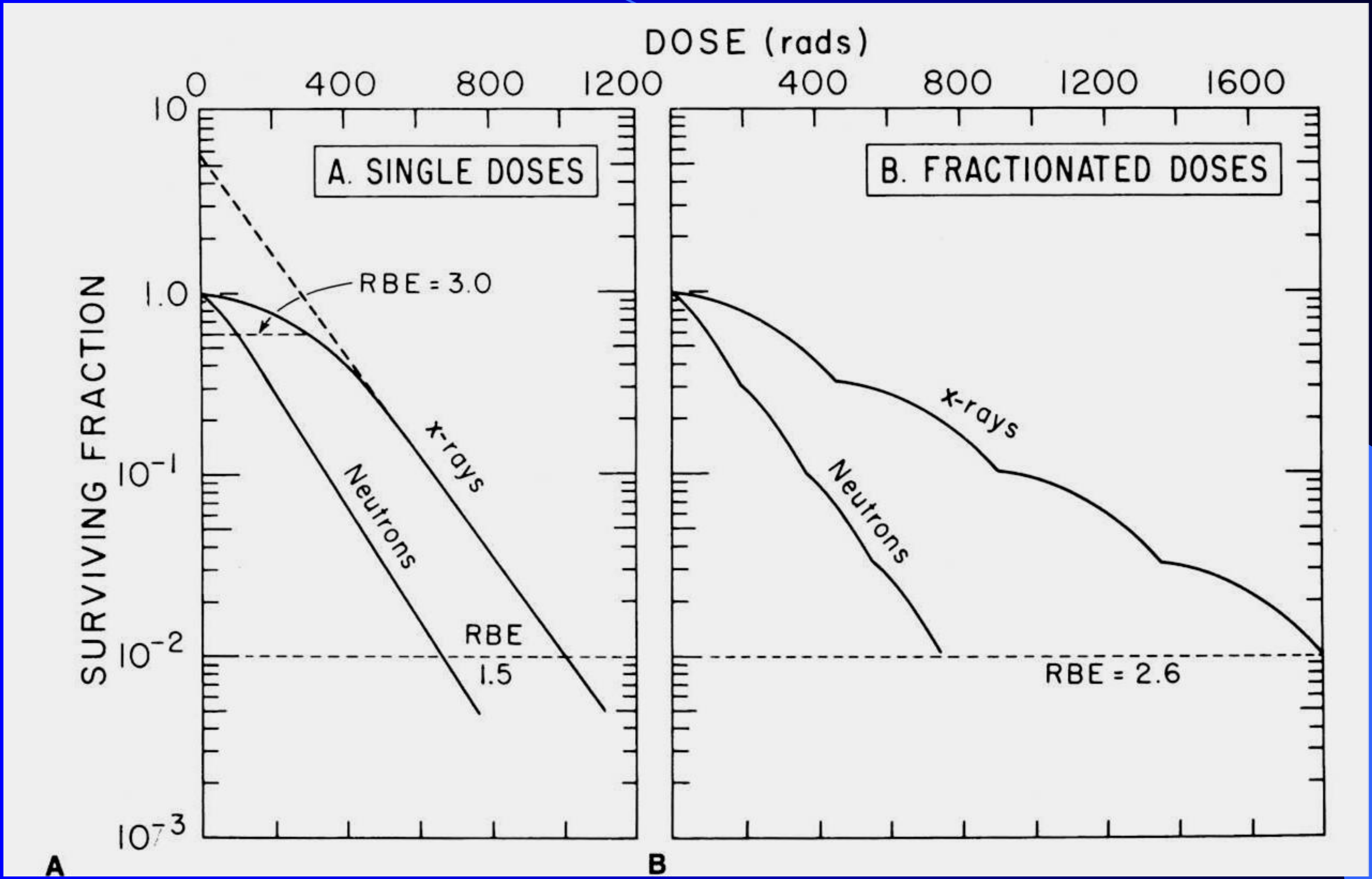
(From Hall 2000)

Therapeutic Gain Factor

- $$\text{TGF} = \frac{\text{RBE(tumor)}}{\text{RBE(normal tissue)}}$$

- For high LET to be a more efficacious therapy, TGF must be greater than 1.0

RBE Depends on Fractionation



(from Hall 2000)

RBE increases with fractionation.
Effect is due to shoulder on the X-ray curve

Sublethal Damage Repair is Reduced at High LET

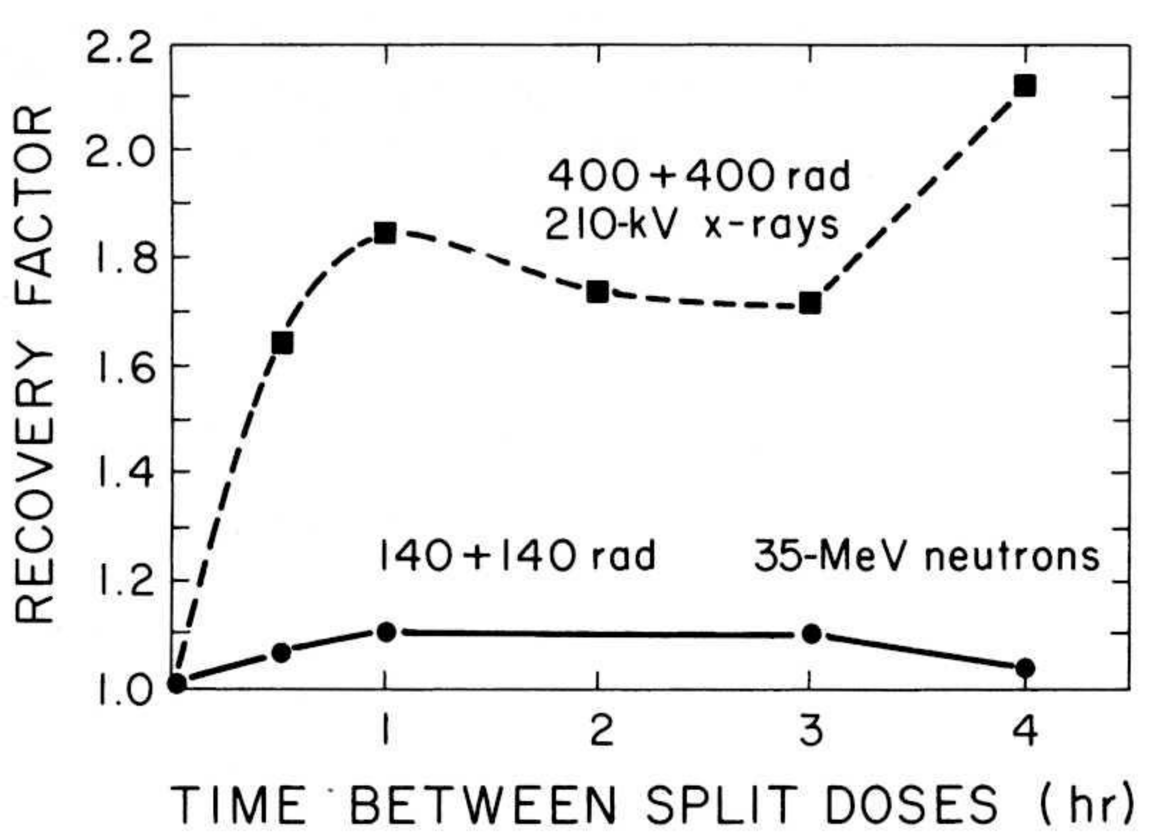
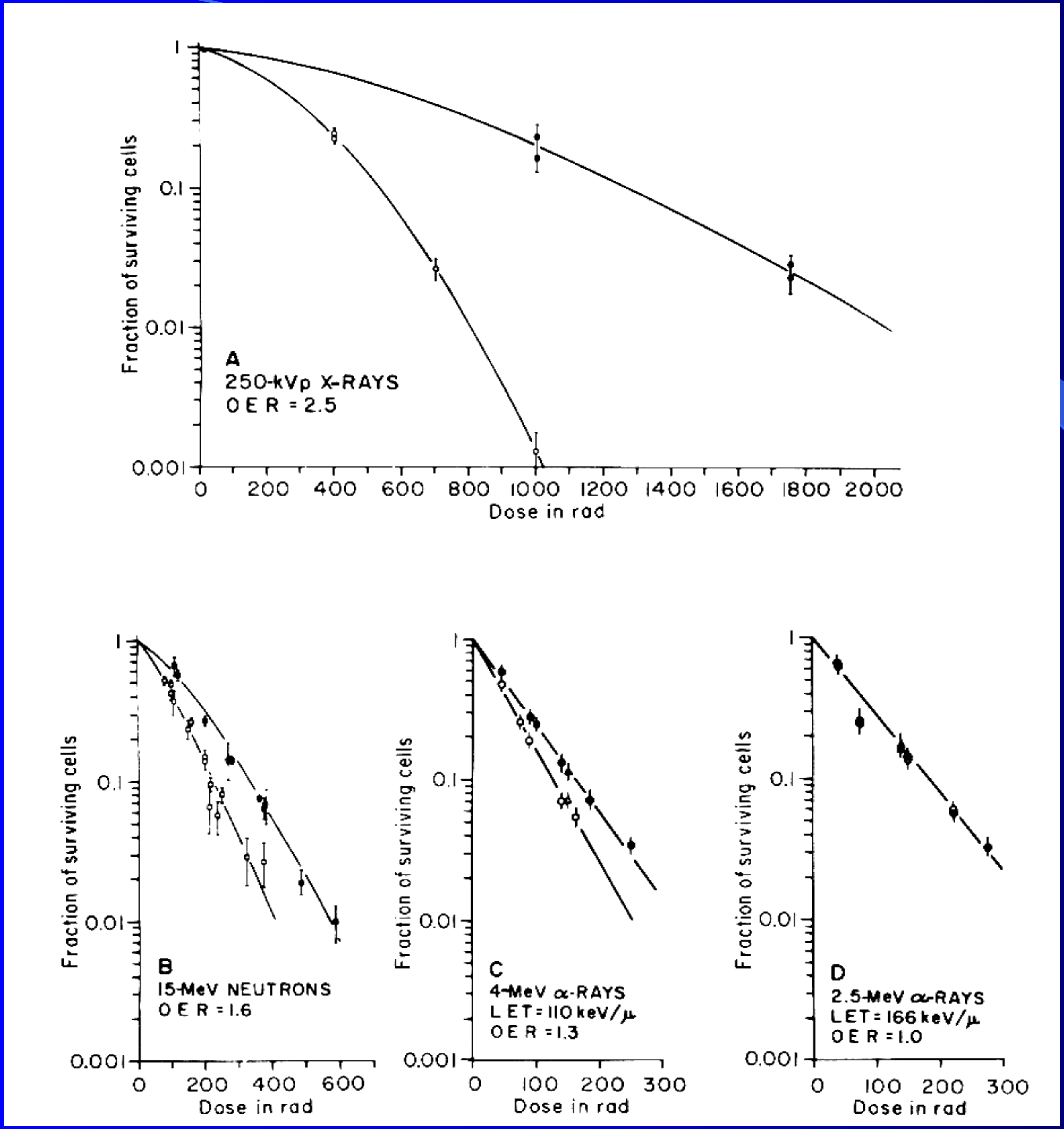


Figure 5.7. Split-dose experiments with Chinese hamster cells. For 210-kV x-rays, two 4-Gy (400-rad) doses, separated by a variable interval, were compared with a single dose of 8 Gy (800 rad). For neutrons (35-MeV $d^+ \rightarrow$ Be), two 1.4-Gy (140-rad) doses were compared with a single exposure of 2.8 Gy (280 rad). The data are plotted in terms of the recovery factor, defined as the ratio of surviving fractions for a given dose delivered as two fractions compared with a single exposure. It is evident that repair of sublethal damage during the interval between split doses is virtually nonexistent for neutrons but is a significant factor for x-rays. (From Hall EJ, Roizin-Towle L, Theus RB, August RS: Radiology 117:173–178, 1975, with permission.)

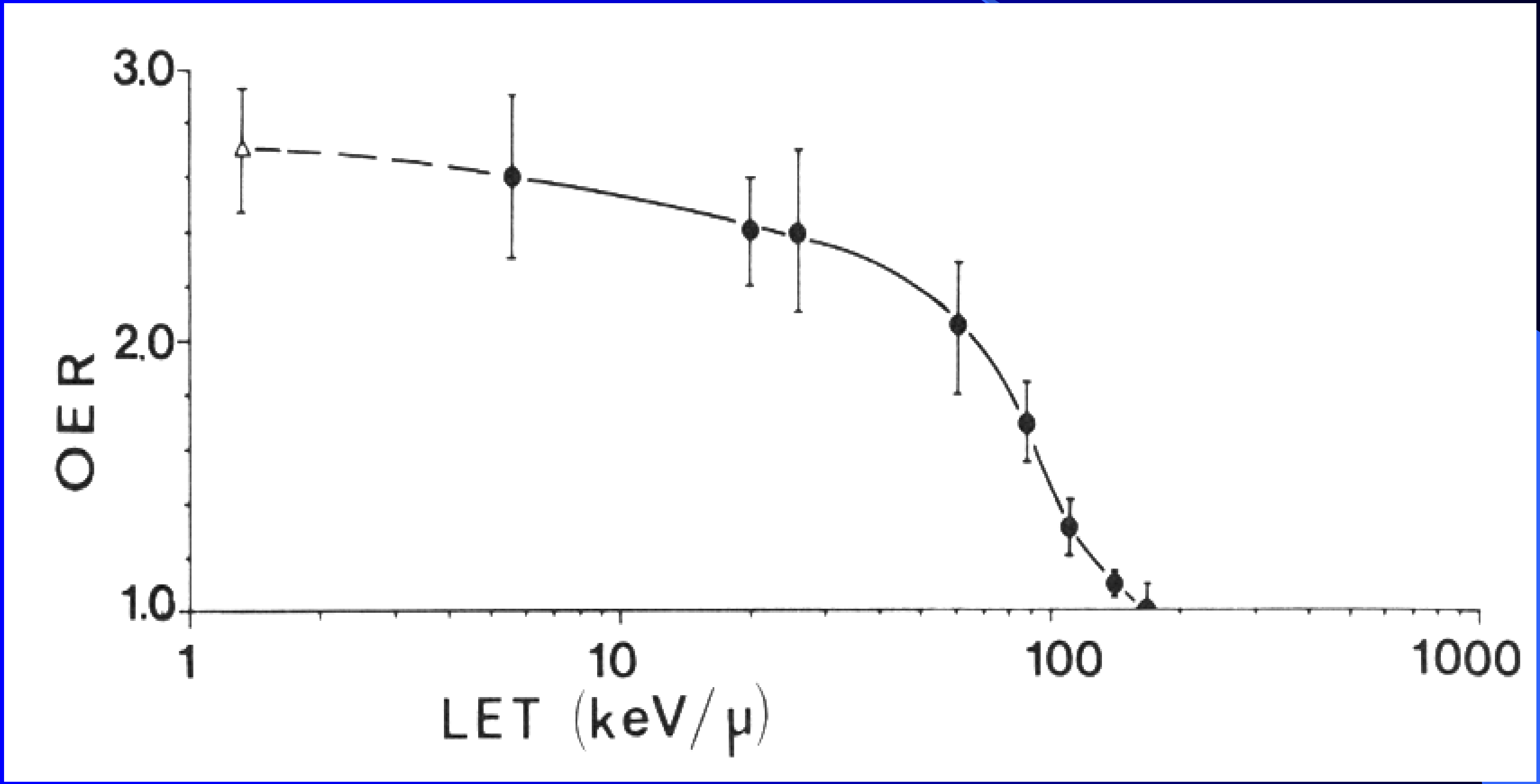
(from Hall 2000)

OER depends on LET



(From Hall 2000)

OER Depends on LET



(From Hall 2000)

Summary of LET Effects

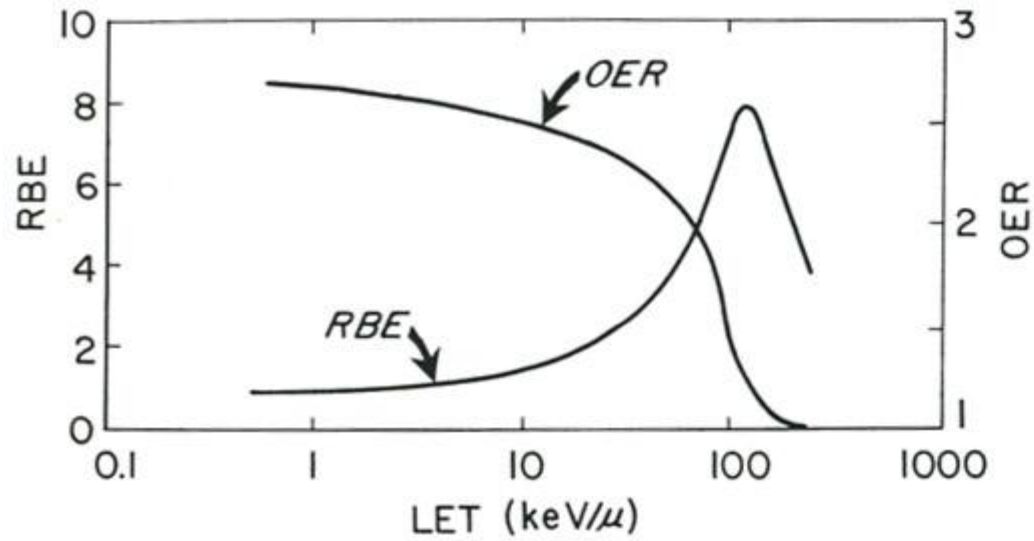


Figure 7.10. Variation of the oxygen enhancement ratio and the relative biologic effectiveness as a function of the linear energy transfer of the radiation involved. The data were obtained by using T1 kidney cells of human origin, irradiated with various naturally occurring α-particles or with deuterons accelerated in the Hammersmith cyclotron. Note that the rapid increase of relative biologic effectiveness and the rapid fall of the oxygen enhancement ratio occur at about the same linear energy transfer, 100 keV/μm. (Redrawn from Barendsen GW: In: Proceedings of the Conference on Particle Accelerators in Radiation Therapy, pp 120–125. LA-5180-C. US Atomic Energy Commission, Technical Information Center, 1972, with permission.)

(from Hall 2000)

Potential Biological Advantages of High LET Radiations

- Reduced OER
- Reduced repair
- Reduced cell cycle differential
- Higher RBE for slowly cycling tumors

Clinical Trials with Neutrons

- Have been tested at a number of centers world-wide
- Disappointing results
  - high incidence of late complications
  - relatively poor depth dose distribution; fixed horizontal beams
  - reoxygenation in conventional radiation may reduce importance of hypoxic cells
  - poor patient selection
- Current uses primarily limited to salivary gland and prostate cancers, and (limited) soft tissue sarcomas

Results of neutron clinical trials

Tumors where fast neutrons are superior to photons:

- Salivary glands (locally extended, well differentiated)
- Paranasal sinuses (adenocarcinoma, squamous, adenoid cystic)
- Head and neck: locally extended, metabolic
- Soft tissue, osteo- and chondrosarcomas
- Pelvis: prostate, bladder, uterus
- Melanomas

Depth Dose Distribution of Neutrons

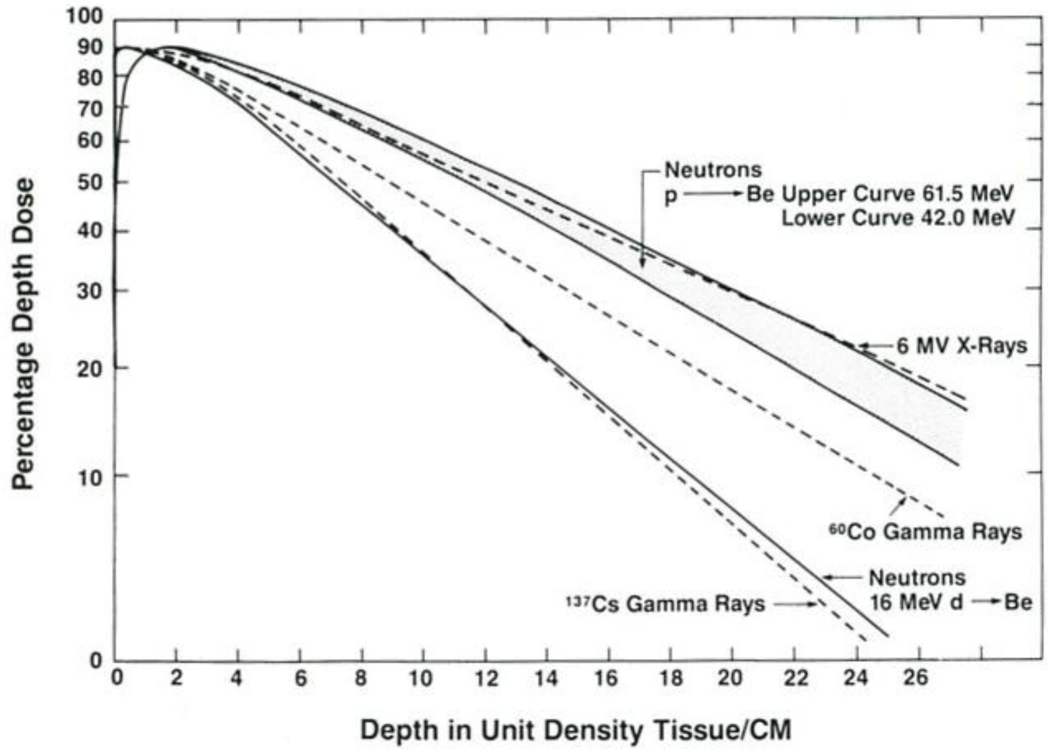


Figure 24.3. A comparison of the percentage depth doses for selected neutron beams with x- and γ-rays. Neutrons generated by 16-MeV $d^+ \rightarrow$ Be have poor depth doses, comparable to a cesium-137 unit with a short source–skin distance. To obtain depth doses comparable to megavoltage photon beams requires about 50 MeV, using either the $d^+ \rightarrow$ Be or the $p^+ \rightarrow$ Be reaction. A cyclotron to accelerate protons to this energy is much smaller and can be accommodated in a hospital. (Compiled from data published by Dr. Paul Kliauga.)

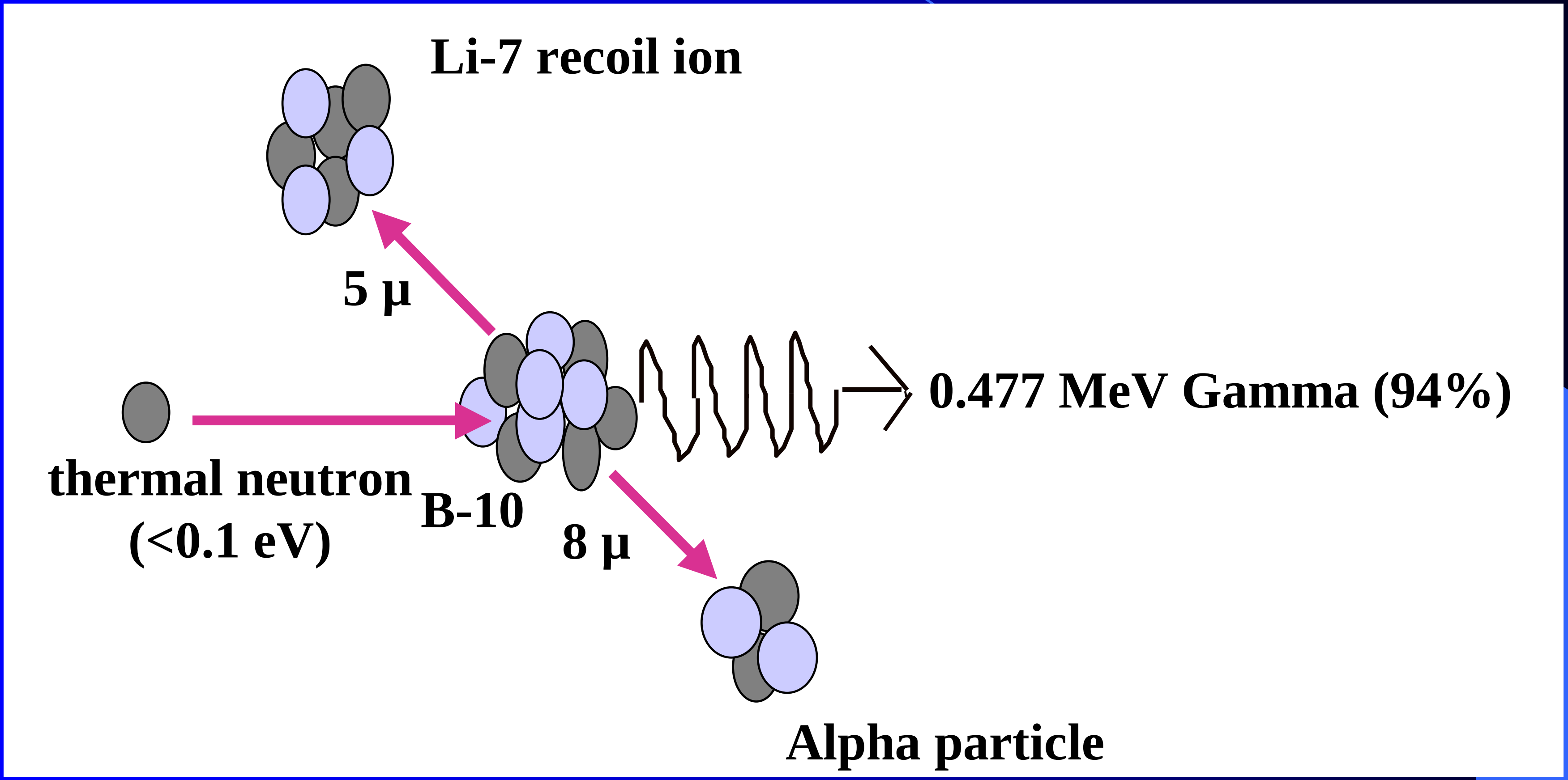
(from Hall 2000)

Rationale for the use of “right” energy neutrons

- **Depth-dose distribution: the higher energy, the better penetration in tissue**
- **OER *versus* LET: expected 1.3 for LET 100 - 120 keV/μm**
- **RBE versus LET: RBE deceases for high energy neutrons with LET 100 - 120 keV/μm**
- **RBE ~ Volume doubling time > 200 days; thus good for slow growing tumors**

“Right energy” neutrons: p(~ 60) → Be

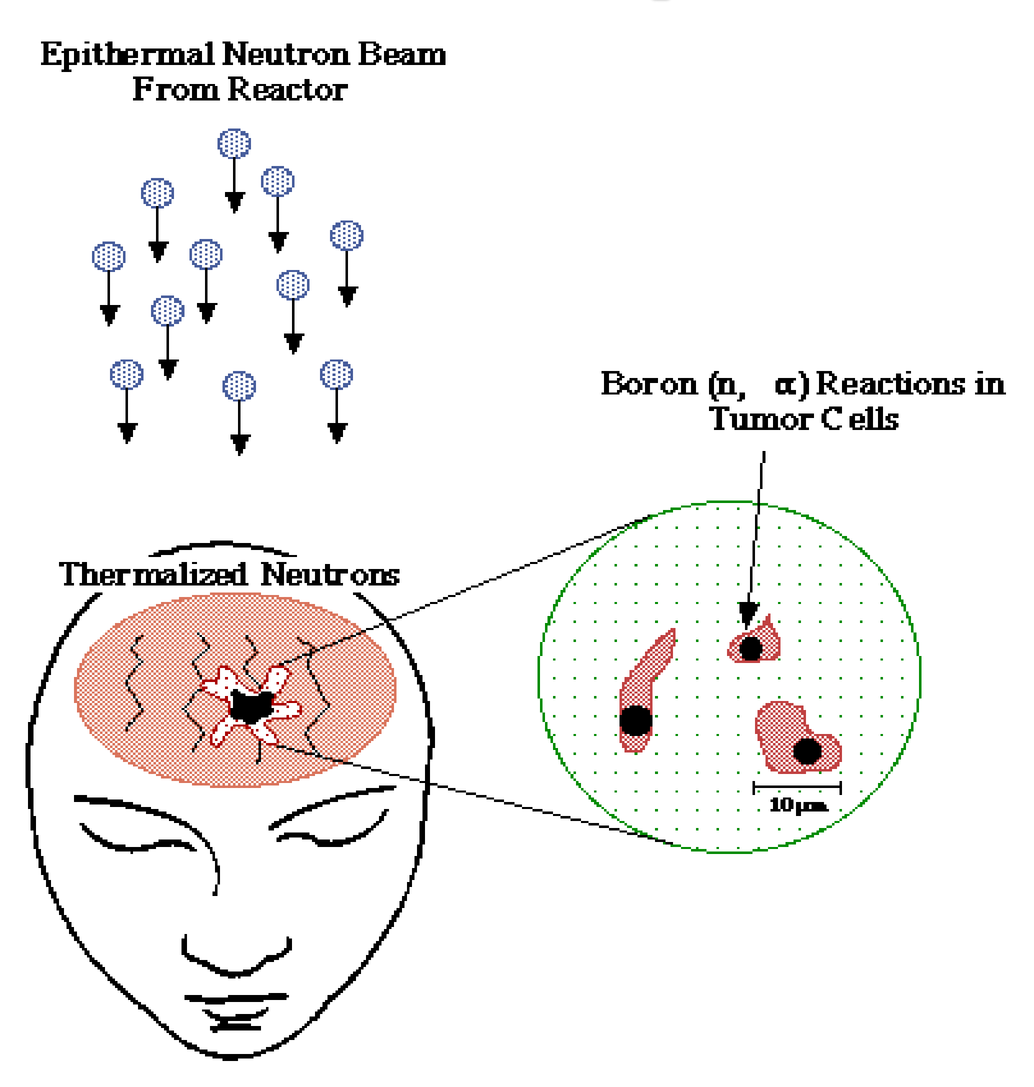
Boron Neutron Capture Therapy (BNCT)



LET ~ 200-300 keV/mm

RBE high
OER low

Concept of BNCT



Boron-10 dose ratio tumor-to-normal tissue 3:1 to 4:1 (rarely achieved)

Why boron-10?

- A stable isotope that can be concentrated in tumor cells by attaching it to tumor-seeking compounds
- Non-radioactive and readily available, comprising 20% of naturally occurring boron
- The secondary particles from $^{10}B(n,\alpha)^{7}Li$ are high LET; cells killed by α particles and Li ions
- The combined path lengths of α and ^{7}Li are ~ one cell-diameter, i.e., ~ 12 μm
- Well understood chemistry of boron allows it to be easily incorporated into man-made chemical compounds

BNCT

- Limitations
  - Lack of boron compounds with specificity for tumor rather than normal tissue
  - Thermal neutrons are poorly penetrating
- Tumors tested clinically
  - Glioblastoma multiforme
  - Cutaneous melanoma
- Currently few sites conducting studies

Protons

- Good dose distribution (Bragg peak)
- Biological properties (RBE and OER) similar to X-rays

Proton therapy: the Bragg peak

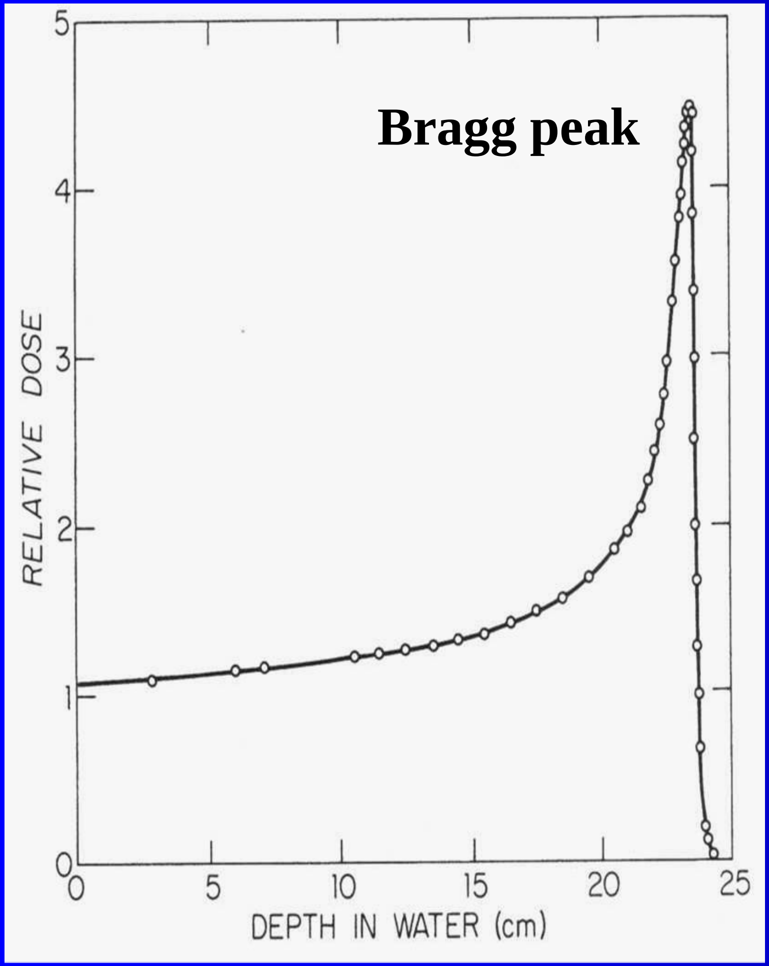
- Low dose in front of the tumor (RBE = 1), high dose in the **Bragg peak region (RBE = 1.2)**, very small dose behind the tumor
- Position of the Bragg peak: ~ energy
- 235 MeV protons: Bragg peak @ ~27 cm

  Suitable for 1.5-cm diameter tumor

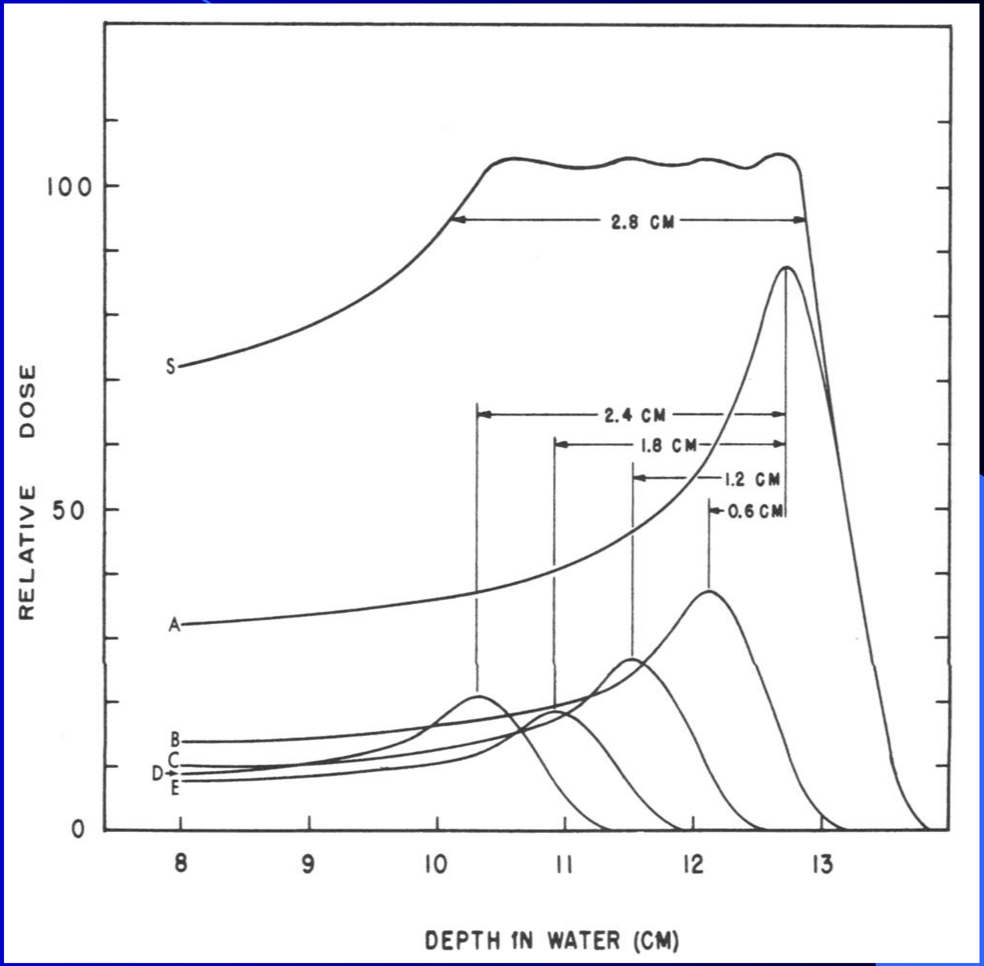
  Skin dose ~ 30% of maximum dose

Protons

187 MeV Protons



160 MeV Protons SOBP



(from Hall 2000)

Spread out Bragg Peak

- Several beams of different energy added up together ("energy modulated beam")
- 235 MeV SOBP beam

  ± 5% uniformity over a 9-cm volume

  Suitable for 9-cm diameter tumor

  Skin dose 68% of maximum dose

Protons

- A number of facilities operating world-wide.
  - Over 40,000 patients now treated
- Due to excellent dose distributions, have shown clear efficacy for:
  - Choroidal melanoma
  - Some spinal cord and brain tumors
- Also being used for a wide spectrum of tumors (e.g., prostate, children, lung, breast, head and neck, etc.)

Heavy Charged Particles

- Biological advantages of high LET
- Good dose localization (Bragg peak)

Carbon Ions

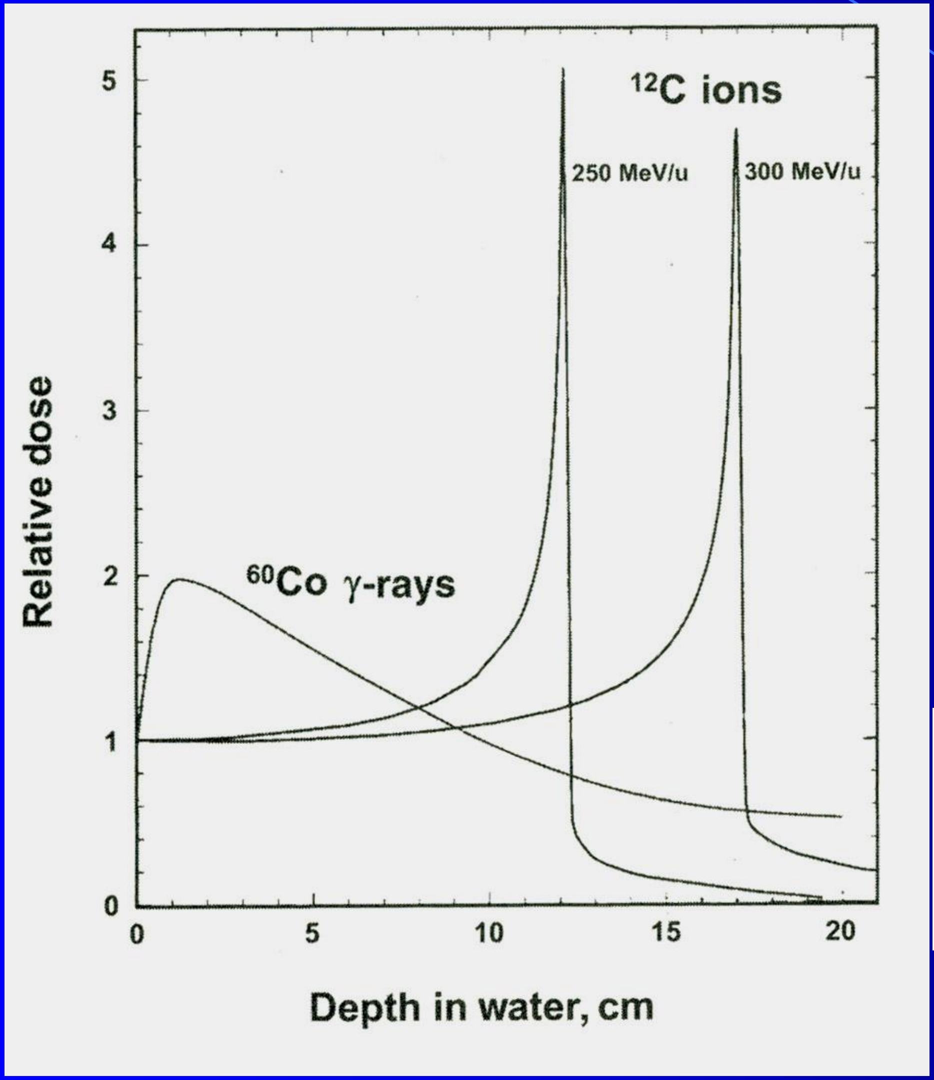


FIGURE 24.7 ● Comparison of the depth–dose profiles of carbon ions of two different energies with that of ^{60}Co γ-rays. (Adapted from Kraft G: Tumor therapy with heavy charged particles. *Progress in Particle and Nuclear Physics* 45:S473–S544, 2000.)

(from Hall and Giaccia 2005)

Carbon Ions

- Must use SOBP so RBE will vary
- An additional advantage may be ability to use PET to image target volume

Charged Particles

- Currently, only heavy ion clinical facilities are in Japan and Darmstadt, Germany
  - Over 2,000 patients now treated with carbon

Rationale for heavy ion therapy

- Heavier than protons, so less scatter and sharper-edge definition for the radiation field
- Since ionization energy ~ Z^2, heavy ions have higher LET than protons
- Low OER, less sensitivity to fractionation

Problems with heavy ion therapy

- High energy: For 30-cm range in tissue, 400 MeV/amu for carbon, 600 MeV/amu for neon (expensive to produce)
- "Tail dose": Heavy ions in the medium produce light fragments that travel beyond the stopping power of the primary beam
- Overkill effect (LET > 100 –120 keV/μm in the stopping region with ions heavier than neon

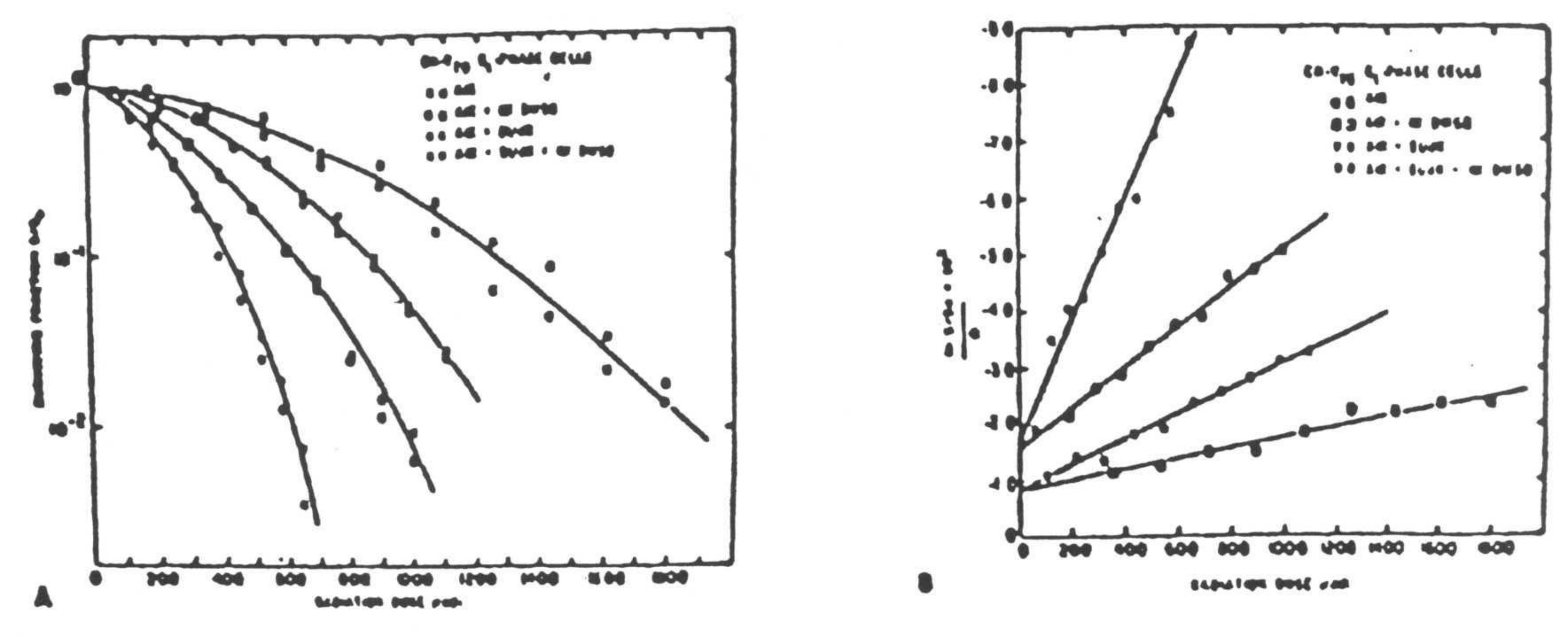
α/β Ratio Calculations

Easy Method to Calculate α and β

Convert equation to a linear form: (ln SF)/D = -α-βD

Graph (ln SF)/D versus D – y-intercept is α

– slope is β



(from Koch et al.)

Use of *In Vivo* Fractionation Data to Determine α/β Ratio

Effect = E = n(αd + βd²)

where d = dose/fraction

n = # identical fractions

E/nd = α + βd

(from Hall 2000)

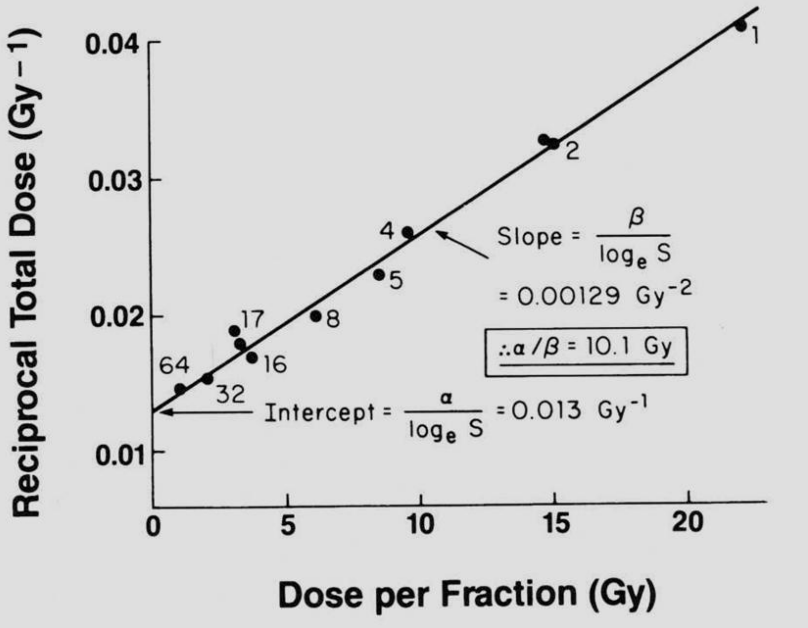


Figure 18.26. Reciprocal of the total dose required to produce a given level of injury (acute skin reaction in mice) as a function of dose per fraction in multiple equal doses. The overall time of these experiments was sufficiently short so that proliferation could be neglected; numbers of fractions are shown by each point. From the values of the "intercept" and "slope" of the best-fit line, the values of α and β and the ratio α/β for the dose–response curve for organ function can be determined. (Adapted from Douglas BG, Fowler JR: Radiat Res 66:401, 1976, with permission.)