

Dr. David J. Grdina

Time, Dose and Fractionation

Department of Radiation

And

Cellular Oncology

The University of Chicago

Dr. David J. Grdina

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**

Four R's of Radiotherapy

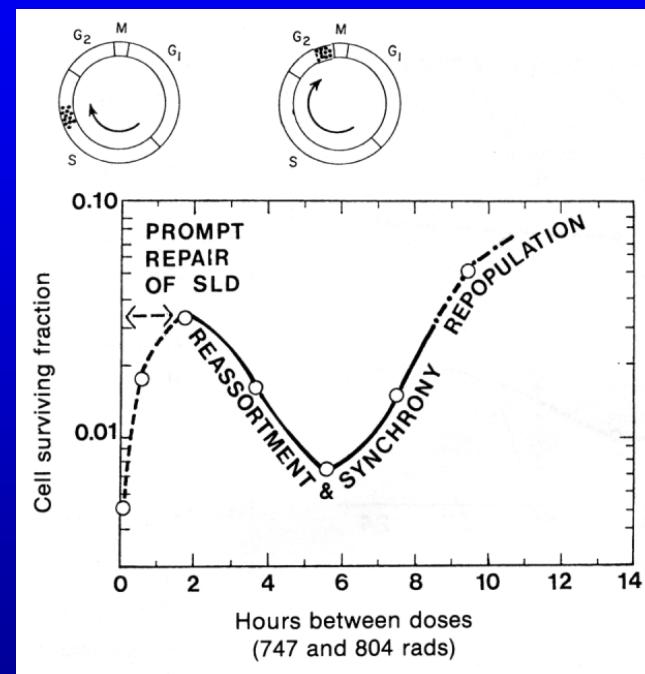
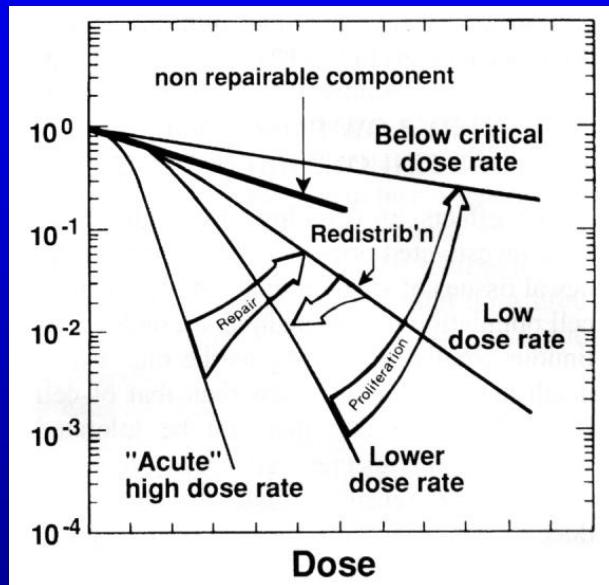
Repair of Sublethal Damage

Reassortment of Cells within the Cell Cycle

Repopulation

Reoxygenation

Factors affecting radiosensitivity



(E.J.H., Fig.5.15, p.79, 2000)
(E.J.H., Fig.5.4, p.71, 2000)

- **Radiation classically interferes with cell renewal or reproduction**
- **Sequelae from effect on renewal systems (skin, mucosa, endothelium)**

These are usually the systems whose effect yields acute sequelae. However if they are compromised, the structural edifice is compromised, and scarring occurs with functional compromise
- **Microvascular reduction:**

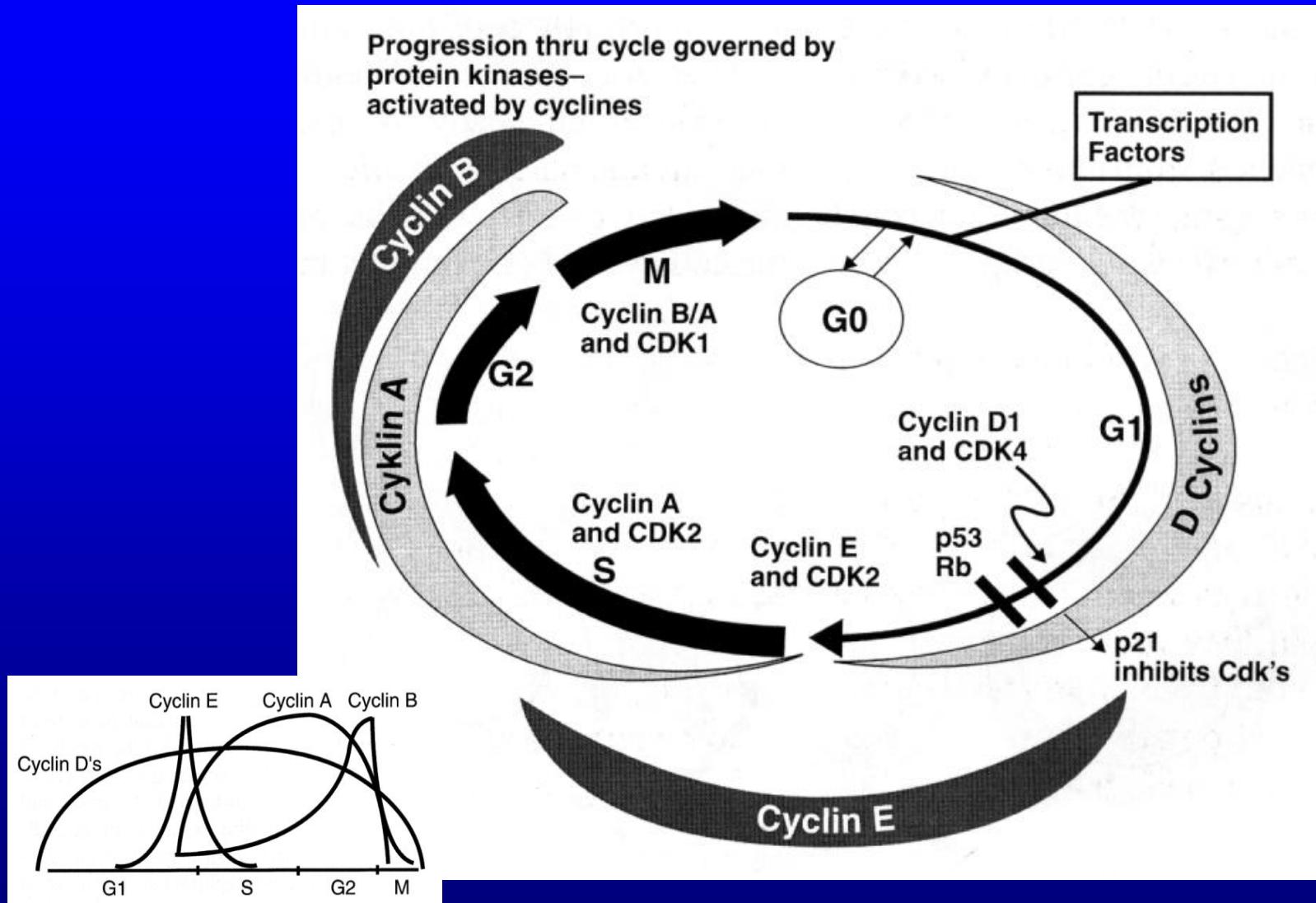
This compromises tissue perfusion and interferes with healing from subsequent trauma
- **Nonproliferating systems:**

If these are injured and are required to proliferate to heal, the long term radiation compromise of reproduction will prevent proper healing and will force necrosis

Fractionation of Radiation Dose and Cell Cycle

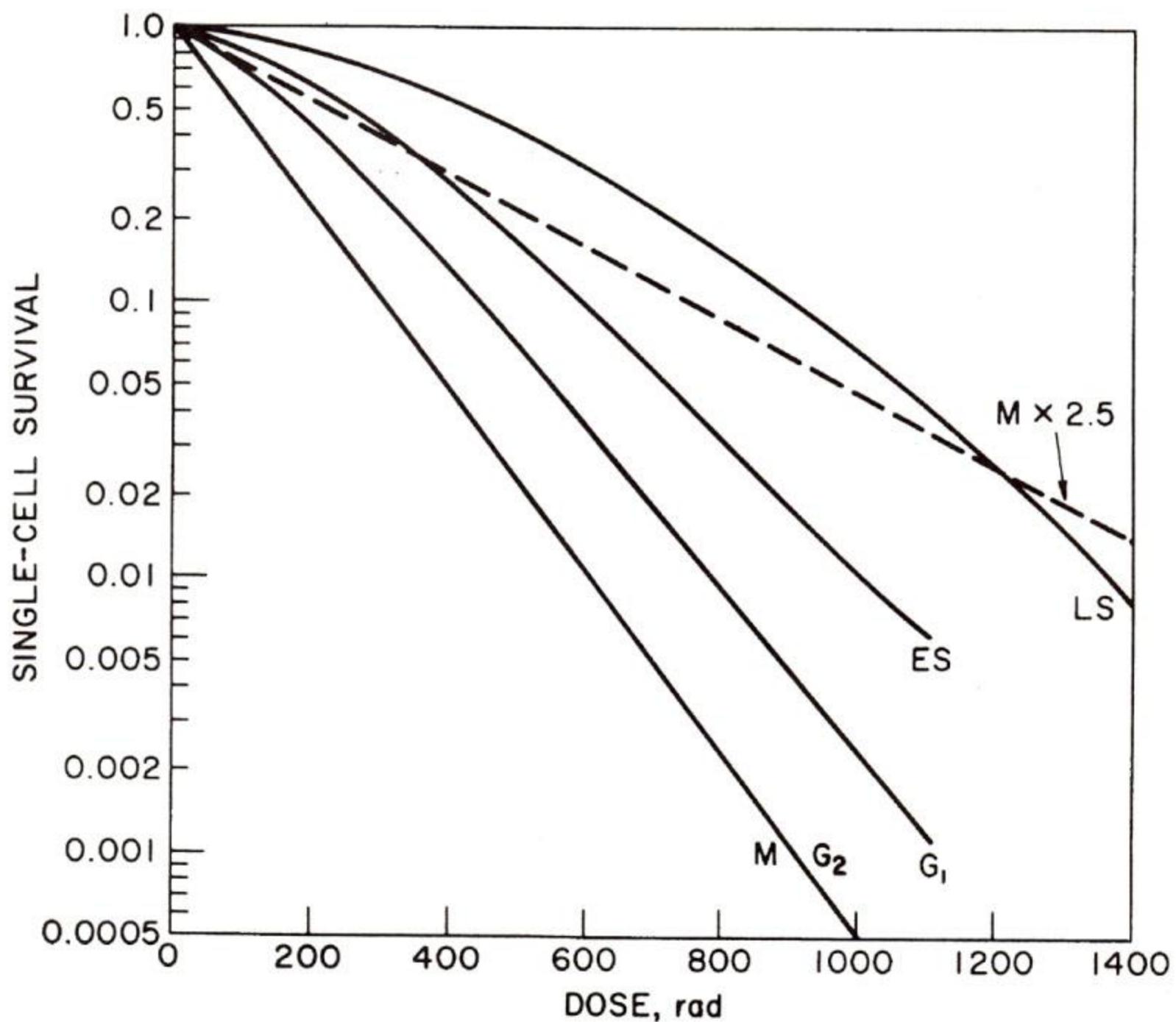
- Those cells in G₂-M and G₁-early S phase will be more sensitive
- Late S phase cells will survive a dose of radiation with higher probability
- If radiation were given in a single fraction the survival curve would be dominated by the cells in late S phase, the least sensitive phase
- Fractionated radiation will allow time for cells to redistribute in the cycle
- Thus, at least in theory, the survival curve is dominated by the most sensitive phase

Phases of the cell cycle and its regulation

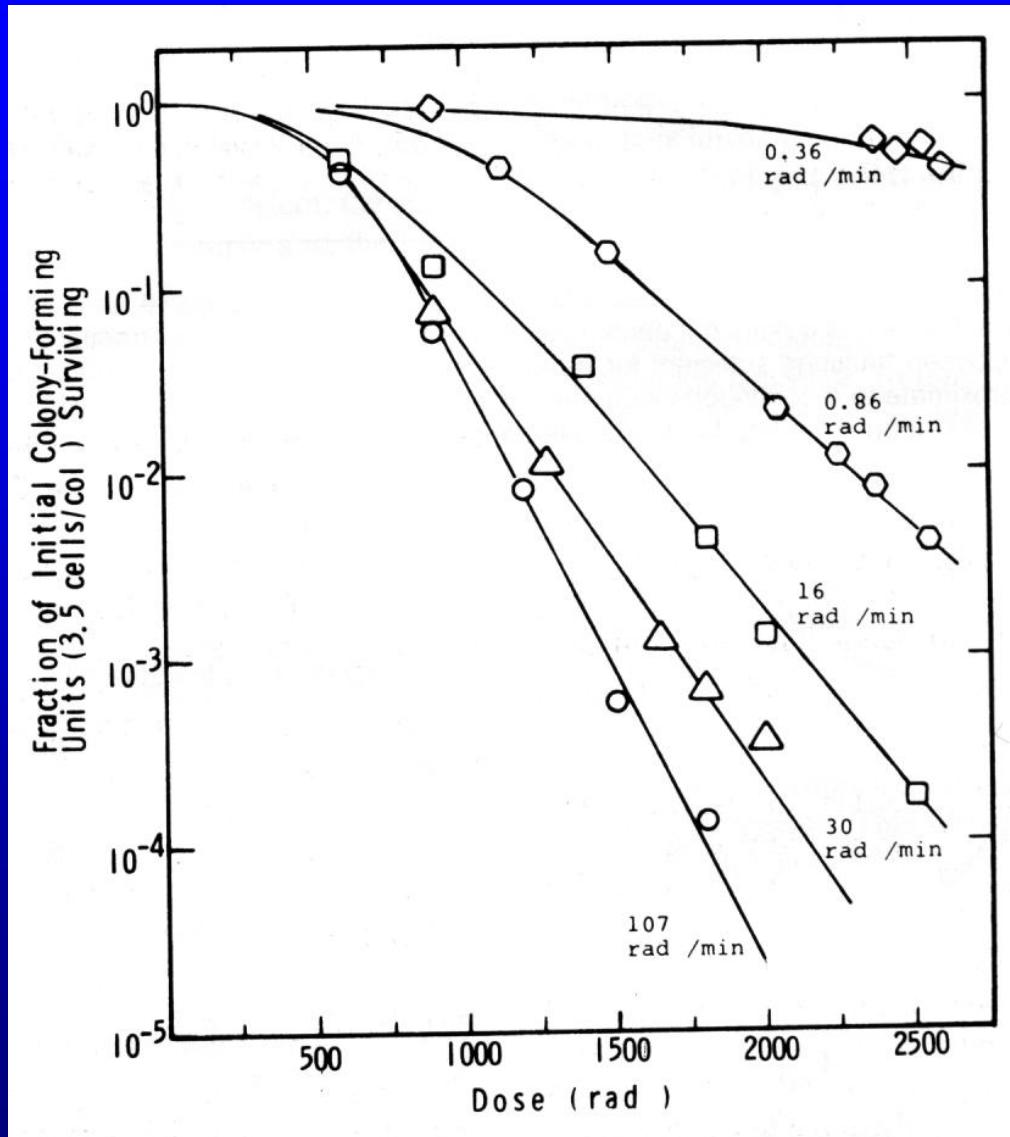


(E.J.H., Fig.4.4, p.55, 2000)

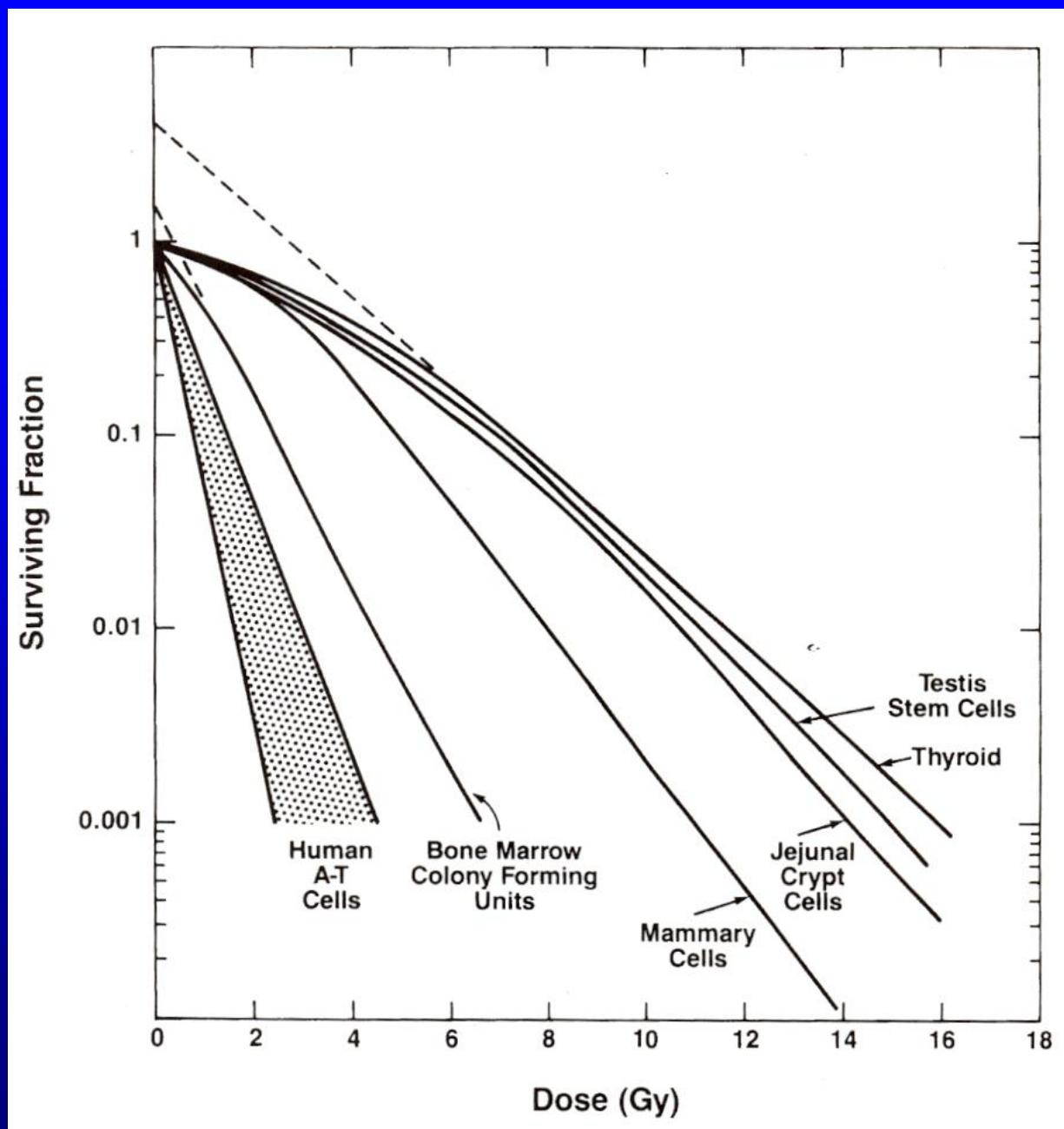
(E.J.H., Fig.17.16, p.304, 2000)



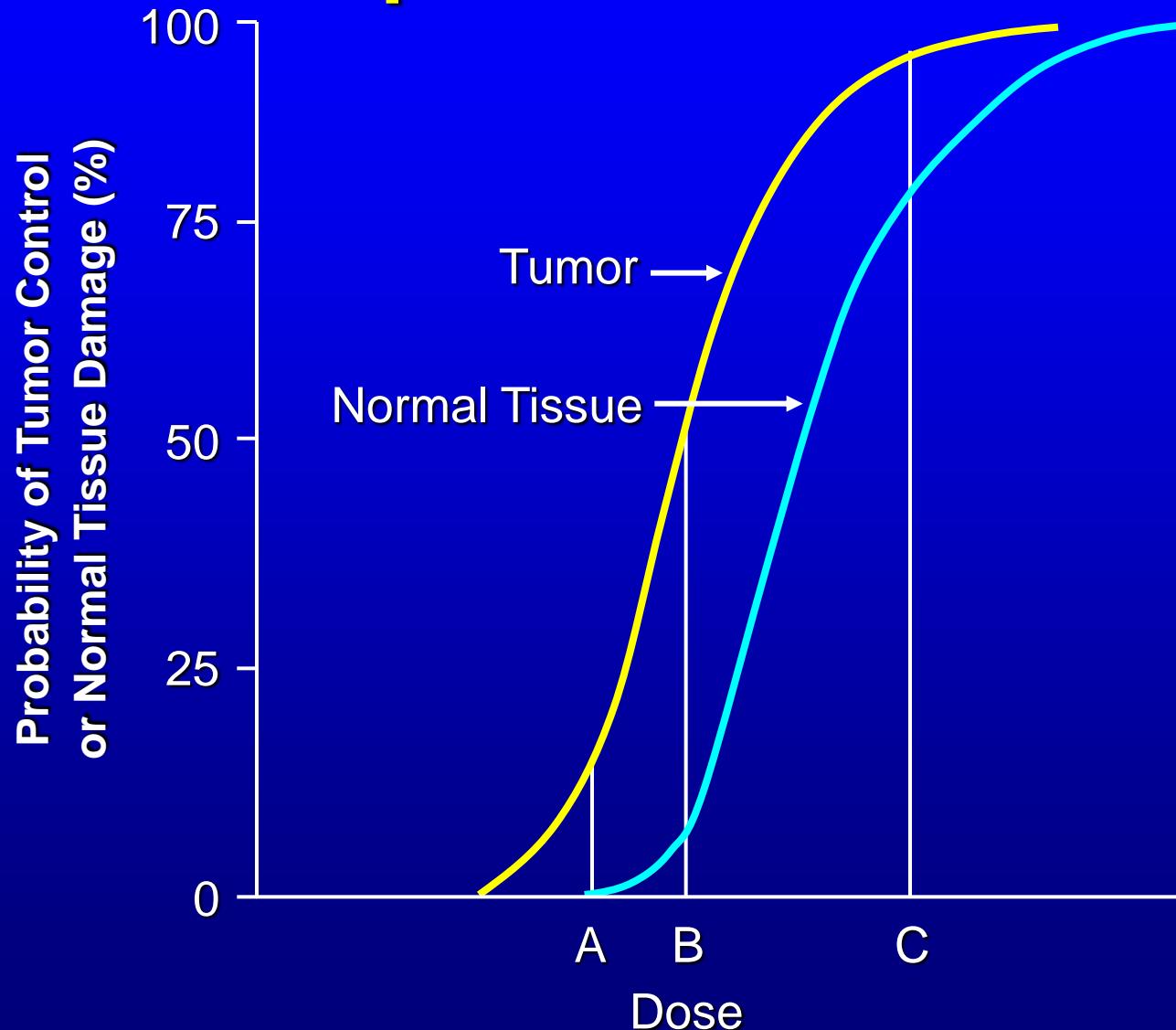
Dose rate effects



(E.J.H., Fig.5.10, p.76, 2000)



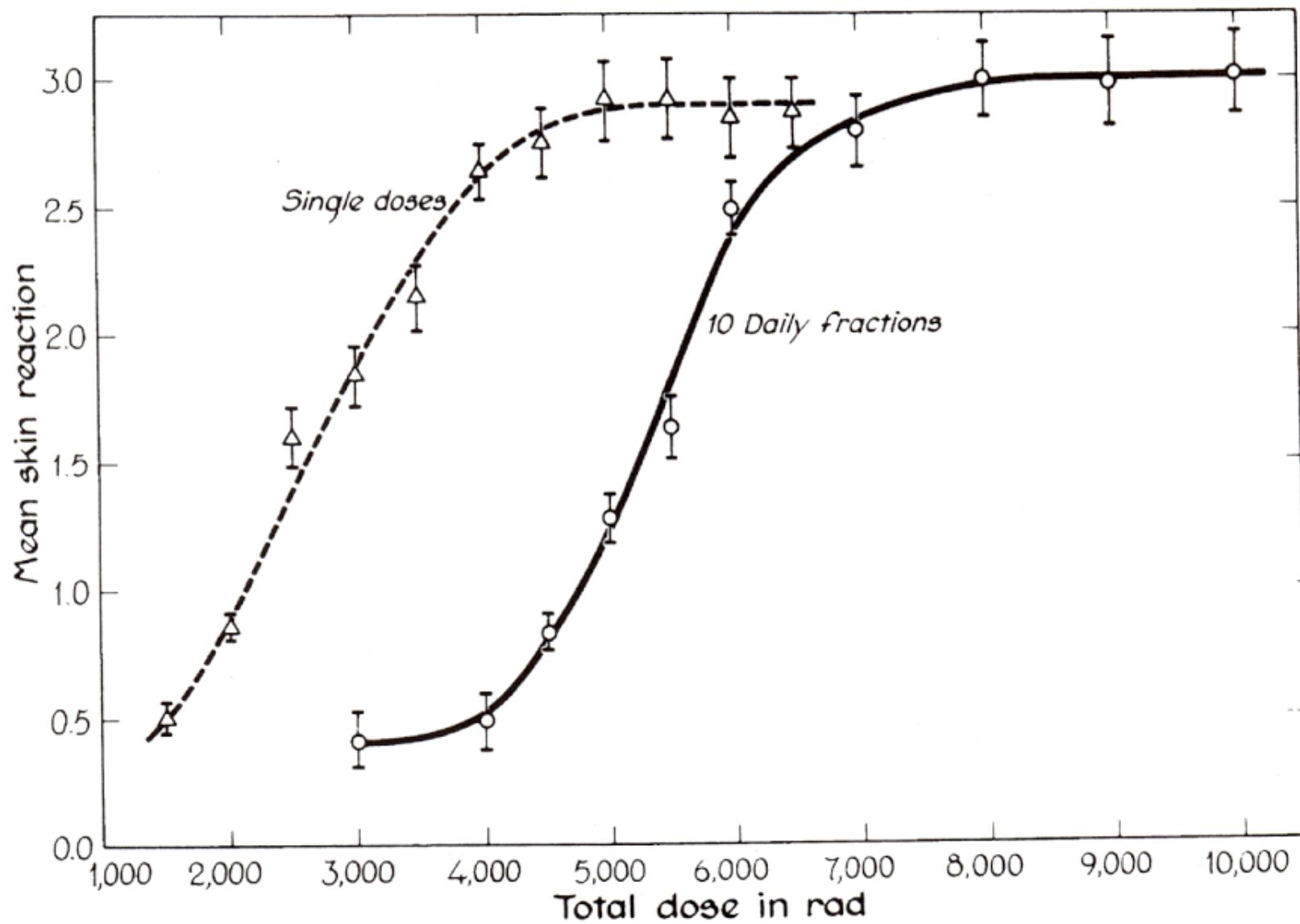
Tumor/Normal Tissue Response Curves



Treatment outcomes depend upon the Probability of Tumor Cure compared to the Probability of Early or Late Complications

Both tumor and normal tissue have a sigmoidal response

These curves demonstrate the concept of Therapeutic Ratio (TR). The majority of cancers have overlapping tumor control and NT injury. If the tumor curve is to the “left” of the NT then the TR is positive, but if the tumor curve is to the “right” of the NT then the TR is negative. A negative TR says that RT is not indicated except for palliation.



From clinical experience since Grubbe first gave radiation to a patient with breast carcinoma in January 1896 we have found the following fractionation scheme to produce acceptable results.

These fractionation schemes and doses derive as much from the need to avoid normal tissue effects as the need to cure a cancer.

Gross tumor, 1-4 cm, 10^9 to 10^{11} cells, 7000 cGy in 35 fractions

Microscopic residual disease, 10^6 to 10^7 cells, 5000 cGy in 25 fractions

Palliation, 3000 cGy in 10 fractions

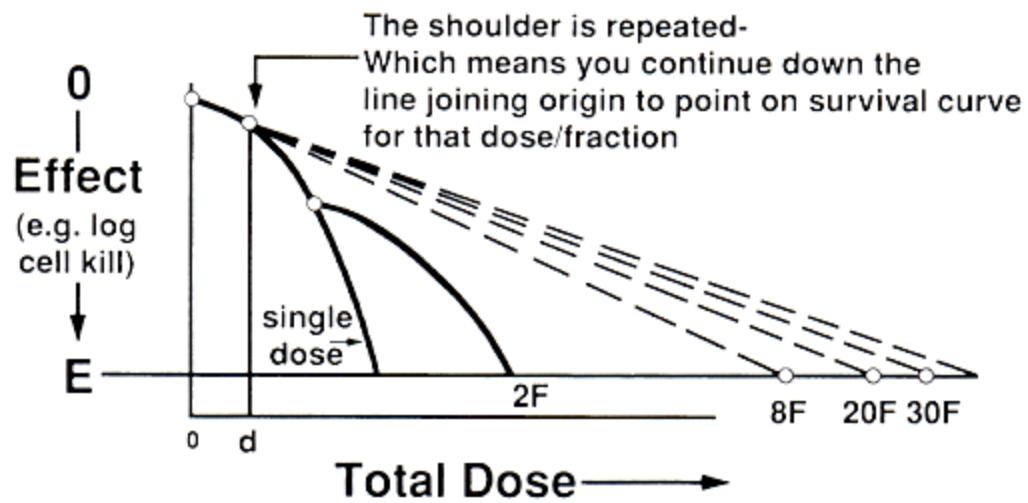
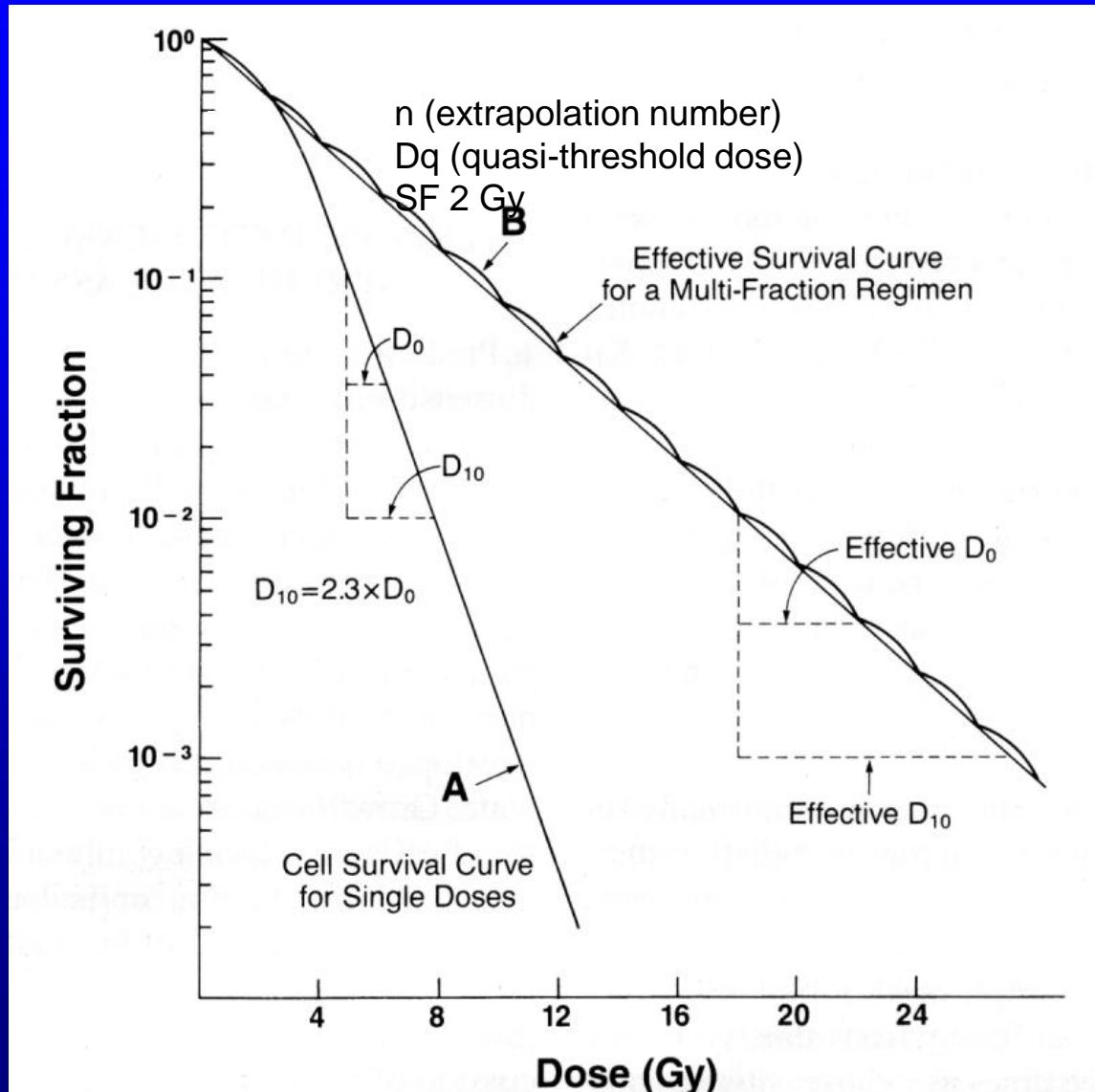


Figure 22.11. Graph illustrating that, if the dose–response relationship is linear-quadratic in form for graded single doses, the effective dose–response curve for a multifraction regimen approaches an exponential function of dose for many doses. The effective dose–response relationship is a straight line from the origin through the point on the single dose survival curve corresponding to the daily dose fraction (typically 2 Gy). (Based on the concepts of Fowler.)

Radiobiological parameters



Dose calculations:

Typical D_0 is ~200 cGy and typical D_Q is 150 cGy

For multifraction regimen, 200 cGy per fraction, this will give an effective D_0 of ~300 cGy with no shoulder

Examples

Tumor 1 cm Average mammalian cell size ~10 μm , so 10^9 cells.
Assume these all to be clonogens.

$$e^{-1} = 0.368 \quad e^{-2.3} = 0.1$$

Thus a dose of 2.3 times the effective D will cause a tumor cell kill of 90%, 10% surviving. $2.3 \times 300 = 690$

For a 90% tumor cure probability we need a tumor cell depopulation of 10^{-10} or 10 logs of cell killing. With D_0 as above, we will need

$$300 \text{ cGy} \times 2.3 \times 10 = 6900 \text{ cGy radiation}$$

This is approximately the dose necessary to cure a small, 1 cm head and neck cancer with a 90% probability

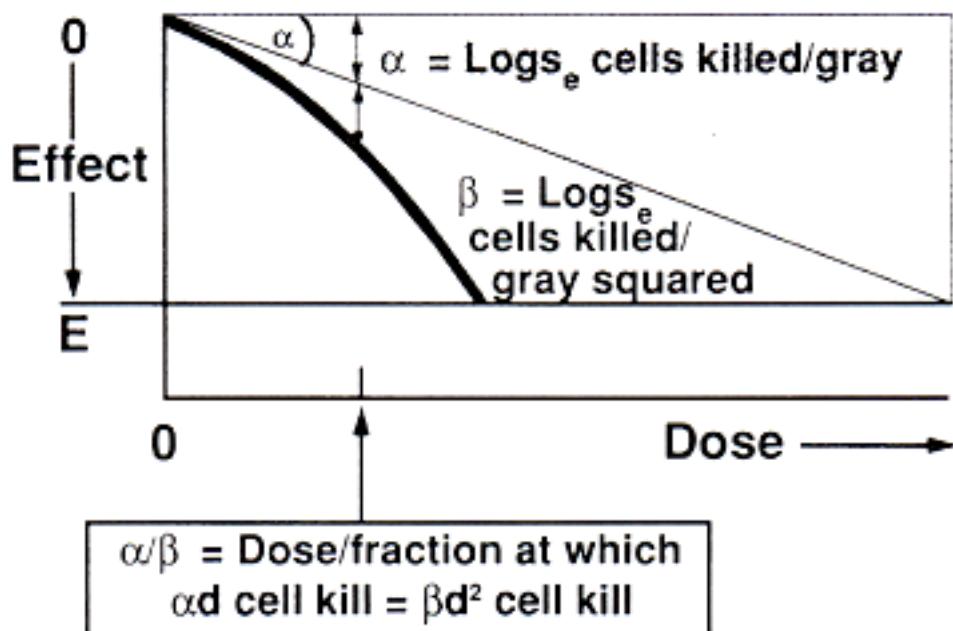


Figure 22.12. Graph illustrating the linear-quadratic nature of the radiation cell survival curve, $S = e^{-\alpha D - \beta D^2}$ in which S is the fraction of cells surviving a dose D, α is the number of logs of cell kill per gray from the linear portion of the curve, and β is the number of logs of cell kill per (gray)² from the quadratic component. The linear and quadratic components of cell kill are equal at a dose $D = \alpha/\beta$.

Two mathematical descriptions

- $D_Q - D_0$ or threshold linear exponential

$$\ln(s/s_0) = 0 \quad \text{for } D < D_Q$$

$$= \exp(-(D-D_Q)/D_0) \quad \text{for } D \geq D_Q$$

- alpha-beta one hit vs two hits

$$\ln(s/s_0) = \exp(-\alpha D - \beta D^2)$$

The probability to hit a critical target is proportional to dose:

the alpha component

The probability to hit two critical targets will be the product of those probabilities, therefore it will be proportional to dose²:

the beta component

Alpha/Beta formula for fractionated radiotherapy

$$SF = e^{-n(\alpha d + \beta d^2)}$$

Where

n = number of fractions

d = dose/fraction

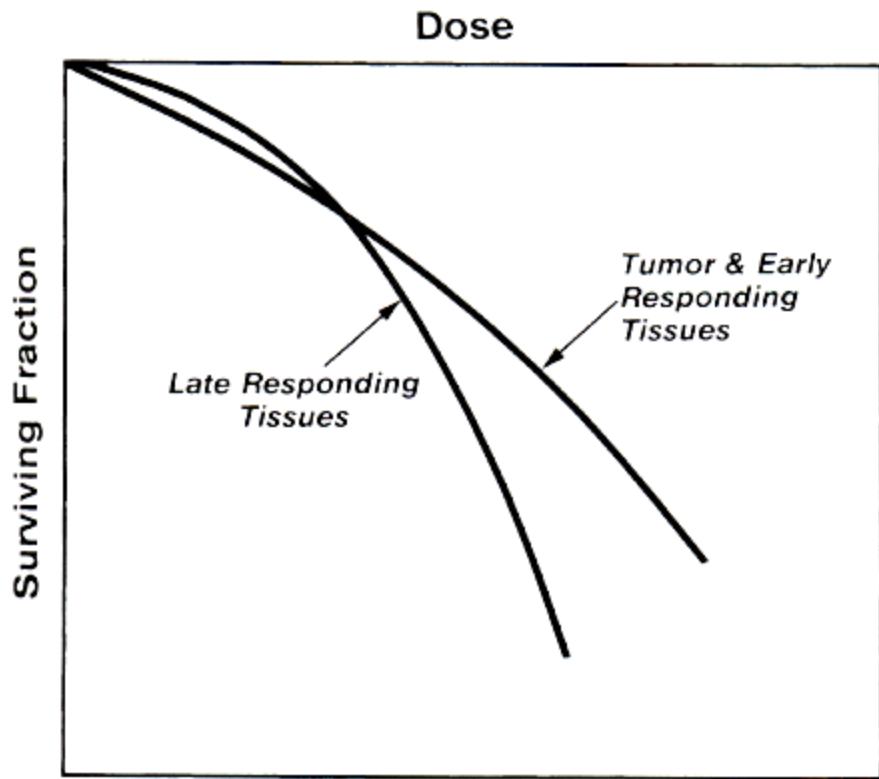
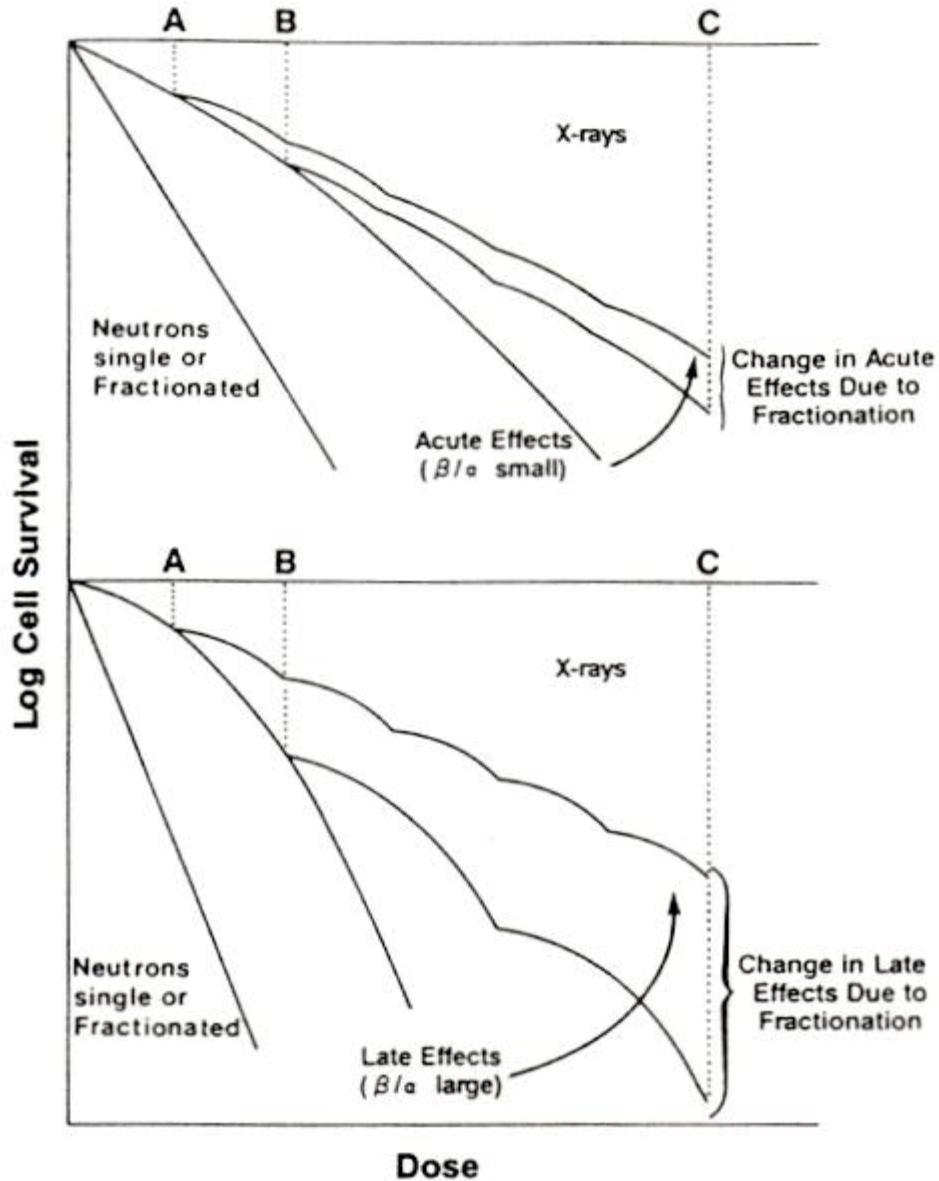


Figure 22.6. The dose-response relationship for late-responding tissues is more curved than for early-responding tissues. In the linear-quadratic formulation this translates into a larger α/β for early than for late effects. The ratio α/β is the dose at which the linear (α) and the quadratic (β) components of cell killing are equal: that is, $\alpha D = \beta D^2$. (Based on the concepts of Withers.)

Clinical and experimental evidence shows that:

- When low d/f is replaced with high d/f (with equal acute response) late effects are more severe
- RBE is larger for late effects than acute effects
- Hyperfractionation with 2 relatively low doses/day results in fewer late effects
- Isoeffect curves are steeper for late than acute effects

Fractionation results in somewhat different curves depending upon the dose per fraction and whether the effects considered are acute or late



Late Effects: Dose/Fraction most important

Acute Effects: Fraction size is less important

The shoulder or threshold dose, or the onset of the squared dose response appears to be smaller for long term sequelae than for acute reacting normal tissues or for tumor tissue

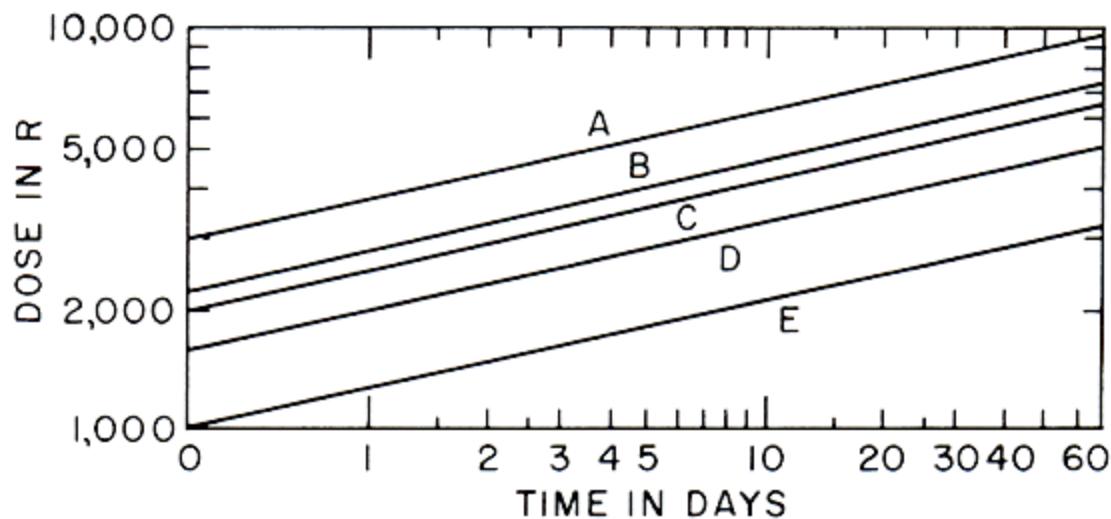


Figure 22.2. Isoeffect curves relating the total dose to the overall treatment time for skin necrosis (A), cure of skin carcinoma (B), moist desquamation of skin (C), dry desquamation of skin (D), and skin erythema (E). (Adapted from Strandquist M: Acta Radiol 55[suppl]:1–30O, 1944, with permission.)

Ellis (1969) improved on this formula

Total dose proportional to $N^{0.24} \times T^{0.11}$

This became the “Ellis Formula”

Total dose = NSD $\times N^{0.24} \times T^{0.11}$

Where

N = number of fractions

T = overall time

NSD = nominal single dose (RETS)

Example: **What is the NSD for 60 Gy given 2 Gy/fraction over 6 weeks?**

$$60 \text{ Gy} = \text{NSD} \times 30^{0.24} \times 42^{0.11}$$

$$60 \text{ Gy} = 17.58 \text{ RETS}$$

This formula has been used to equate different dose regimens, but because the formula is based on **skin reactions**, it can not predict late effects.

Another weakness is the exponent on T. Because there is accelerated proliferation after irradiation, this factor can not be a constant.

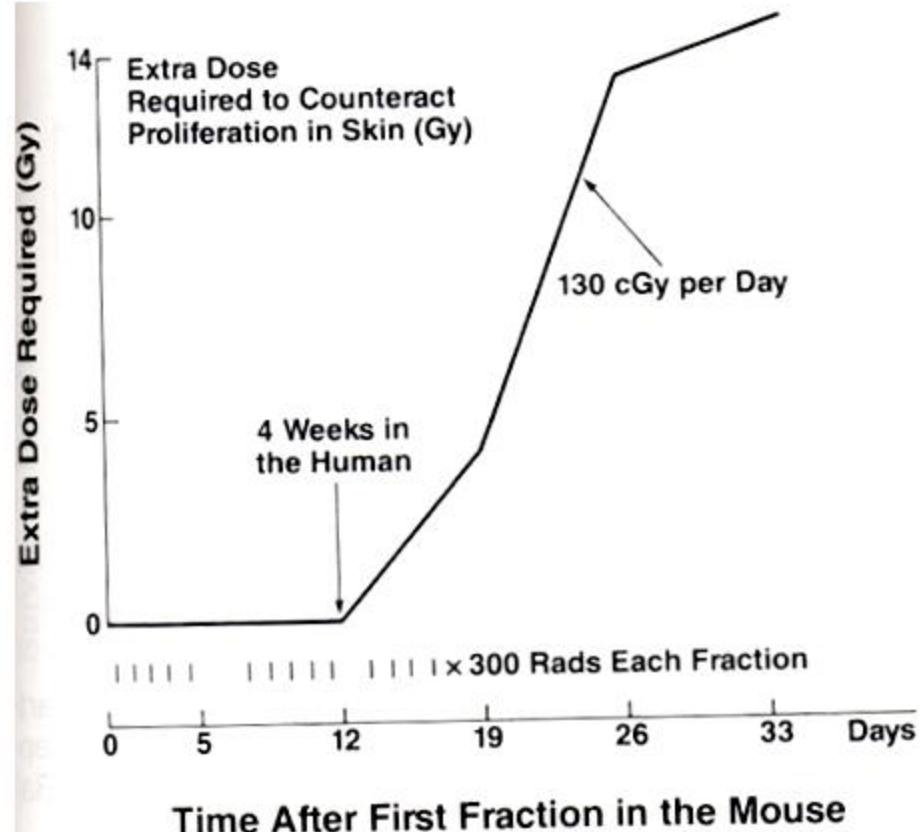


Figure 22.3. The extra dose required to counteract proliferation in the skin of mice as a function of time after starting daily irradiation with 300 cGy per fraction. A delay followed by a rapid rise is typical of time factors in proliferating normal tissues. In mouse skin the delay is about 2 weeks; in humans it is about 4 weeks. (Adapted from Fowler JF: Acta Radiol 23:209–216, 1984, with permission; data from Denekamp J: Br J Radiol 46:381, 1973.)

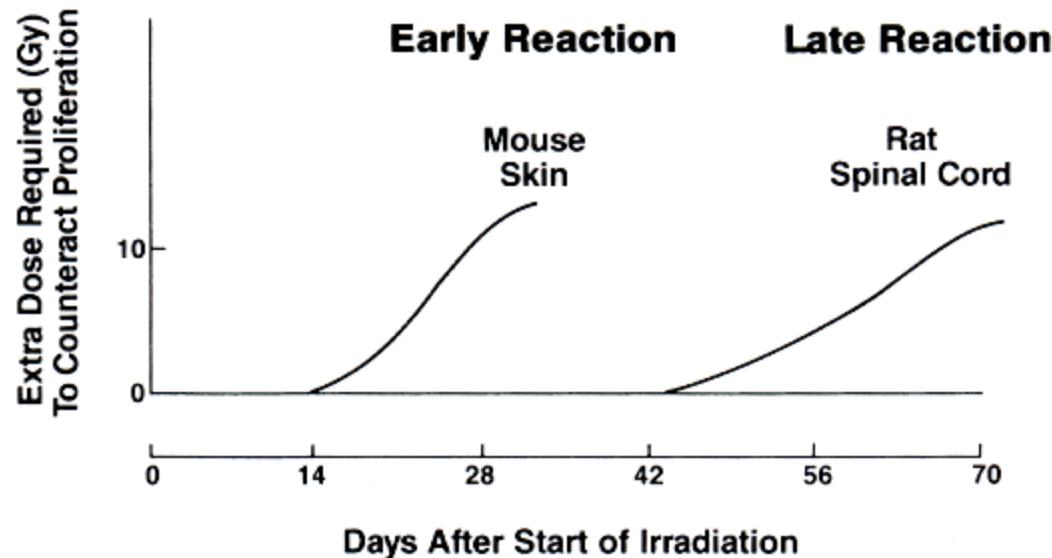


Figure 22.4. The extra dose required to counteract proliferation only as a function of time after starting daily irradiation in rodents. The left curve represents a typical early reaction; the right curve represents a typical late reaction. The delays are much longer in humans. (Adapted from Fowler JF: Radiother Oncol 1:1–22, 1983, with permission.)

What is the effect of proliferation?

Late Effects: Little sparing is noted

Early Effects: Large sparing

LQ calculation of isoeffect

Single Dose:

$$S = e^{-(\alpha D + \beta D^2)}$$

Fractionated Doses:

$$S = e^{-n(\alpha d + \beta d^2)}$$

Take natural log (\ln) of both sides

$$-\ln S = n(\alpha d + \beta d^2)$$

Factor out dose/fraction (d)

$$-\ln S = nd(\alpha + \beta d)$$

Divide by alpha

$$\frac{-\ln S}{\alpha} = nd(1 + \frac{d}{\beta}) = BED$$

Remember $nd = D = \text{Total dose}$

Biologically Effective Dose

BED

Practice Problem

The planned treatment for a head and neck cancer patient is 70 Gy in 35 daily fractions. What are the BED values for acute skin reactions and for late fibrosis? (Assume α/β ratios of 10 Gy for acute skin reactions and 3.5 Gy for late fibrosis.)

Practice Problem Solution

- $\text{BED} = \text{nd} \times [1 + d/(\alpha/\beta)]$
- Acute skin reaction: $\text{BED} = 70 \times [1 + 2/10] = 84 \text{ Gy}_{10}$
- Late fibrosis: $\text{BED} = 70 \times [1 + 2/3.5] = 110 \text{ Gy}_{3.5}$

Practice Problem

Assume tolerance for whole brain irradiation at 1.8 Gy/fraction is 50.4 Gy and that α/b for brain is 2.0. What is the tolerance of the brain at 3 Gy/fraction?

Practice Problem Solution

- $(nd/n_1d_1) = (\alpha/\beta + d_1)/(\alpha/\beta + d)$
- $n_1 = nd(\alpha/\beta + d)/((\alpha/\beta + d_1)d_1)$
 $= (50.4/1.8) \times 1.8 \times (2.0 + 1.8)/(2.0 + 3) \times 3$
 $= 13 \text{ fractions}$

Therefore, tolerance dose, $nd = 13 \times 3 = 39 \text{ Gy}$

What is the BED of 30F x 2 Gy/6 weeks (Early)?

$$\begin{aligned} & 30 \times 2 (1 + \underline{2}) \\ & \qquad \qquad \qquad 10 \\ & = 72 \text{ Gy}_{10} \end{aligned}$$

For late effects alpha/beta of 3 is appropriate

$$\begin{aligned} & 30 \times 2 (1 + \underline{2}) \\ & \qquad \qquad \qquad 3 \\ & = 100 \text{ Gy}_3 \end{aligned}$$

CHART (Cont. Hyperfrac. Accel. RT)
36F x 1.5 Gy/12 days (three fractions per day)

$$\begin{aligned} & 36 \times 1.5 (1 + \underline{1.5}) \\ & \qquad \qquad \qquad 10 \\ & = 62.1 \text{ Gy}_{10} \text{ or} \\ & = 81.0 \text{ Gy}_3 \end{aligned}$$

The effect of proliferation:

In treatment regimens over long periods of time, the tumor can repopulate some of the lost cells by proliferation.

$$S = e^{-n(ad + \beta d^2)} \times e^{\gamma t}$$

Where $e^{\gamma t}$ is the fraction of cells added to the population by proliferation during the course of treatment. This can be rewritten as follows:

$$S = e^{-n(ad + \beta d^2) + \gamma t}$$

$$\frac{-\ln S}{\alpha} = \frac{nd(1 + \frac{d}{\alpha}) - 0.693}{\alpha} \frac{t}{T_{pot}}$$

The effect of proliferation is related to T_{pot} and is equal to the $\ln 2/T_{pot}$ or $0.693/T_{pot}$

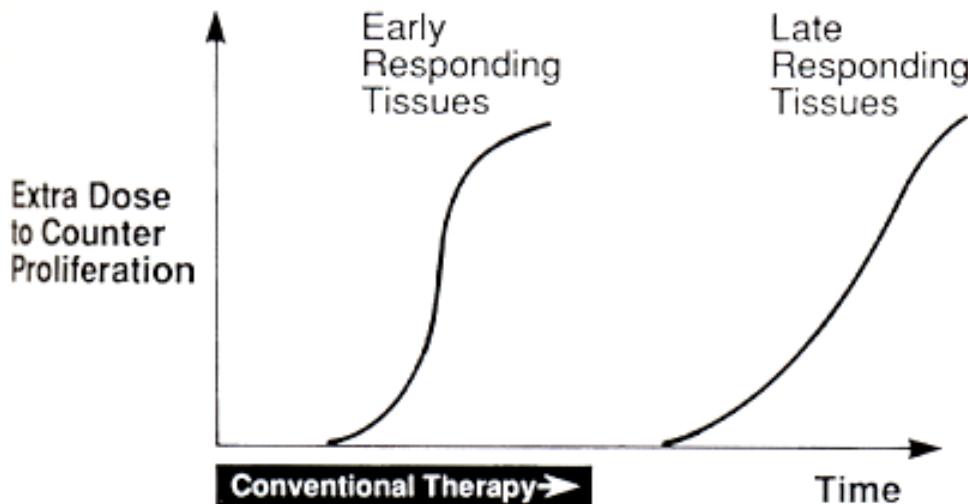
For Isoeffect two regimens are equated:

$$\text{BED}_1 = \text{BED}_2$$

Assume STN regimen is 30F/2 Gy 6 weeks and we want to initiate a hyperfractionation regimen with equal early effects giving 1.2 Gy/fraction. How many fractions are needed?

$$\frac{n_1 d_1 (1 + \frac{\alpha}{\beta})}{d_2 (1 + \frac{\alpha}{\beta})} = n_2$$

$$\frac{30 \times 2(1.2)}{1.2 (1.12)} = 53.6 \text{ fractions}$$



"Prolonging overall treatment time spares
Early but not **Late** responding tissues"

Figure 22.5. Highly speculative illustration attempting to extrapolate the experimental data for early- and late-responding tissue in rats and mice to principles that can be applied in clinical radiotherapy. The extra dose required to counter proliferation in early-responding tissues begins to increase after a few weeks into a fractionated regimen, certainly during the time course of conventional therapy. By contrast, conventional protocols are never sufficiently long to include the proliferation of late-responding tissues.

Spaghetti Plot

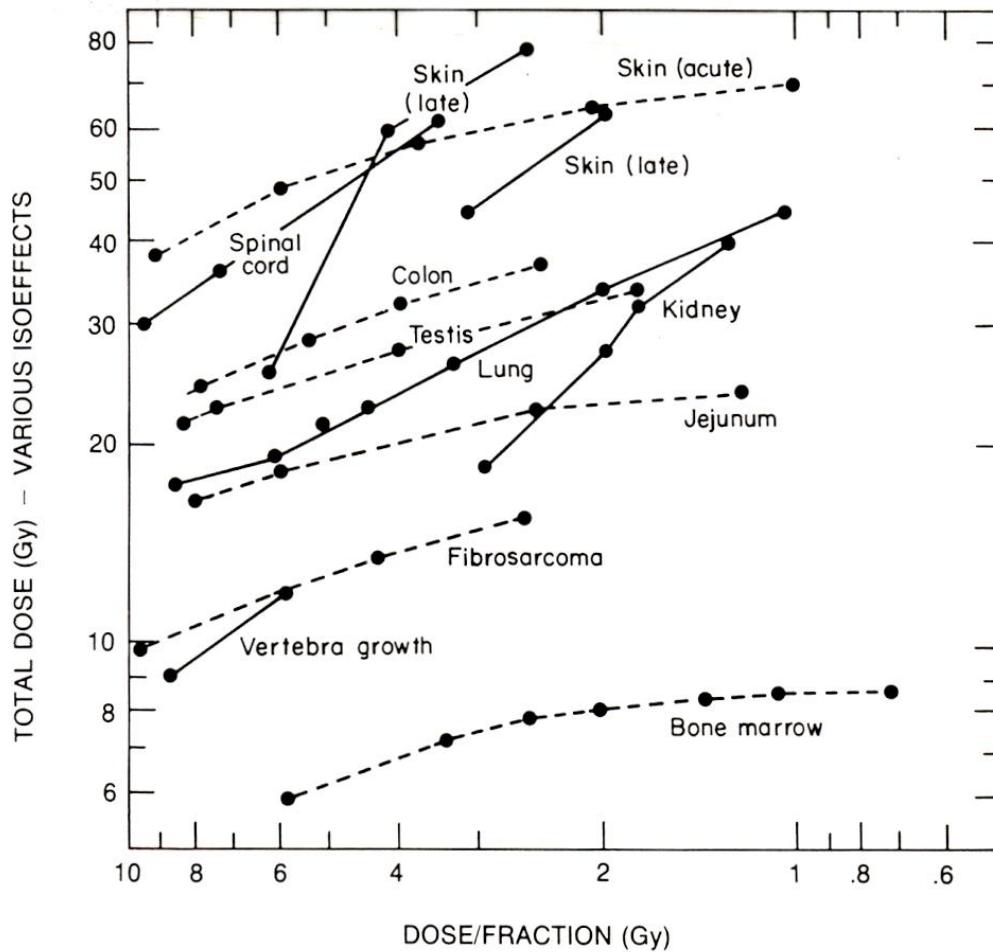


Figure 13-9. Isoeffect curves in which the total dose necessary for a certain effect in various tissues is plotted as a function of dose per fraction. Late effects are plotted with solid lines, acute effects with dashed lines. The data were selected to exclude an influence on the total dose of regeneration during the multifraction experiments. The main point of the data is that the isodoses for late effects increase more rapidly with decrease in dose per fraction than is the case for acute effects. (From Withers HR: Cancer 55:2086, 1985)

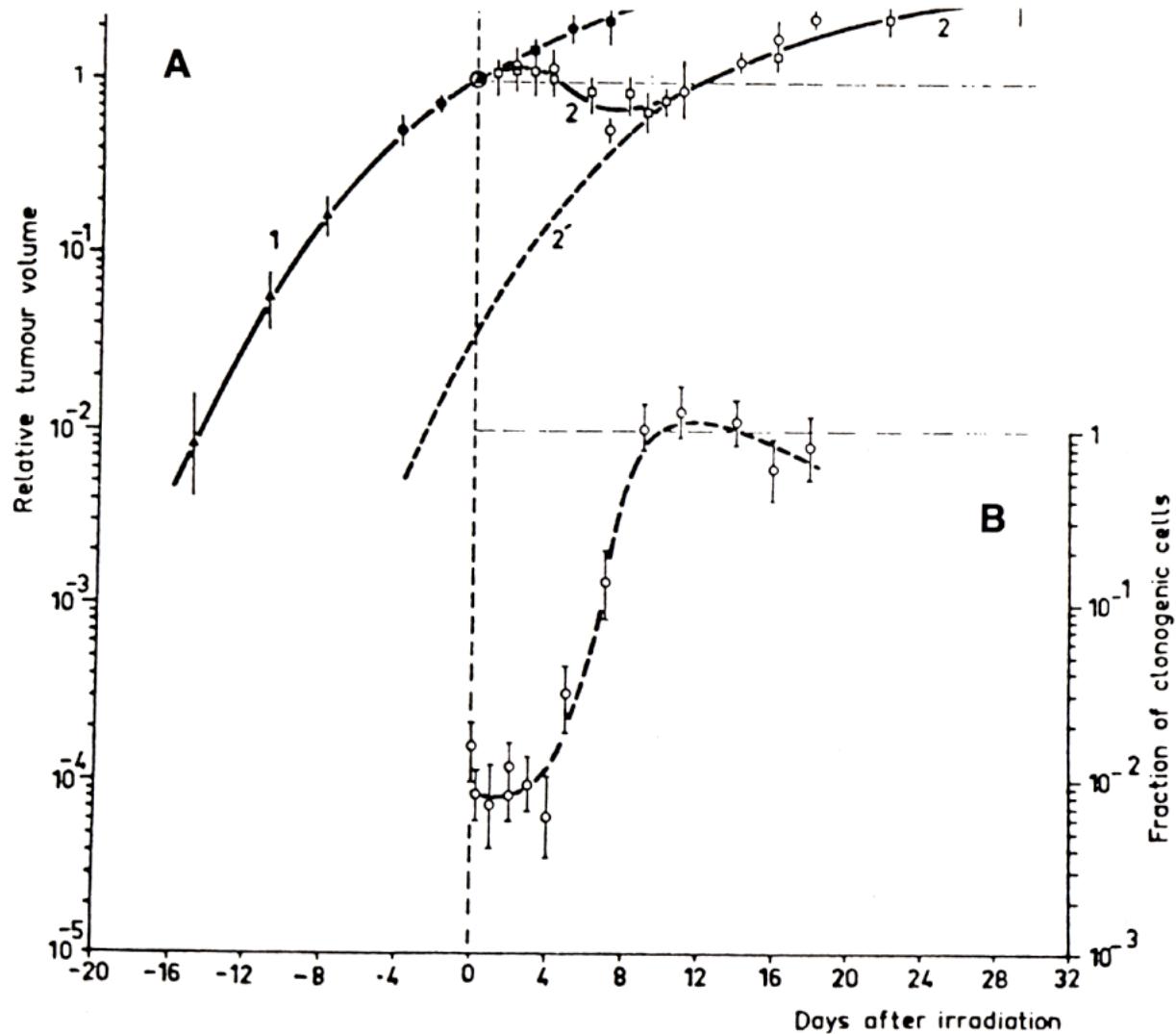


Figure 13-10. Illustrating Accelerated Repopulation. Growth curves of a rat rhabdomyosarcoma showing the shrinkage, growth delay, and subsequent recurrence following treatment with a single dose of 20 Gy (2000 rads) of x-rays. **(A)** Curve 1: Growth curve of unirradiated control tumors. Curve 2: Growth curve of tumors irradiated at time $t = 0$, showing tumor shrinkage and recurrence. **(B)** Variation of the fraction of clonogenic cells as a function of time after irradiation, obtained by removing cells from the tumor and assaying for colony formation in vitro. (From Hermens AF, Barendsen GW: Eur J Cancer 5:173–189, 1969)

Effect of Repopulation or Accelerated Growth

The time of radiation therapy to give 6900 cGy:

7 weeks to give 35, 200 cGy fractions

Assume that the average doubling time is approximately two weeks. Then there will be three cell doublings

$$2^3 = 8, \text{ approximately } 10$$

This will require an additional log of cell kill or an additional 690 cGy,

Total = 7590 cGy

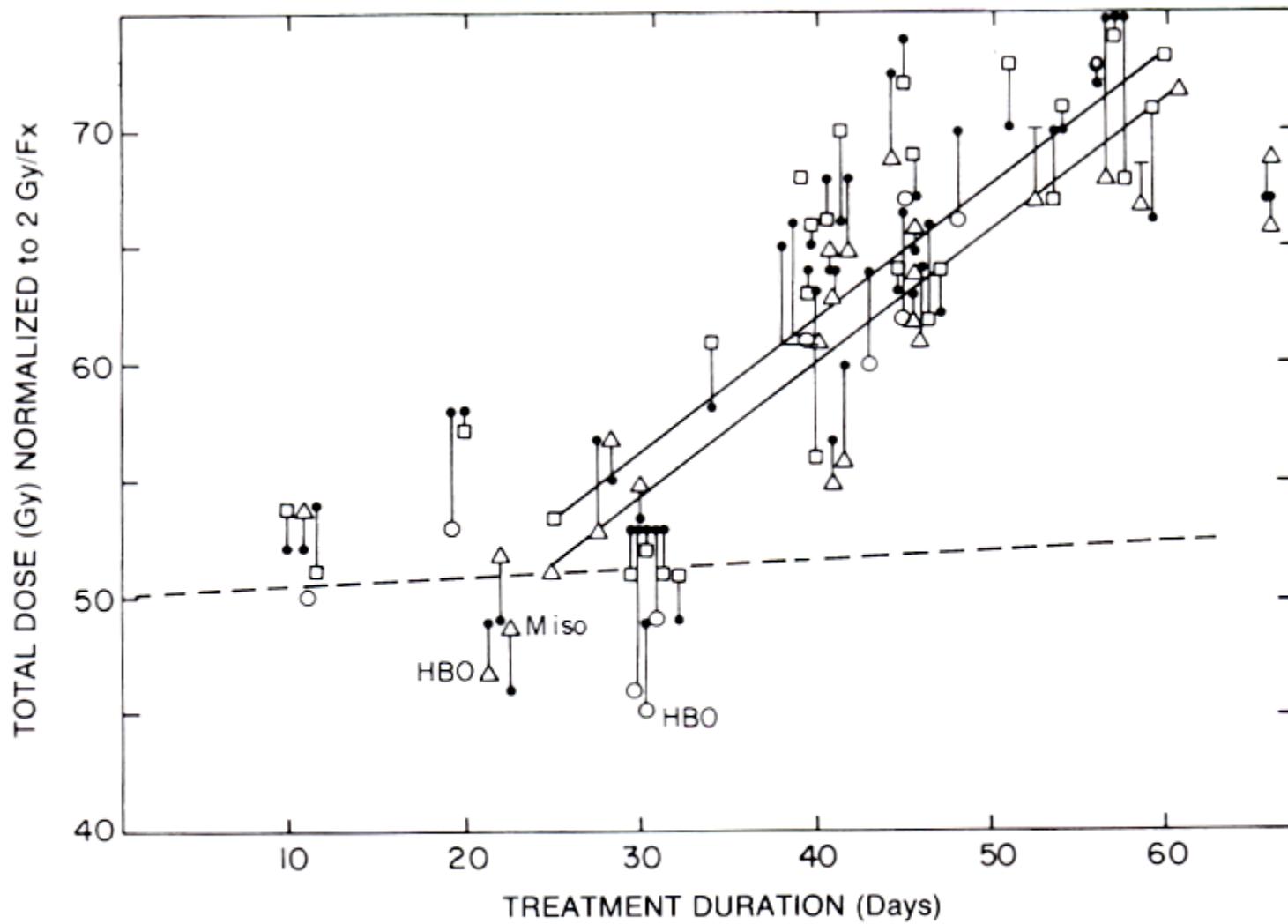


Figure 22.9. Doses to achieve local control in 50% of cases (TCD_{50}), as a function of overall treatment time, for squamous cell tumors of the head and neck. The data points include many published results from the literature, including high-pressure oxygen trials (HBO), and the trial of misonidazole (Miso). The *dashed line* shows the rate of increase in TCD_{50} predicted from a 2-month clonogen doubling rate. (From Withers HR, Taylor JMG, Maciejewski B: The hazard of accelerated tumor clonogen repopulation during radiotherapy. *Acta Oncol* 27:131–146, 1988, with permission.)

Chances of long term sequelae depend on:

Dose

Fraction Size

Volume Treated

Nature of the Cells Treated

Overall Organization of the Tissue

Biologically Effective Dose (BED)

**Not to Be Confused With the
Banana Equivalent Dose Also
Known as (BED)**

BANANA Equivalent Dose

- Bananas are high in potassium (K).
- K40 is 0.0118% of total potassium
- K40: 19.2 Bq (520 pCi) per 150 gm banana.
- 1 year dose, 365 bananas, 3.6 mrems.
- On 4/5/2011 Japan Reactor Release Spiked at 30 bananas and fell to 2 bananas/day
- Three Mile Island Radioactive Iodine Dose in Milk determined to be 20 pCi/liter, much less than a single banana.

Radioactive Elements in Human Adult Body

- K40 4,340 Bq
- C14 3,080 Bq
- Ru87 600 Bq
- Pb210 15 Bq
- H3 7 Bq