Curso de Radiobiología
UDELAR
Facultad de Ciencias
Unidad de Física Médica

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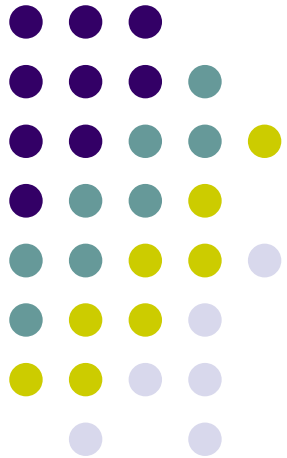
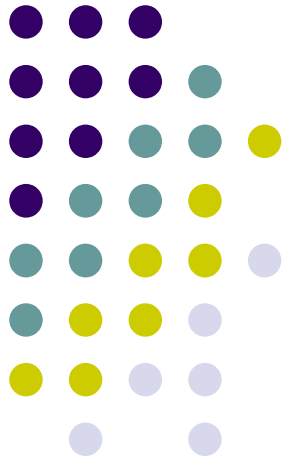


4R. Tasa de dosis

Créditos:

Dr. Jerry Battista



The Story so far…

- *Once upon a time there was natural ionizing radiation.*
- *Uncontrolled ‘man-made’ radiation caused unexpected bad effects (e.g. early radiologists developed leukemia).*
- *Controlled radiation is useful in biomedicine and power generation.*
- *In accidents or in the wrong hands, however, radiation can be deadly.*
- *Radiation knocks out charged particles that can hit molecules or create chemicals that corrupt DNA*
- *We can modulate the effects using different types of radiation (LET) or adding chemicals (radiosensitizers, radioprotectors)*
- *DNA damage, if left unrepaired or misrepaired, leads to funny-looking chromosomes and products that either kill a cell, or cause it to malfunction, or behave very badly (e.g. cancer induction)*
- *Cells react non-linearly to radiation, and are affected by the timing of dose delivery (dose fractionation or dose rate) as well as the 4Rs*

MBP 4467B

Feb 2011

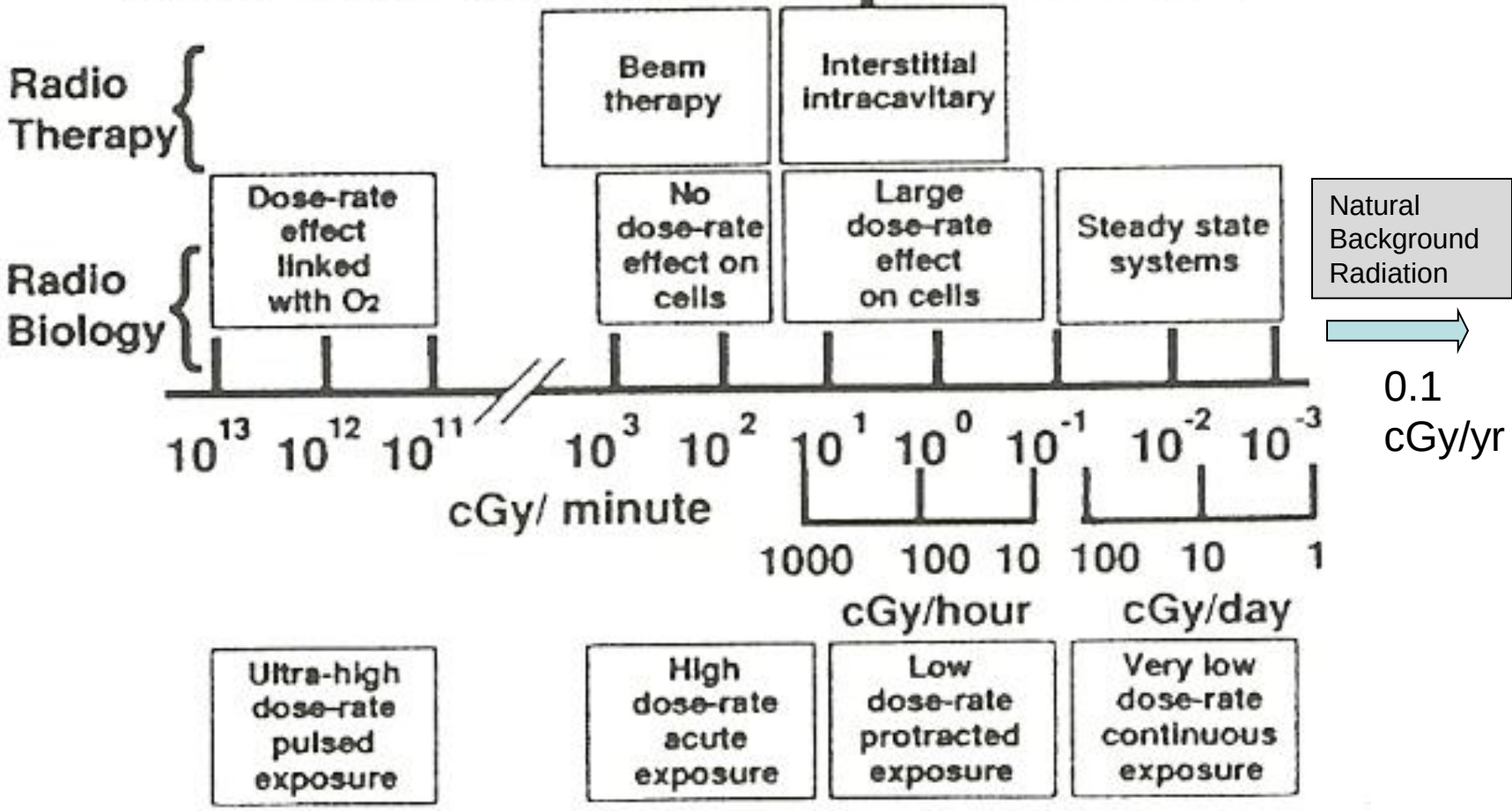
Dose Rate
&
Dose Fractionation

Saying #2: "*It's all a Complex Matter of Space and Time*"

J. Battista, Ph.D.

Chapter 5 and Chapter 22

The Dose-rate Spectrum

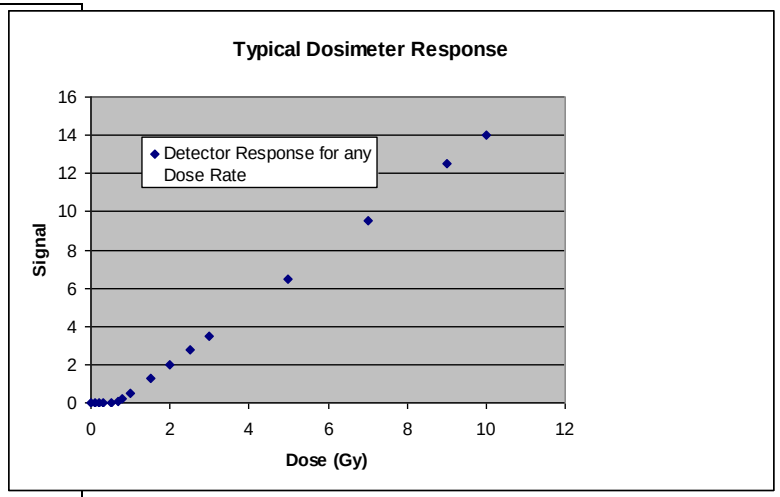


Physical and Biological Systems

Physical Systems (Ideal Dosimeters)

- Respond to Dose (only)
- Linear response
- Independent of dose rate
- Response depends on

  D = Dose Rate x Time (reciprocity holds)



Biological Systems (Non-Ideal Dosimeters)

- Response to LET, O_2, 4Rs, etc.
- "Loggish" shape due to statistics
- Dependent on dose rate/fractionation
- Response does **not** track with
  - Dose Rate x Time (reciprocity failure)

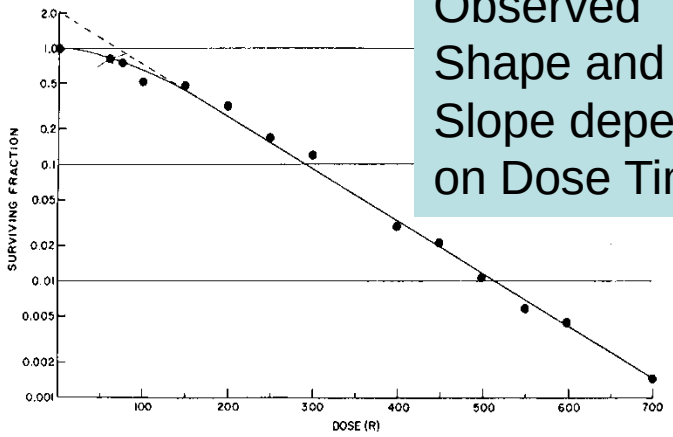


Figure 3-5. Survival curve for HeLa cells in culture exposed to x-rays. Characteristically, this cell line has a small initial shoulder. (From Puck TT, Marcus PI: J Exp Med 103:653, 1956; courtesy of the author and Rockefeller University Press)

Observed Shape and Slope depends on Dose Timing

Some Famous “4’s”

R1 Repair

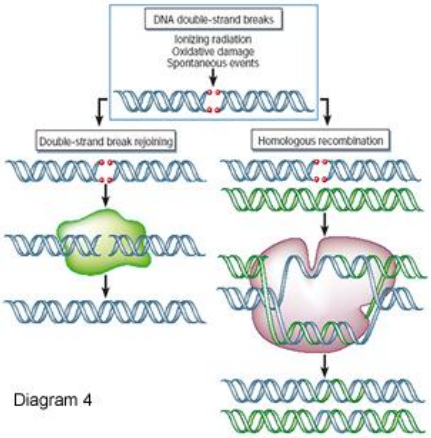
R2 Re-Assortment
(Redistribution)

R3 Repopulation

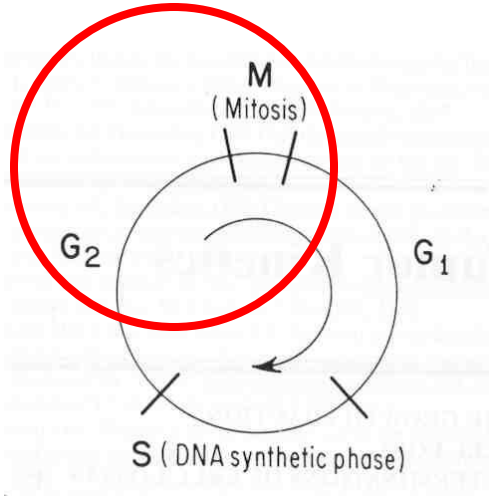
R4 Oxygenation

Radiobiology “4 R’s”

- R1 – Repair of DNA Damage
  - DSB’s are repaired by a set of enzymes
  - SSB Repair time on the order of minutes
  - DSB Repair time on the order of hours

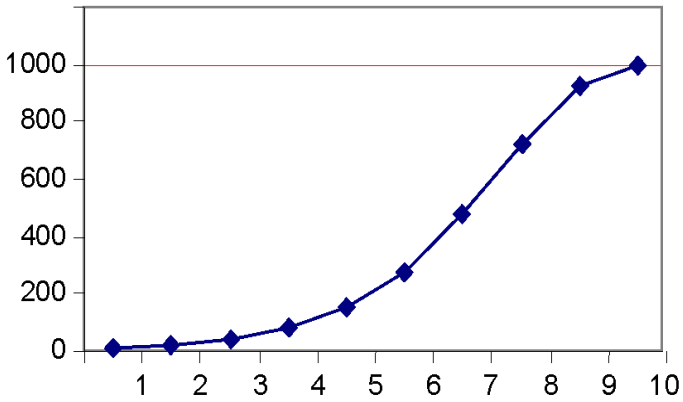


- R2 – Re-Assortment or Redistribution
  - Cell Cycle Effect or Cell age effect
  - Inverse Dose Rate Effect
    - expect the unexpected
  - Exposure times on the order of cell cycle (~ T_c)



Radiobiology “4 Rs”

- R3 – Repopulation or Replication
  - Cell replication competes with cell killing
  - – Critical Dose Rate (equilibrium)
  - – Exposure Time on the order of multiple cell cycles (~ nT_c)



Population growth trajectory ($N_1 = N_0 = (Rm - sN_0)N_0$, Rm = maximum rate of increase, here = 1, s = interaction coefficient, here = 0.0001, and carrying capacity of environment = 1000.

- R4 – Re-Oxygenation
  - – Oxygenated cells are more radiosensitive
  - – Inter-dose time gap offers re-oxygenating opportunity
  - – Dead cells removed, reduced O2 consumption, shorter diffusion distances, angiogenesis ?
  - – Re-oxygenation time on the order of <u>6 hours</u>

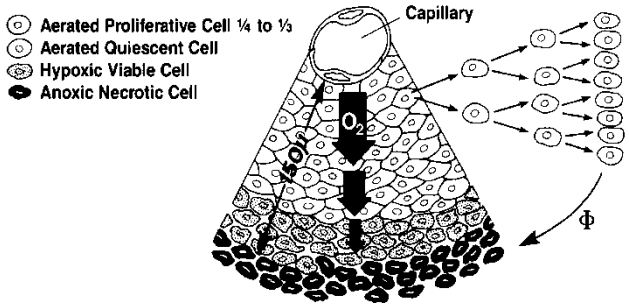
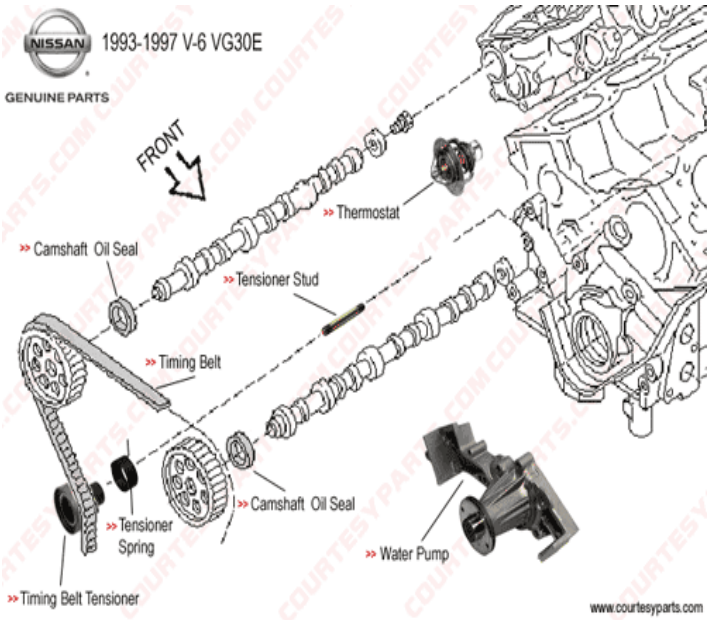


Figure 12-11. The overall pattern of the growth of a tumor. Clonogenic cells consist of proliferative (P) and quiescent (Q) cells. Quiescent cells can be recruited into the cell cycle as the tumor shrinks after treatment with radiation or a cytotoxic drug. In animal tumors the growth fraction is frequently 30% to 50%. Of the cells produced by division, many are lost, principally into necrotic areas of the tumor remote from the vasculature. The cell loss factor (Φ) varies from 0% to 100% and dominates the pattern of tumor growth. As the tumor outgrows its blood supply, some cells become hypoxic. This accounts for some of the quiescent cells that are out of cycle.

Yet another famous J2B saying # 5…

“Timing is Everything”



The duration of the radiation exposure relative to the time of biological processes determines the impact of dose rate and dose fractionation on cell survival.

Dose Rate/Fractionation Effects are due to 4 R's

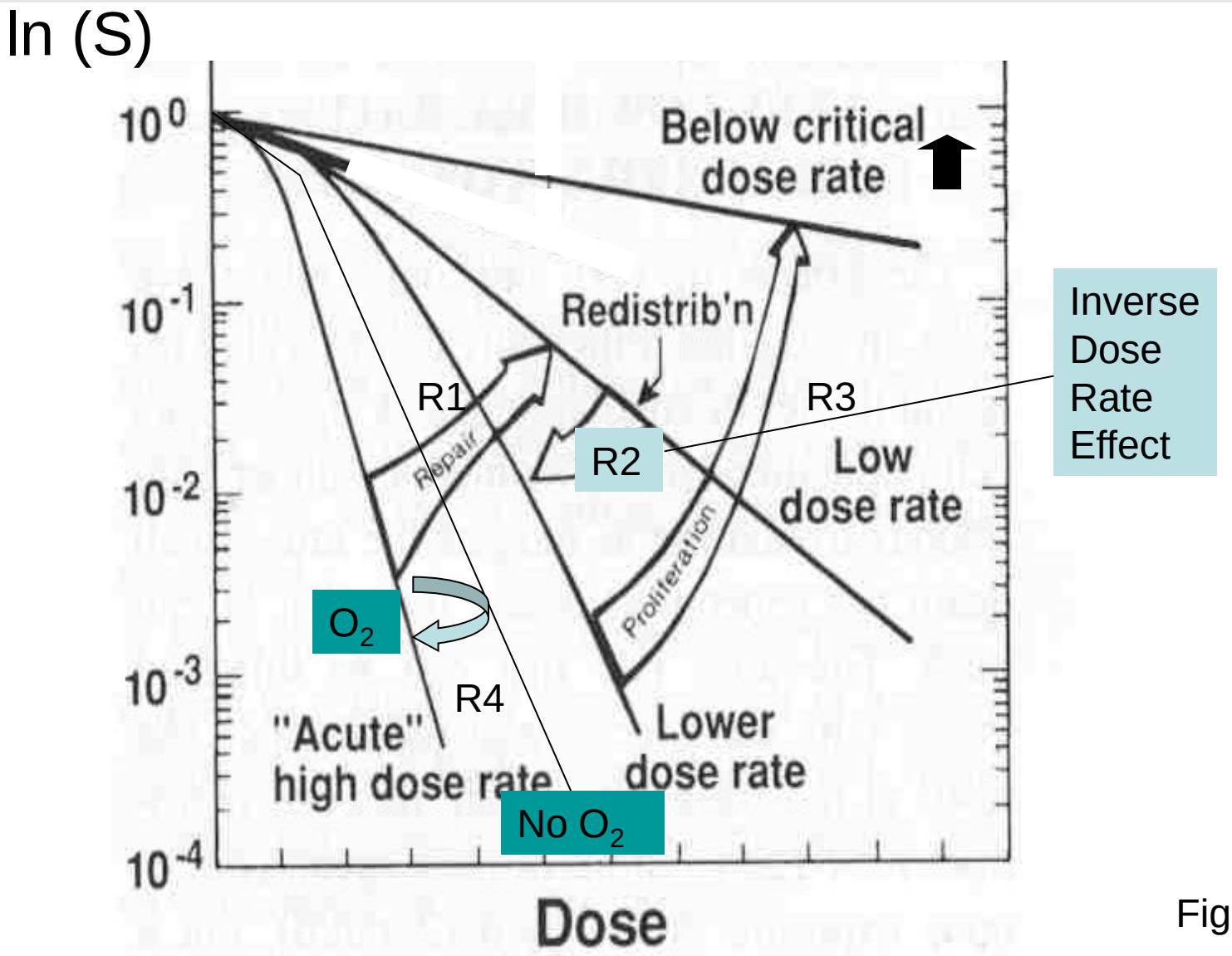


Fig 5.18

The Expected

R1- DNA Repair of Sublethal Damage

DNA Damage "Comet" Assay

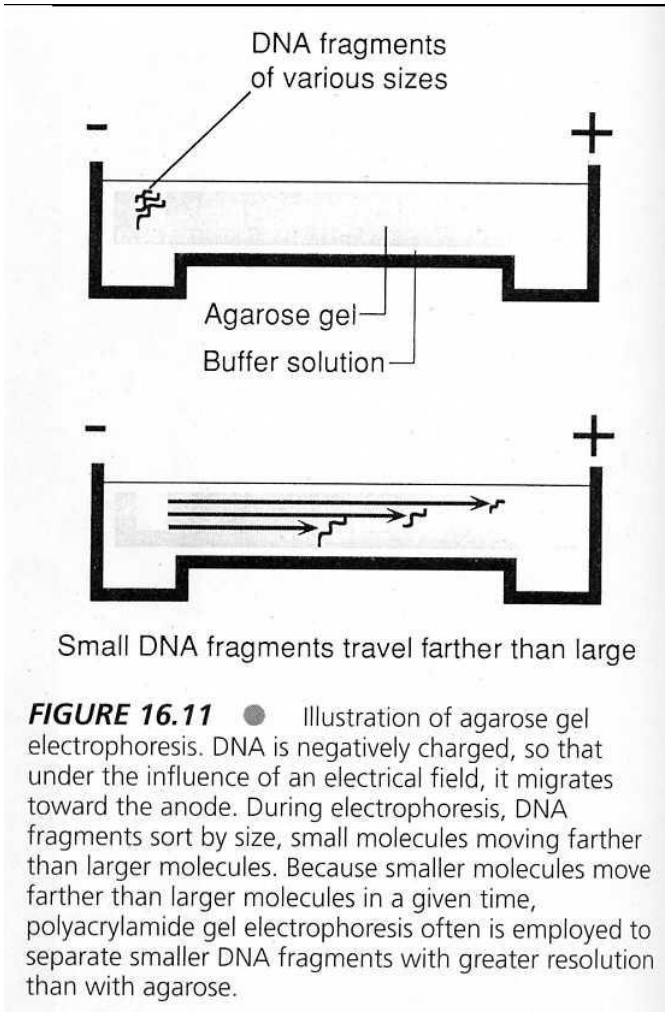
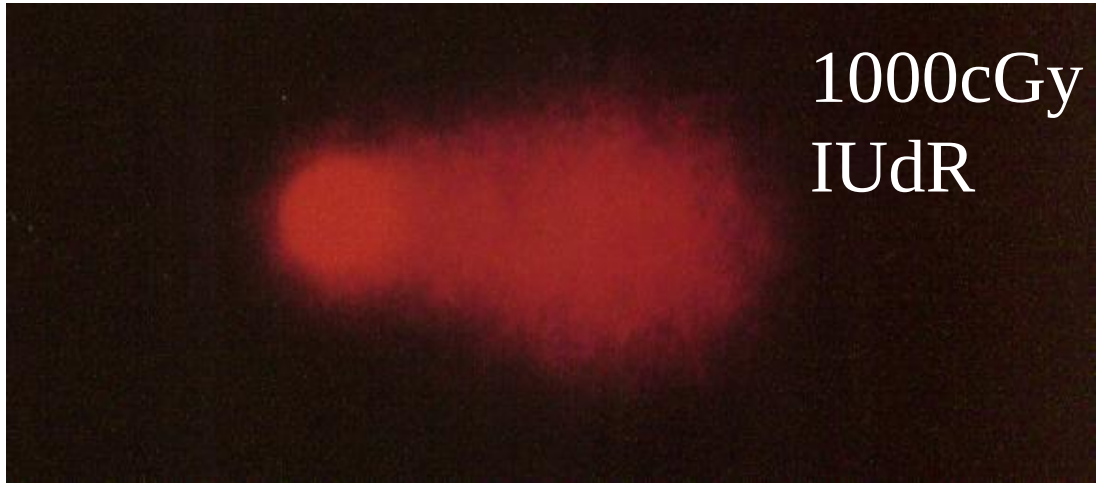
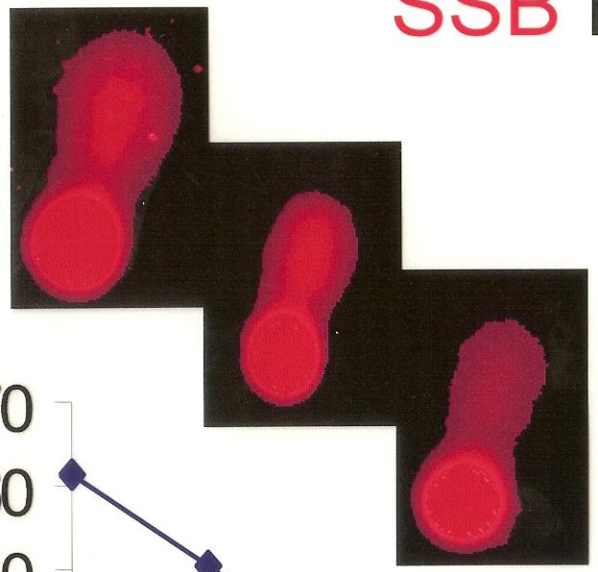


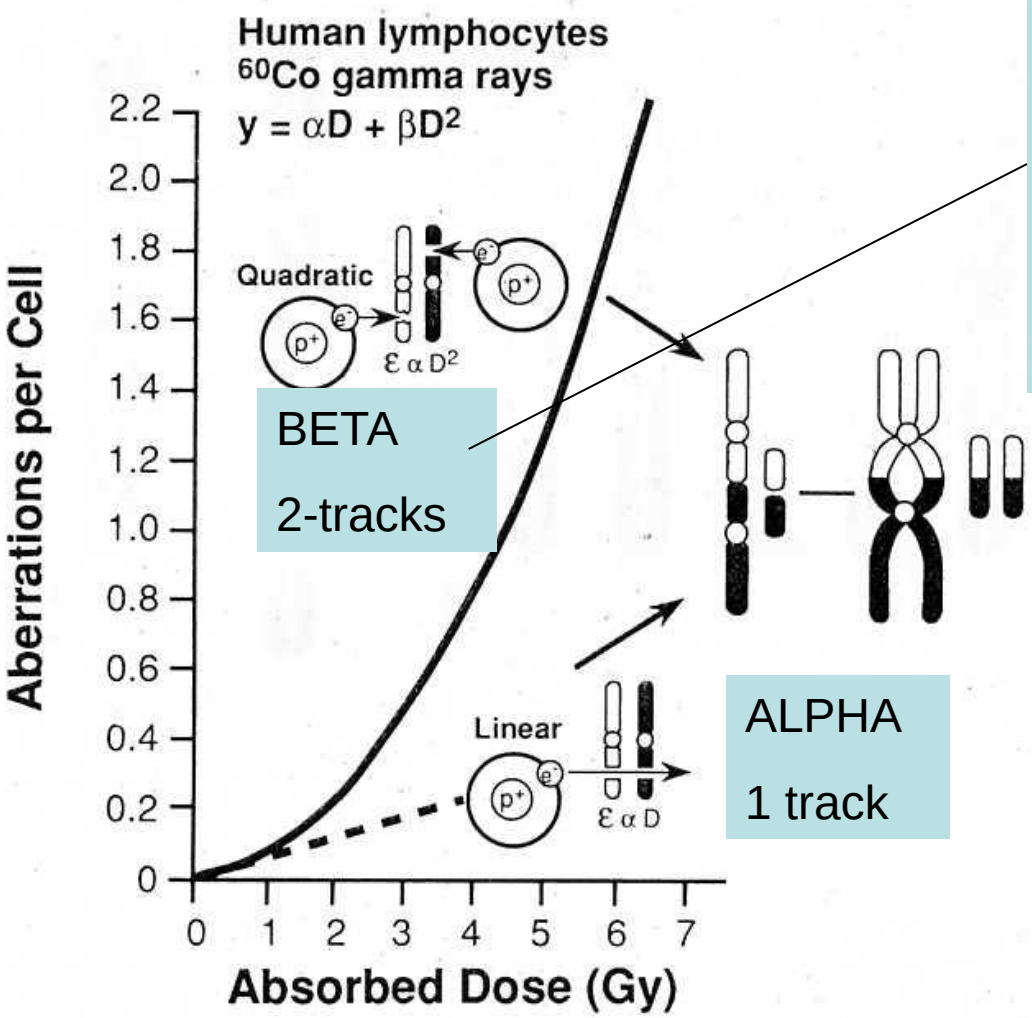
FIGURE 16.11 ● Illustration of agarose gel electrophoresis. DNA is negatively charged, so that under the influence of an electrical field, it migrates toward the anode. During electrophoresis, DNA fragments sort by size, small molecules moving farther than larger molecules. Because smaller molecules move farther than larger molecules in a given time, polyacrylamide gel electrophoresis often is employed to separate smaller DNA fragments with greater resolution than with agarose.



SSB Repair Times



R1- Repair of Sublethal Damage is affected by Dose Rate

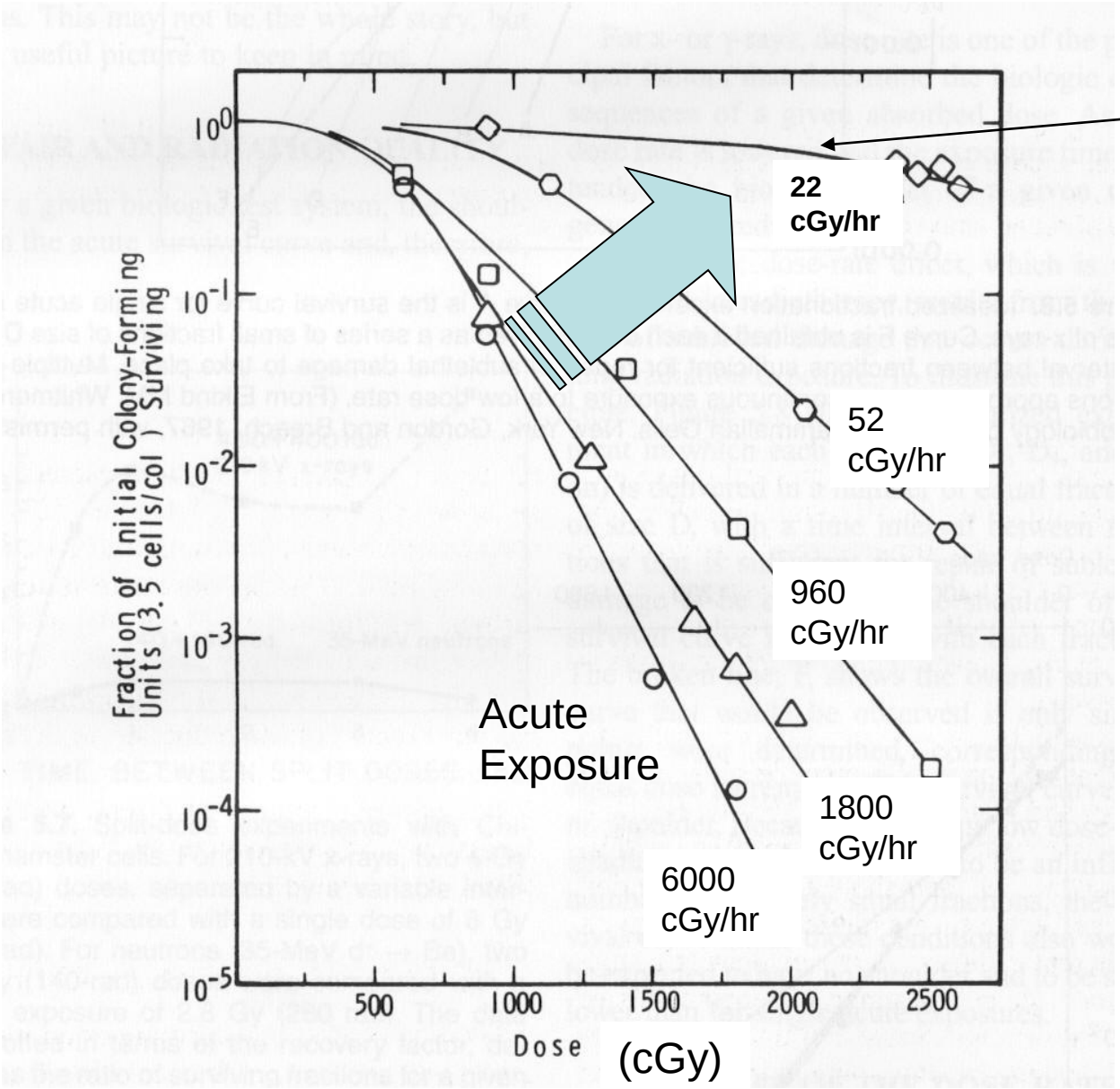


BETA damage depends on Dose Rate and Fractionation

A pair of DSB's can yield fatal chromosome. If one DSB is repaired between "Hits", fewer fatal chromosomes are produced

FIGURE 2.11 The frequency of chromosomal aberrations (dicentrics and rings) is a linear-quadratic function of dose because the aberrations are the consequence of the interaction of two separate breaks. At low doses, both breaks may be caused by the same electron; the probability of an exchange aberration is proportional to dose (D). At higher doses, the two breaks are more likely to be caused by separate electrons. The probability of an exchange aberration is proportional to the square of the dose (D^2).

Lower Dose Rate helps R1- Concurrent Repair



Critical Dose Rate

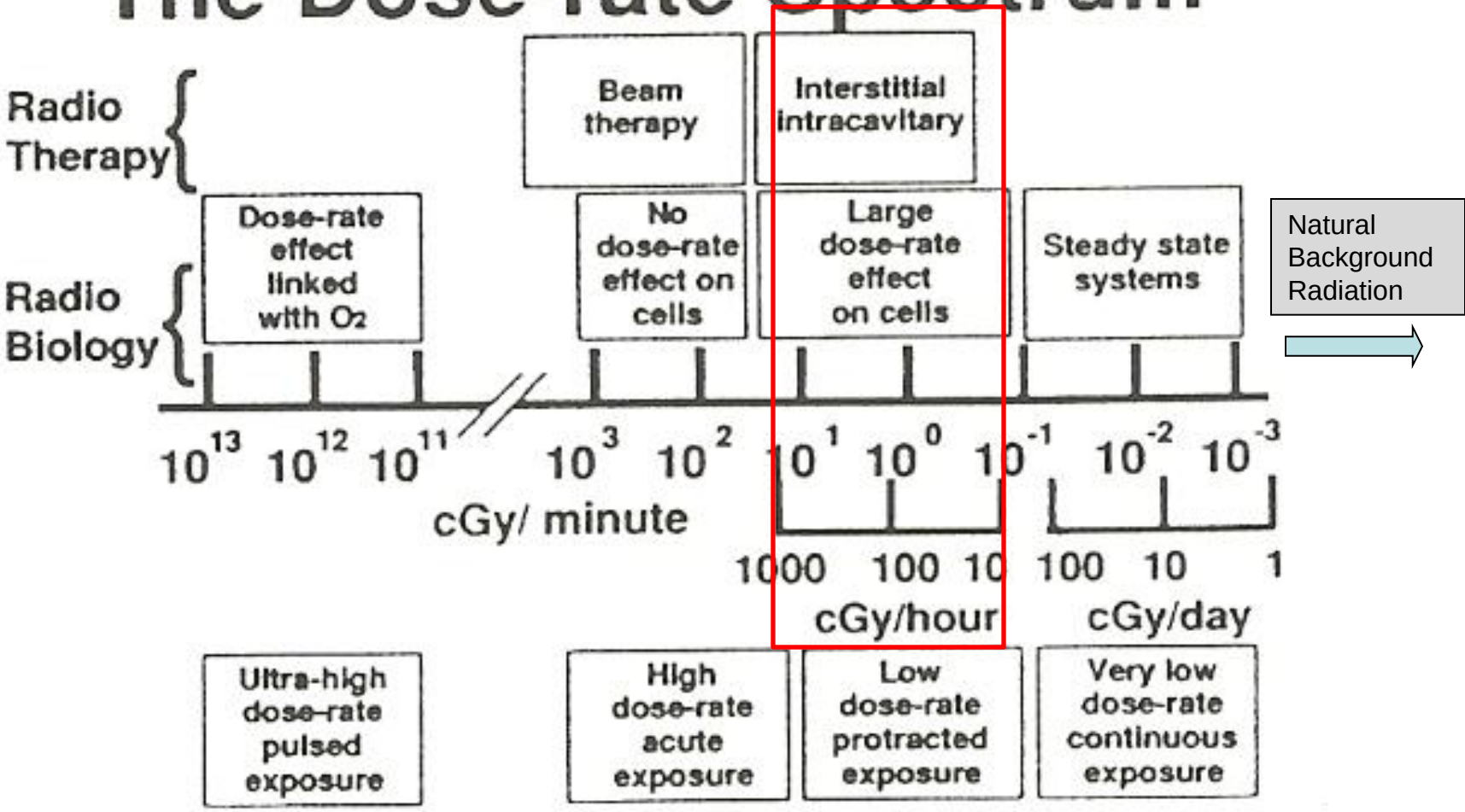
Break-Even

Cell Killing Rate =

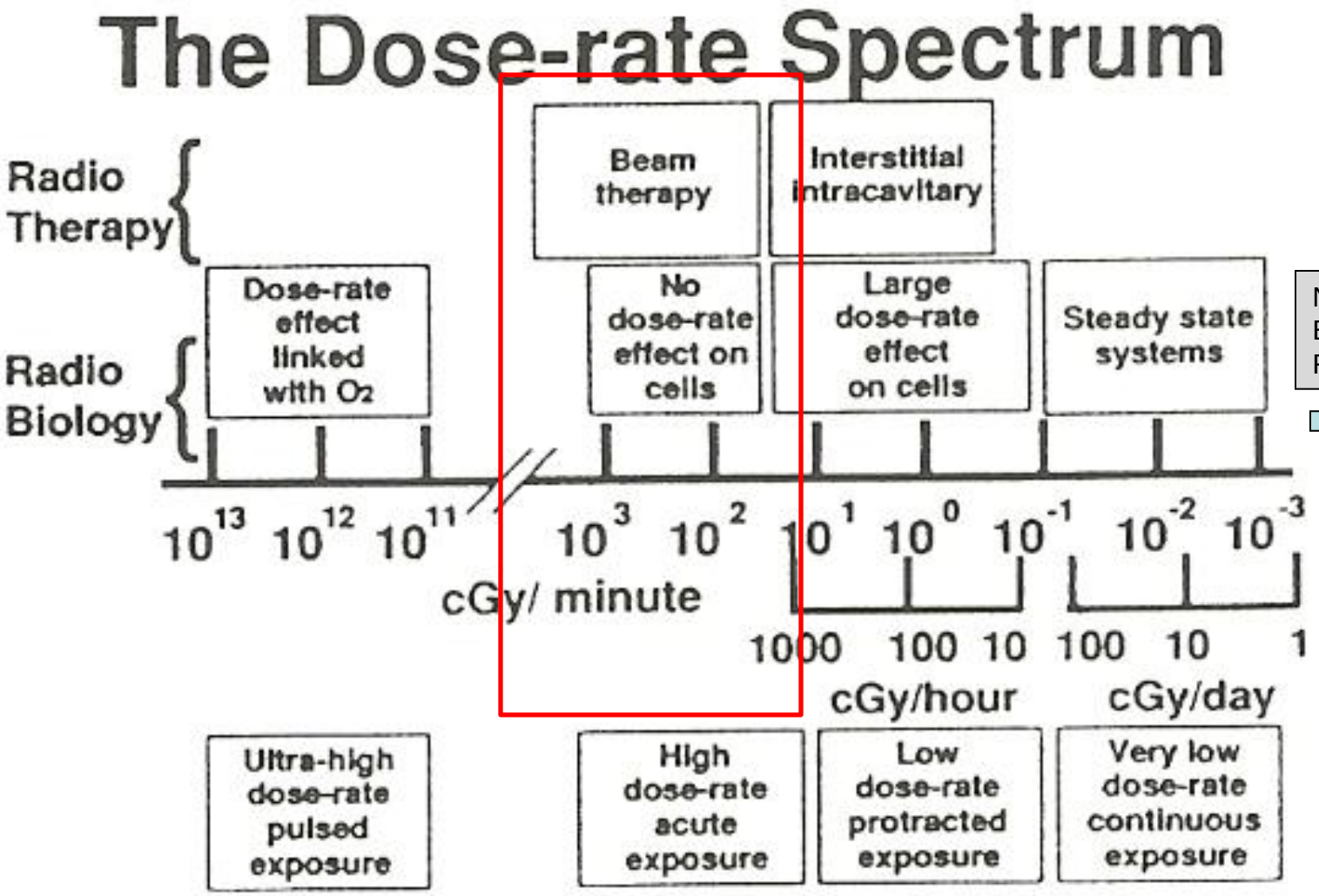
Cell Replication Rate

Figure 5.13

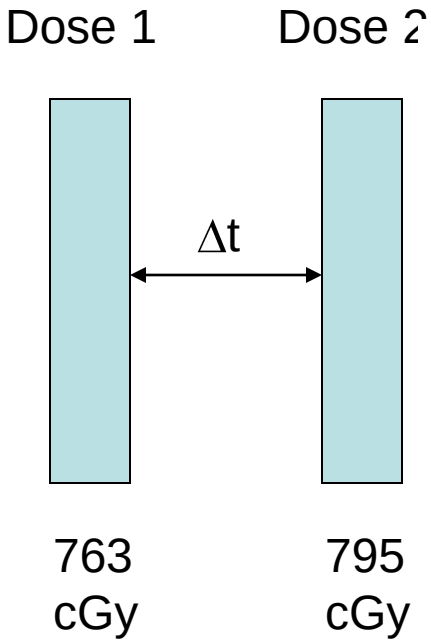
The Dose-rate Spectrum

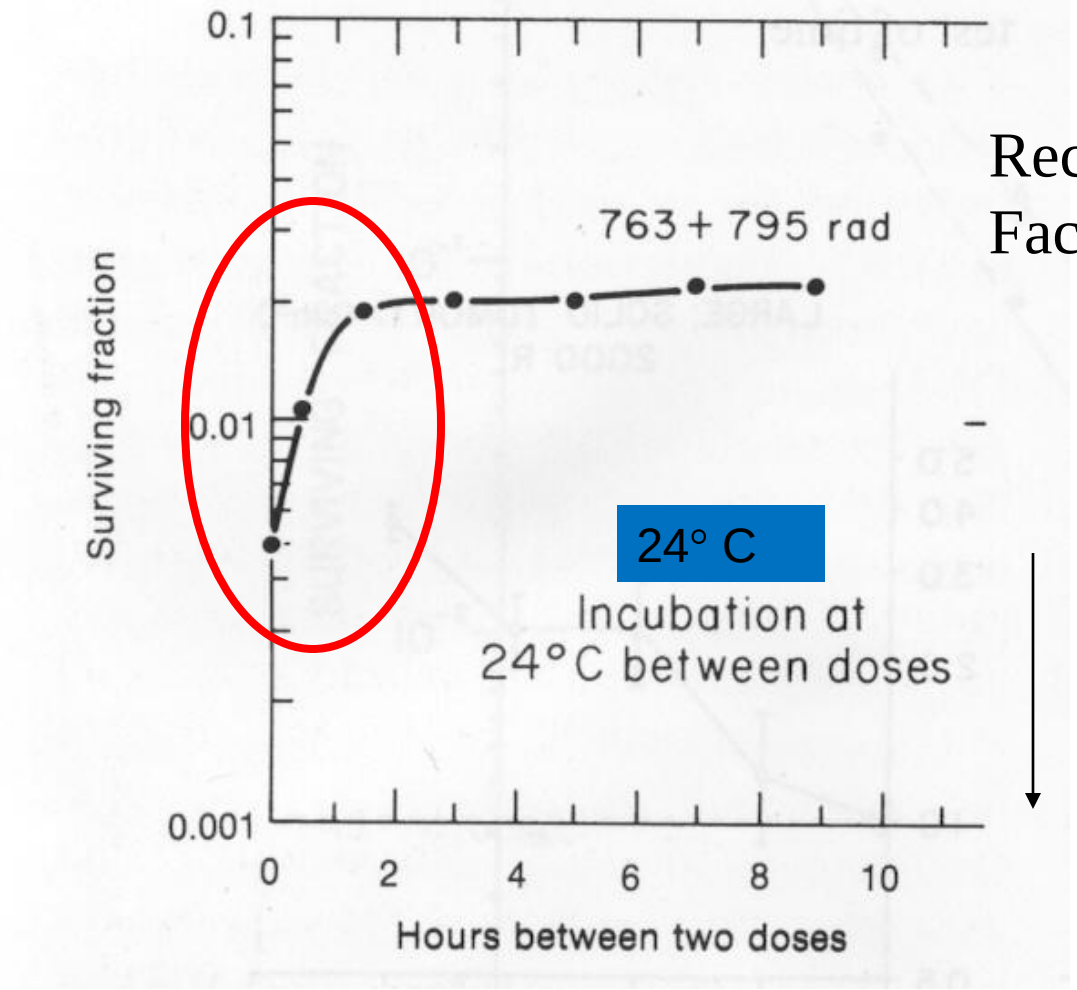


What if high dose rate dose is fractionated ?



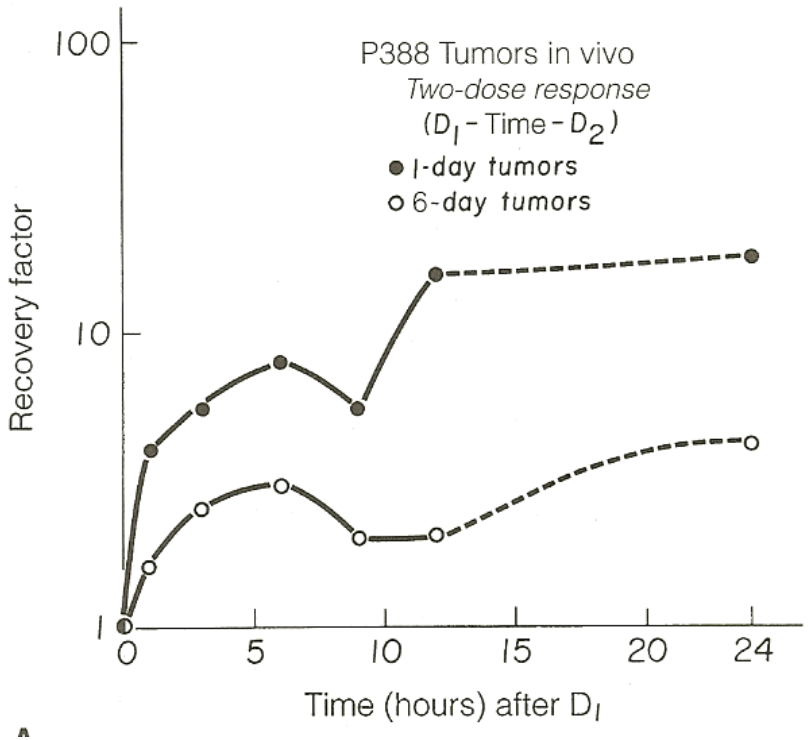
Split-Dose Fractionation Experiments





Recovery Factor

Fig 5.6



Recovery Factor = Survival (with delay) / Survival (no delay)

Leukemic Cells In Vivo

FIGURE 5.8 ● Repair of sublethal damage in two *in vivo* mammalian cell systems. **A:** Split-dose experiments with P388 lymphocytic leukemia cells in the mouse. The recovery factor is the ratio of the surviving fraction resulting from two-dose fractionation to the survival from a single equivalent dose. One-day-old tumors are composed predominantly of oxygenated cells; the cells in 6-day-old tumors are hypoxic. (From Belli JA, Dicus GJ, Bonte FJ: Radiation response of mammalian tumor cells: 1. Repair of sublethal damage *in vivo*. *J Natl Cancer Inst* 38:673–682, 1967, with permission.)

Dose Fractionation – “Choppy” Survival Curves

Curvature due to BETA effect.

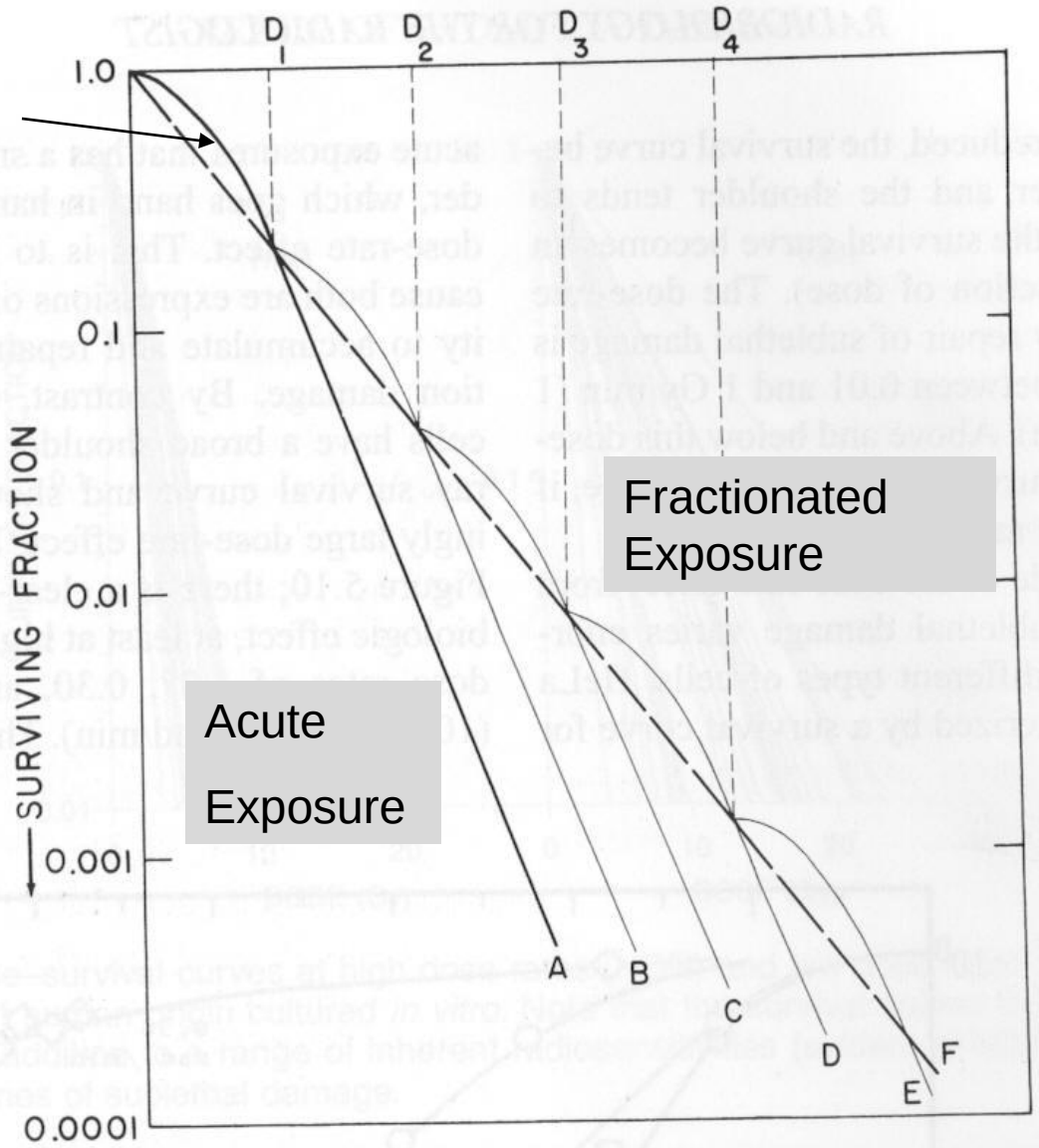
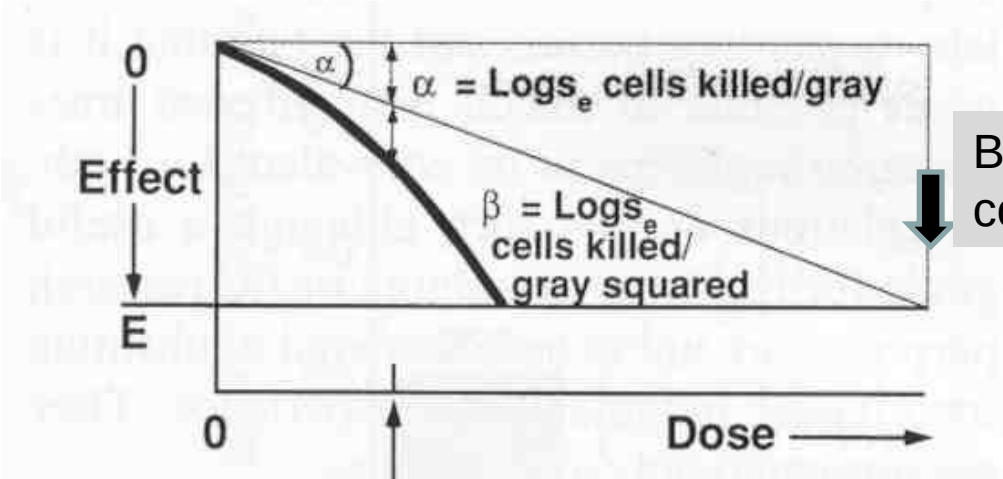


Figure 5.11

Flashback to α/β

- See Lecture on Cell Survival Models (LQ)
- α /β ratio is an indicator of "insensitivity" to dose fractionation or dose rate

α	β	α /β	Tissue Type	Sensitive to dose rate or dose fractionation
High	Low	High	Tumour Early reactions	Not so much
Low	High	Low	Normal Late reactions	Very much so

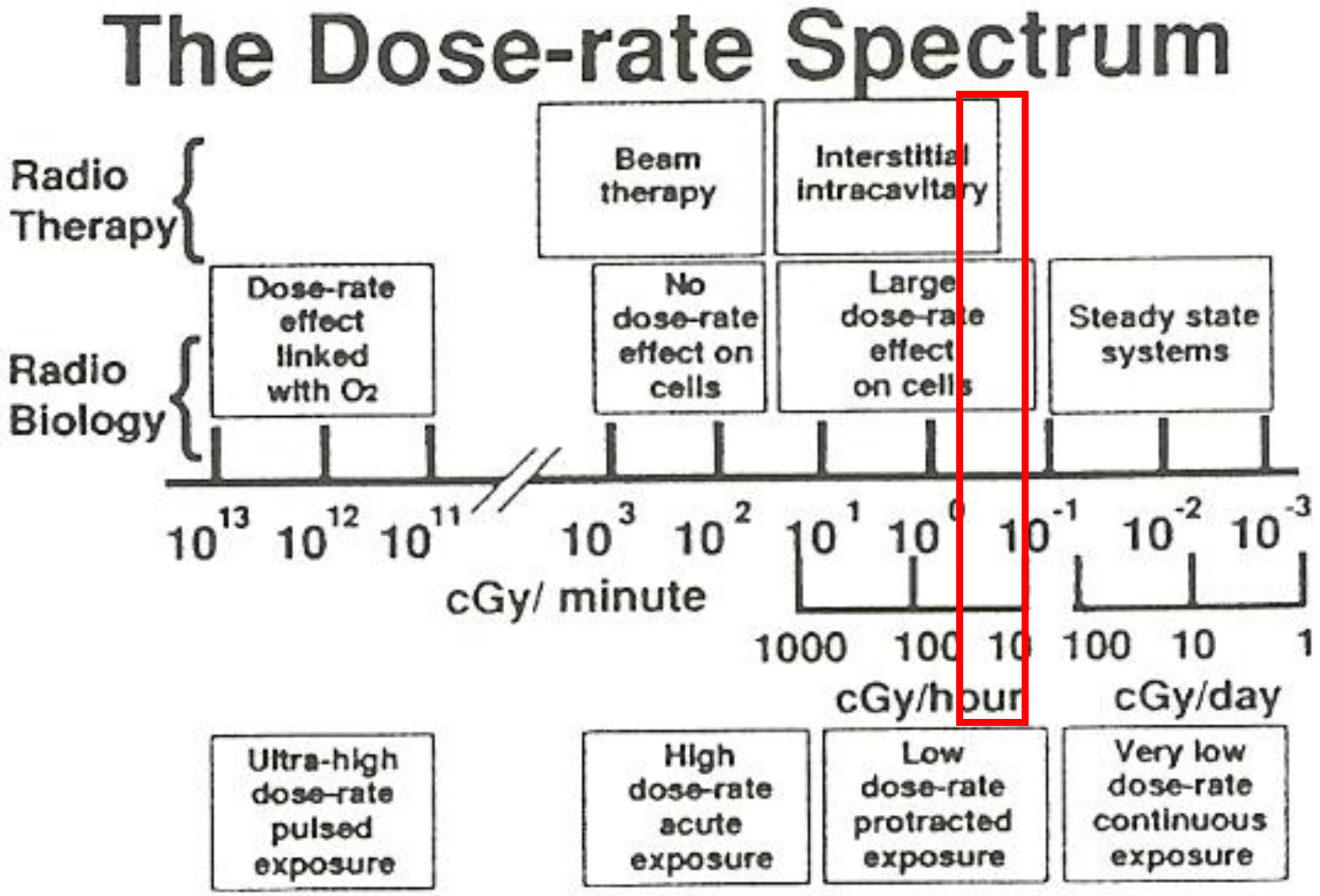


BED – dose for continuous low dose rate

Another Saying # 6

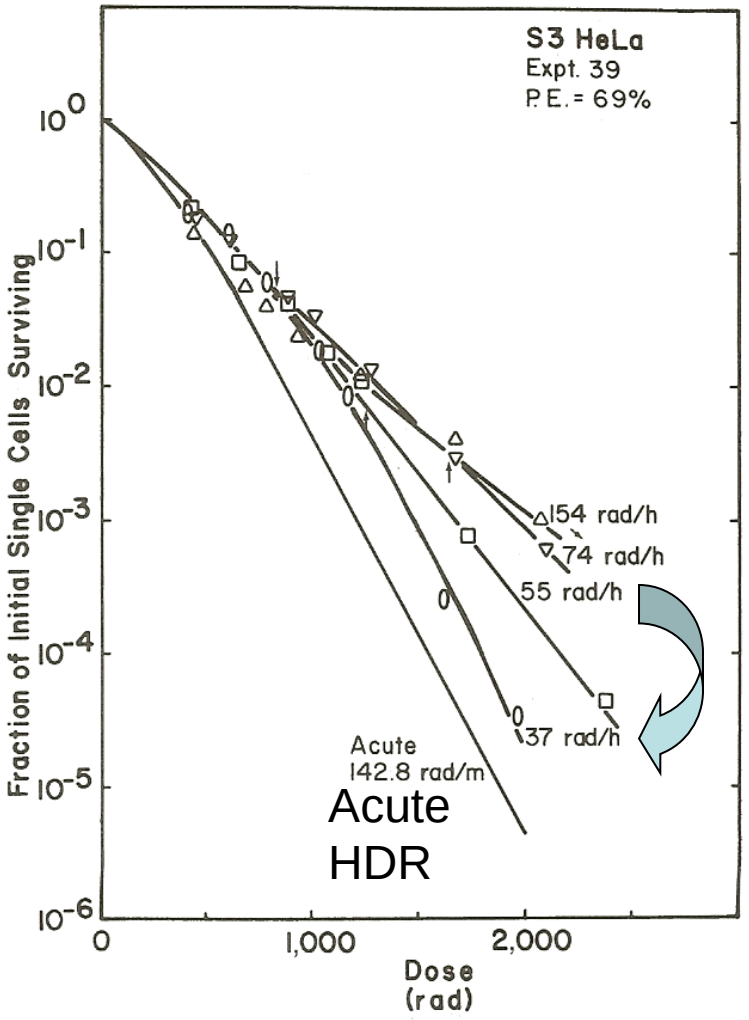
“In Radiobiology, Expect the Unexpected”

R2
Re-Assortment
(aka Re-Distribution)



LDR Brachytherapy

Inverse Dose Rate Effect



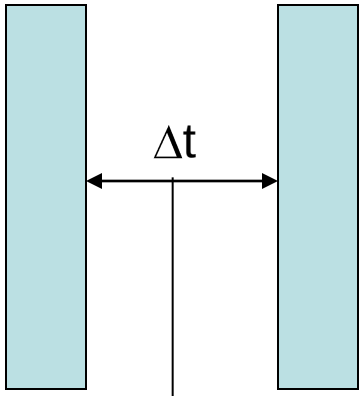
Poorer survival at

Lower Dose Rate (in LDR range) !!!!

FIGURE 5.16 ● The inverse dose-rate effect. A range of dose rates can be found for HeLa cells such that lowering the dose rate leads to more cell killing. At 1.54 Gy/h (154 rad/h), cells are "frozen" in the various phases of the cycle and do not progress. As the dose rate is dropped to 0.37 Gy/h (37 rad/h), cells progress to a block in G_2, a radiosensitive phase of the cycle. (From Mitchell JB, Bedford JS, Bailey SM: Dose-rate effects on the cell cycle and survival of S3 HeLa and V79 cells. *Radiat Res* 79:520–536, 1979, with permission.)

More Fractionation Experiments

Dose 1 Dose 2



750 cGy 750 cGy

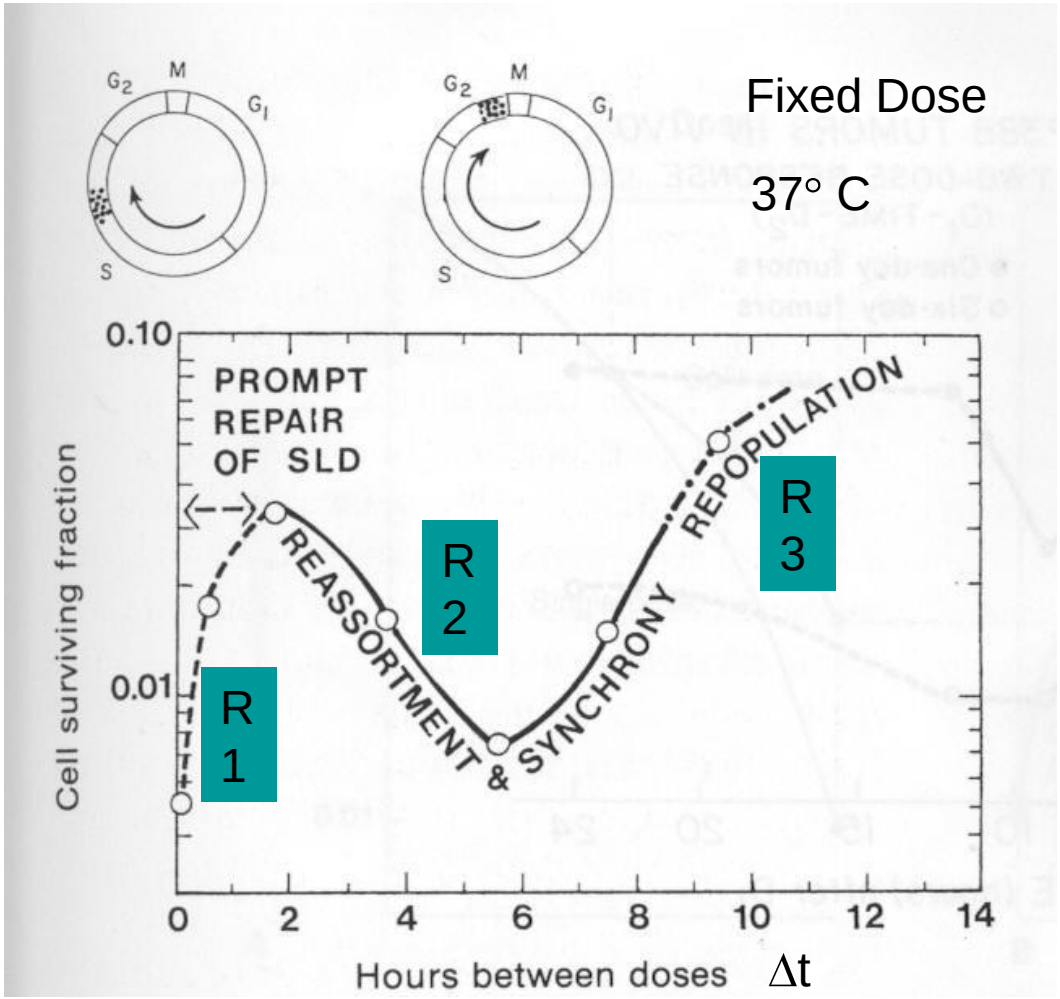
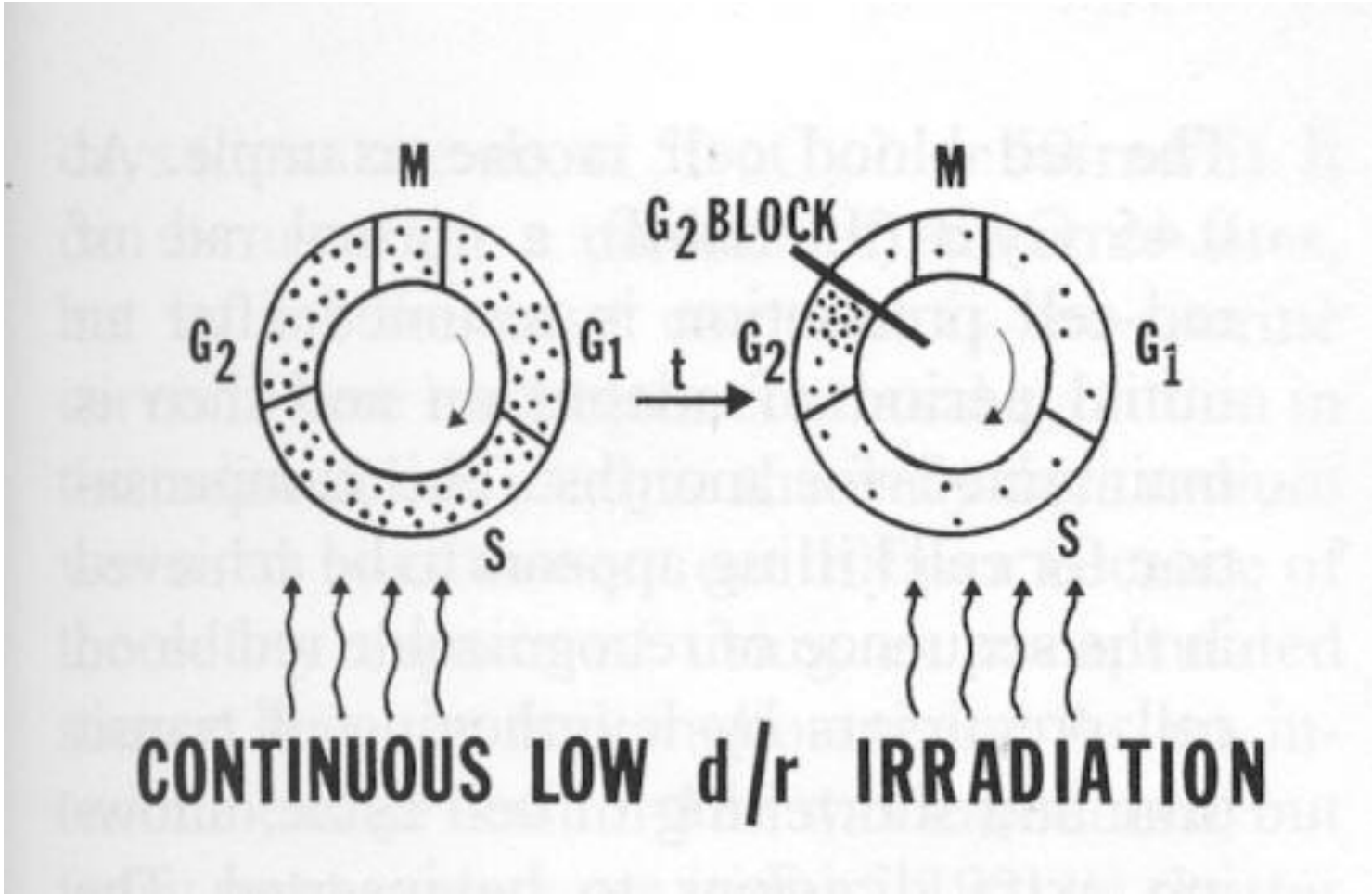


Fig 5.7

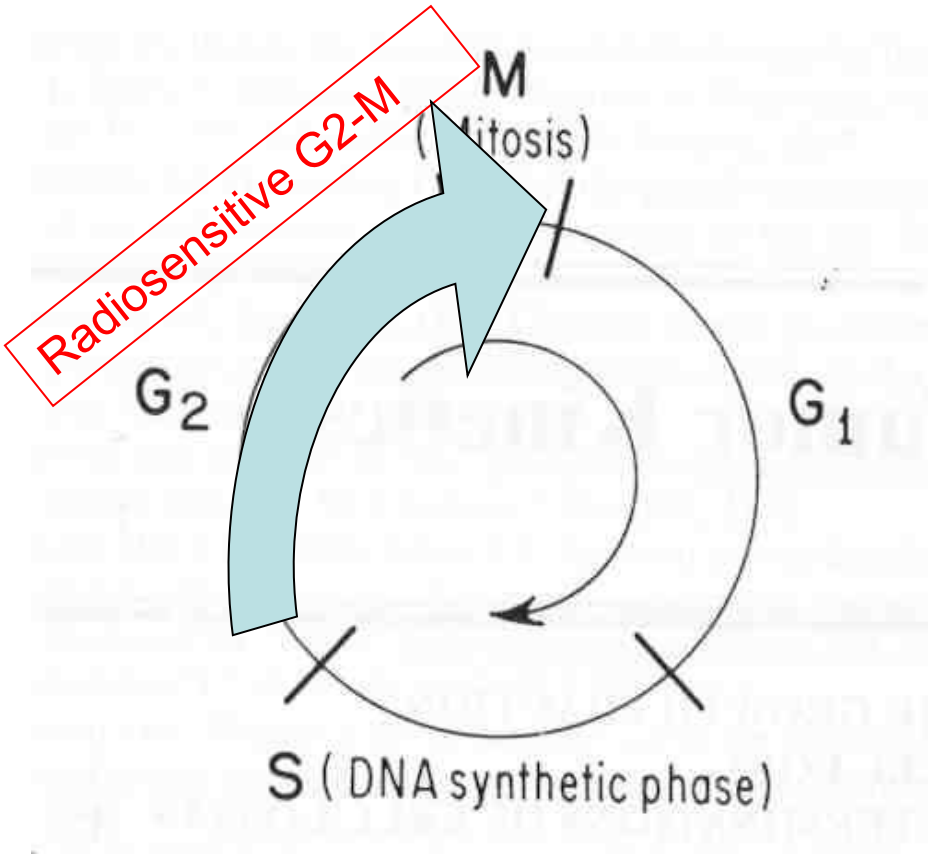
Inverse Dose Rate Effect

(Cells get “bunched” in G2-M)



Inverse Dose Rate Explained

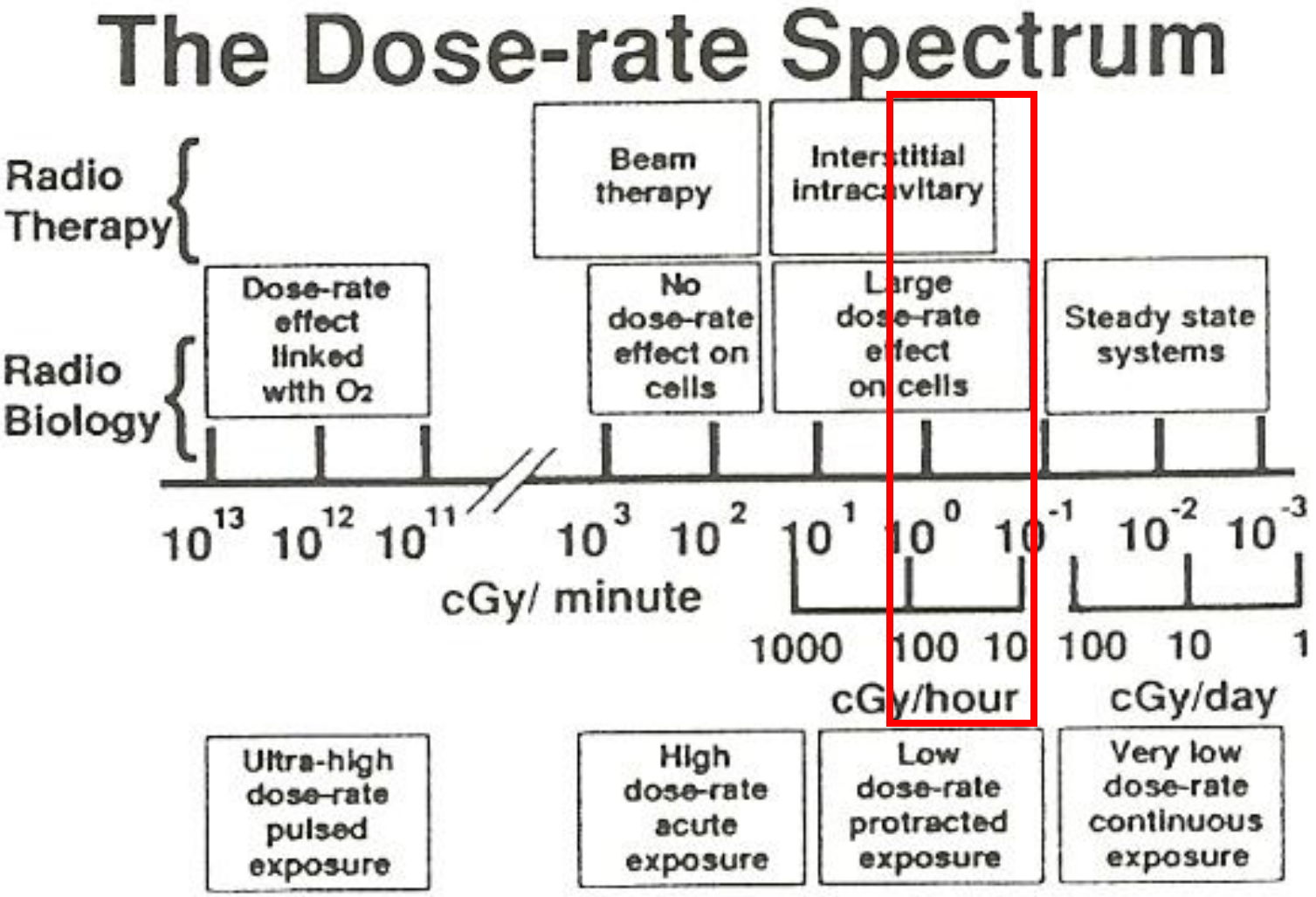
R2 - Cell Cycle Effect



R3

Repopulation

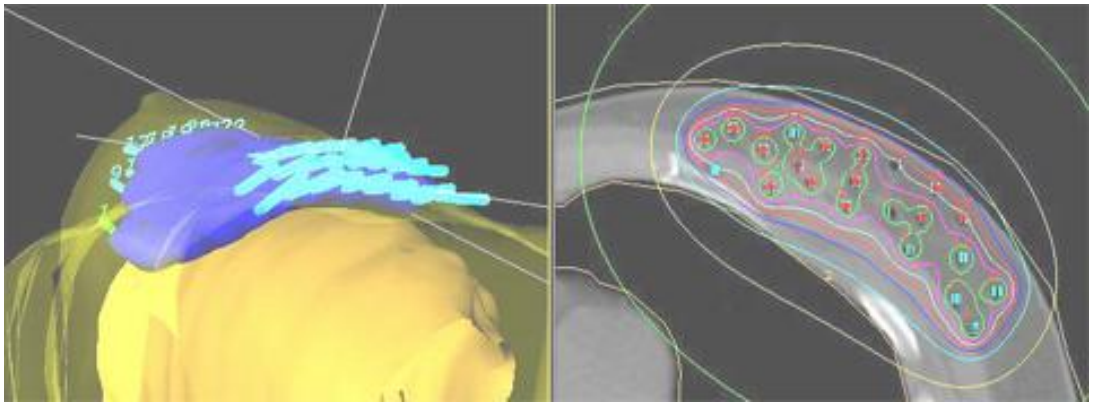
Cell Killing *versus* Cell Replication
(Equilibrium idea)



LDR Brachytherapy

Dose Rate Effects in Brachytherapy

(implanted radioactive seeds)



R3 effect

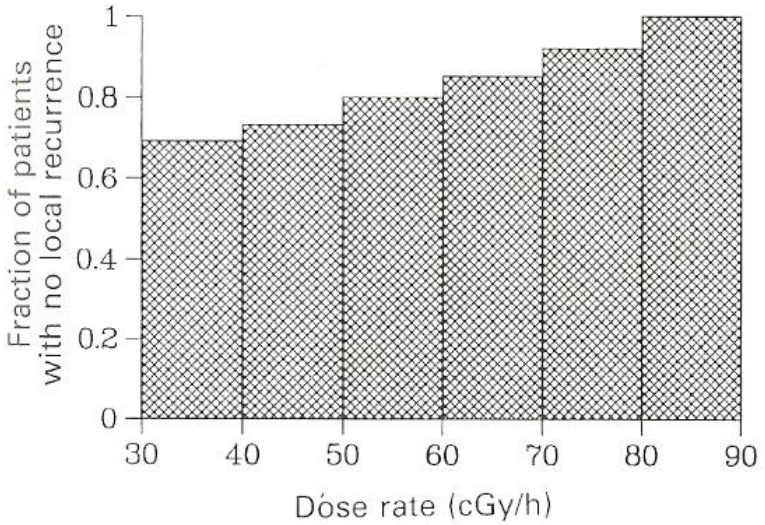


Figure 5.18. Percentage of patients who showed no local recurrence as a function of dose rate in treatment for breast carcinoma by a combination of external-beam irradiation plus iridium-192 interstitial implant. The implant was used to deliver a dose of 37 Gy (3,700 rad); the dose rate varied by a factor of 3, owing to different linear activities of the iridium-192 wire and different volumes implanted. (Data from Mazeron JJ, Simon JM, Crook J, et al: Influence of dose rate on local control of breast carcinoma treated by external beam irradiation plus iridium-192 implant. Int J Radiat Oncol Biol Phys 21: 1173–1177, 1991.)

Variable Dose Rate Optimization

(R3 and R2 Effects as source decays)

TABLE 5.1 Give higher dose rate "up front"

Characteristics of Radionuclides for Intracavitary or Interstitial Brachytherapy

Radionuclide	Photon Energy, keV		Half-Life	HVL[a], mm Lead
	Average	Range		
Conventional				
Cesium-137	662	—	30 y	5.5
Iridium-192	380	136–1060	74.2 d	2.5
New				
Iodine-125	28	3–35	60.2 d	0.025
Gold-198	412	—	2.7 d	2.5
Americium-241	60	—	432 y	0.125
Palladium-103	21	20–23	17 d	0.008
Samarium-145	41	38–61	340 d	0.06
Ytterbium 169	100	10–308	32 d	0.1

Data computed by Dr. Ravinder Nath, Yale University.

[a] HVL = Half Valve Layer, the thickness required to reduce the incident radiation by 50%.

R4

Re-Oxygenation

Fractionate to Re-Oxygenate !

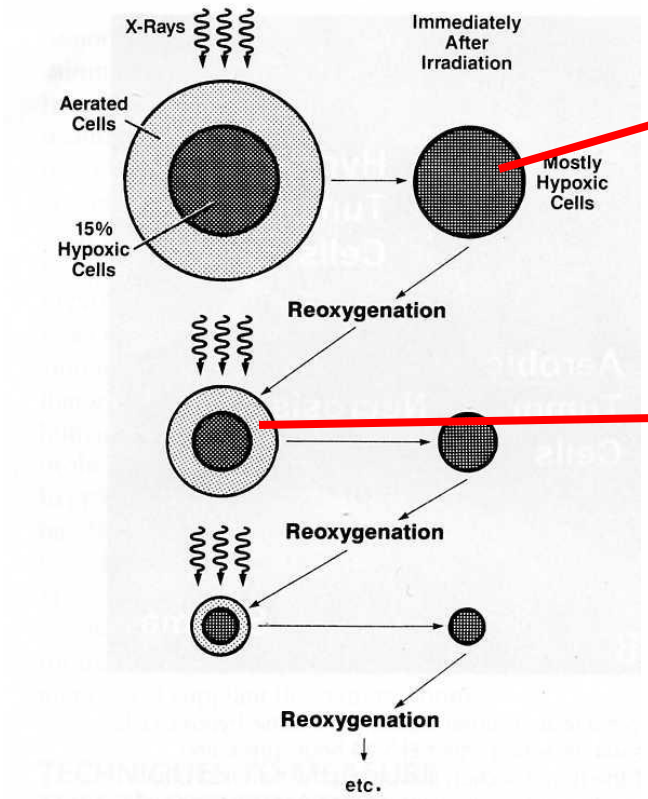


FIGURE 6.13 ● The process of reoxygenation. Tumors contain a mixture of aerated and hypoxic cells. A dose of x-rays kills a greater proportion of aerated cells than hypoxic cells because aerated cells are more radiosensitive. Therefore, immediately after irradiation, most cells in the tumor are hypoxic. However, the preirradiation pattern tends to return because of reoxygenation. If the radiation is given in a series of fractions separated in time sufficient for reoxygenation to occur, the presence of hypoxic cells does not greatly influence the response of the tumor.

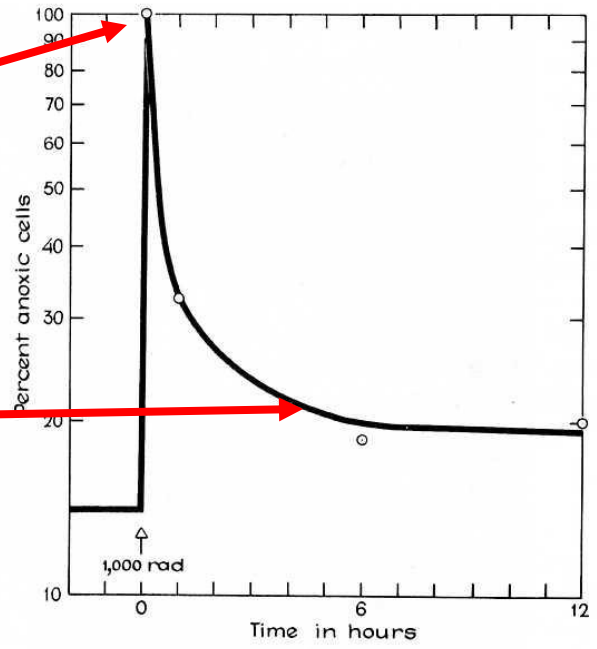


FIGURE 6.14 ● Percentage of hypoxic cells in a transplantable mouse sarcoma as a function of time after a dose of 10 Gy (1,000 rad) of x-rays. Immediately after irradiation, essentially 100% of the viable cells are hypoxic, because such a dose kills a large proportion of the aerated cells. In this tumor, the process of reoxygenation is very rapid. By 6 hours after irradiation, the percentage of hypoxic cells has fallen to a value close to the preirradiation level. (From Kallman RF, Bleehen NM: Post-irradiation cyclic radiosensitivity changes in tumors and normal tissues. In Brown DG, Cragle RG, Noonan JR [eds]: *Proceedings of the Symposium on Dose Rate in Mammalian Radiobiology, Oak Ridge, TN, 1968*, pp 20.1–20.23. USAEC Report CONF-680410. Springfield, VA, Technical Information Service 1968, with permission.)

Dose Rate and 4R's

- Concurrent or intermediate repair of DNA – R1
- Repopulation versus cell killing – R3

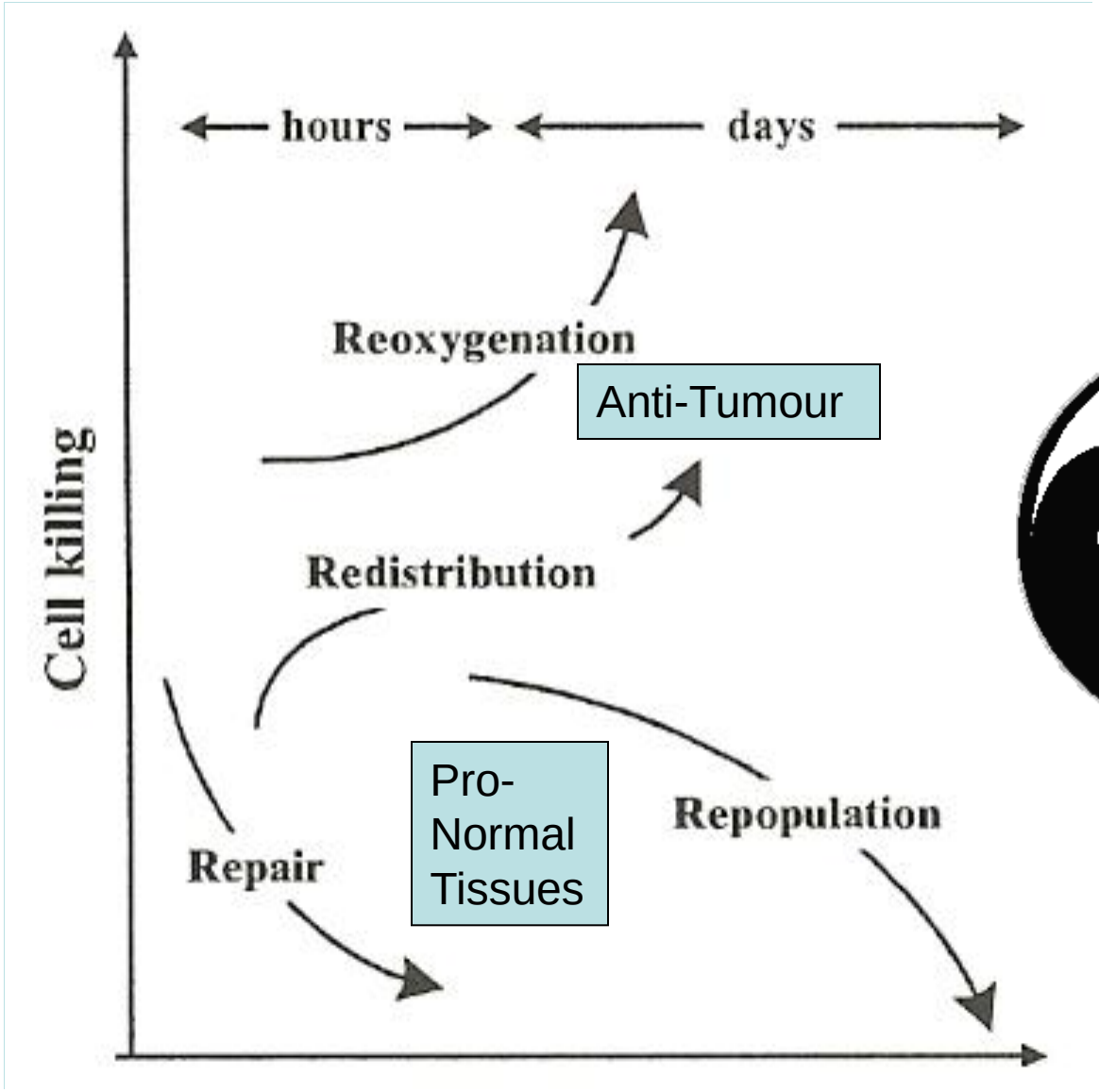
BUT…

- Re-assortment into sensitive cell phases – R2
- Re-oxygenation has time to occur – R4

Differential Effects on Tumour and Normal Tissues

4Rs	Tumour Cells	Normal Cells
Repair		
Re-Assortment		
Re-Population		
Re-Oxygenation		

Balance is affected by Dose Rate/Fractionation



Duration of Chronic Exposure or

Time Gap between Acute Radiation Exposures

RD Stewart et al.