Chapter 5 – Fractionated Radiation and the Dose-Rate Effect

9/26/2024

Outline

- **Operational Classifications of Radiation Damage**
- Repair and Radiation Quality
- The Dose-Rate Effect
- The Inverse Dose-Rate Effect
- Brachytherapy
- Dose Rate and IMRT

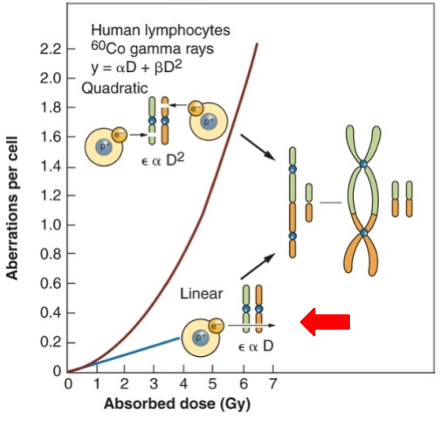
Classification of Radiation Damage

- Radiation damage to mammalian cells can operationally be divided into 3 categories
  - **Lethal Damage**
  - **Potentially Lethal Damage (PLD)**
  - **Sublethal Damage (SLD)**

Lethal Damage

- This is damage that is irreversible and irreparable, and therefore irrevocably leads to cell death

- Relates to the α-type damage in the linear-quadratic model



Will come back to this later

Potentially Lethal Damage (PLD)

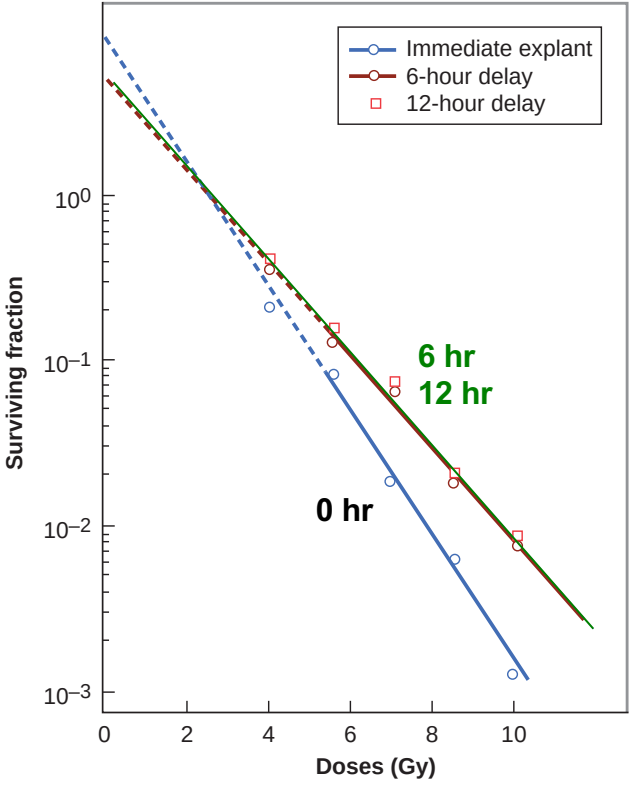
- This is the component of radiation damage that can be modified by **post-irradiation environmental conditions**
- Under normal conditions, PLD is lethal
- By *manipulation* of the post-irradiation **environment**, PLD can be repaired
- PLD is believed to be complex DSBs that are repaired slowly as compared to simple DSBs

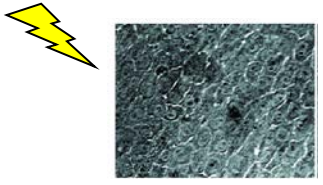
Examples of PLD

- Cells incubated in a balanced salt solution instead of a full growth medium for several hours after radiation

- Cells maintained in a stationary phase after irradiation can exhibit PLD repair

PLD – Density-Inhibited Stationary-Phase Cells



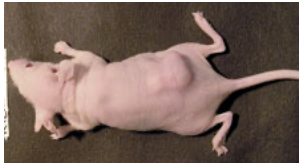


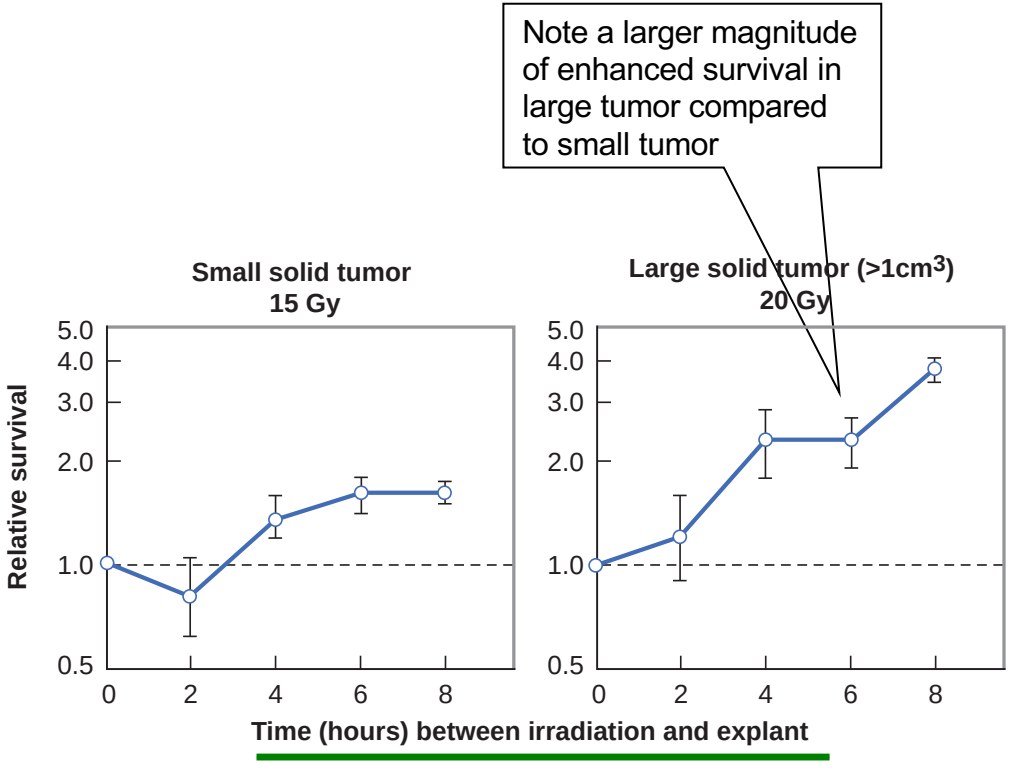
Experiment – ***density arrested cells*** are irradiated, and either plated immediately or **maintained in density-inhibited stationary phase for 6-12 hours** before plating out for survival curve

Observation – survival enhanced if cells are left for 6-12h in density-inhibited state

Interpretation – if mitosis are delayed by **suboptimal growth conditions**, PLD (complex as opposed to simple DSBs) can be repaired

Repair of PLD *In Vivo*





Experiment – tumors were irradiated *in situ* and then **explanted at various times**; they were prepared into single-cell suspensions for cell survival curves

Observation & Interpretation – Increased survival occurs if time is allowed in *vivo* before explant: this is PLD Repair

Clinical Relevance – the importance of PLD repair to clinical radiotherapy is debatable (? radioresistance <-> PLD repair)

PLD Repair Summarized

- The fraction of cells surviving a given dose of x-rays is enhanced if post-irradiation conditions are suboptimal for growth, so that cells do not have to attempt the complex process of **mitosis** while their chromosomes are damaged

- If mitosis is delayed by suboptimal growth conditions, DNA damage can be repaired = **potentially lethal damage**

Sublethal Damage (SLD)

- SLD Repair is the operational term for the ↑ in cell survival if a given dose is split into two fractions separated by **a time interval**

- Cell survival will also ↑ due to SLD repair **if the dose rate** is reduced – this is called the "dose-rate effect"

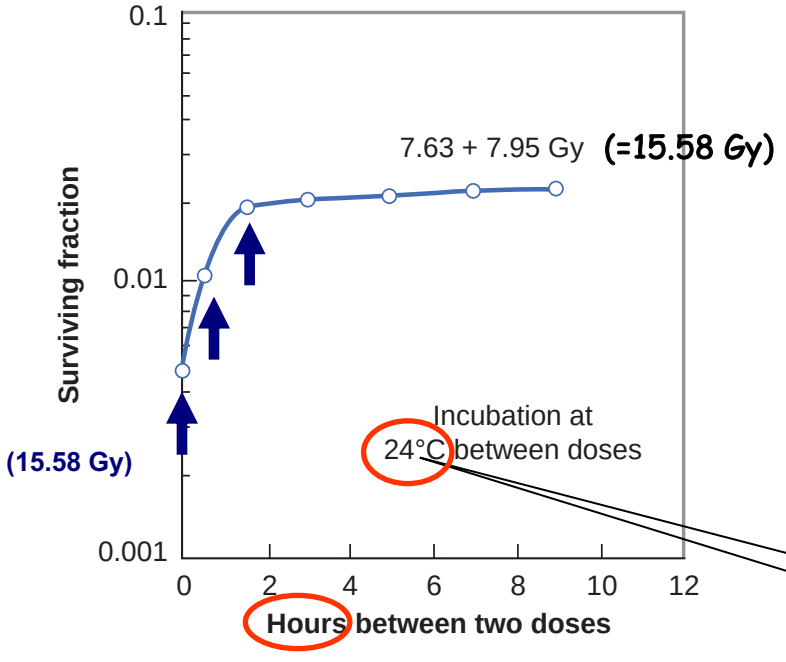
Will come back to this later

Sublethal Damage (SLD)

- SLD by itself is not lethal to the cells
- It can be repaired in hours unless additional SLD is added (e.g., from further radiation exposure) with which it can interact to form lethal damage
- This is the β-type damage of the linear-quadratic model
- Represents shoulder on cell survival curve

Note that there is now a **"Time"** factor as opposed to the **"Environment"** factor as in PLD repair

Split-Dose Experiment



Experiment – a dose of 15.58 Gy was divided into 2 equal fractions separated by various times

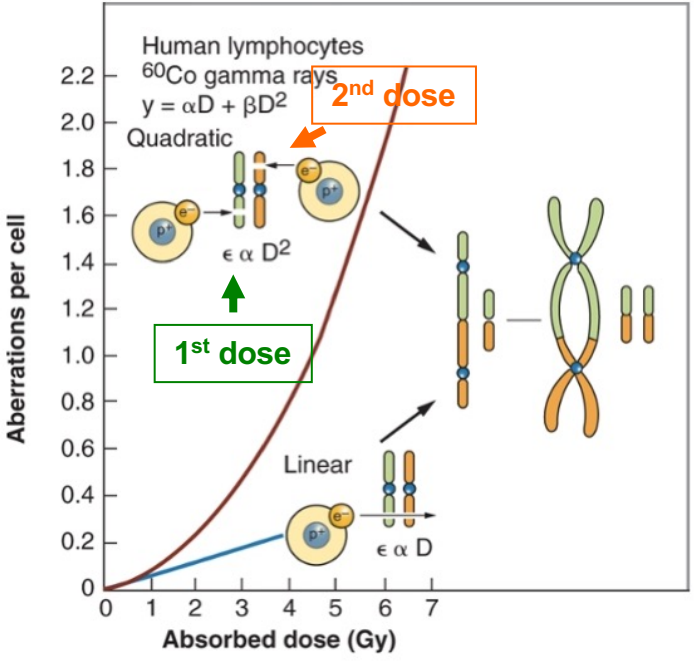
Observation – survival is enhanced as the time interval is extended, reaching a plateau at ~ 2 hours

Interpretation – the $t_{1/2}$ for SLD repair is of the order of 0.5 hour or less

SLD repair is the operational term for the increase in cell survival that is observed if a given radiation dose is split into 2 fractions separated by **a time interval**

Note that cells are maintained at room temperature to prevent cycling

Mechanism of SLD Repair



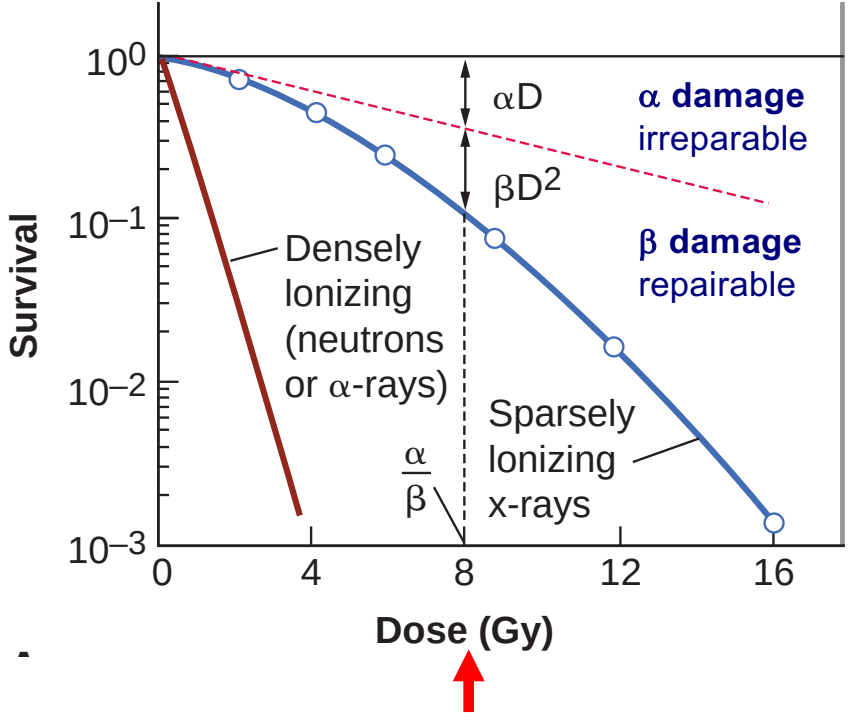
Recall that a lethal aberration (e.g., dicentrics) requires the interaction of 2 DSBs

β component – 2 DSBs result from multiple-track damage. Thus a DSB produced by the 1st dose may be repaired before the 2nd dose is given, unavailable to form dicentrics

α component – 2 DSBs result from single-track damage, therefore unmodifiable by split-dose

The repair of SLD reflects the repair and rejoining of DSBs before they can interact to form lethal lesions

α/β Model Revisited



α/β ratio is the dose where α-damage equals β-damage

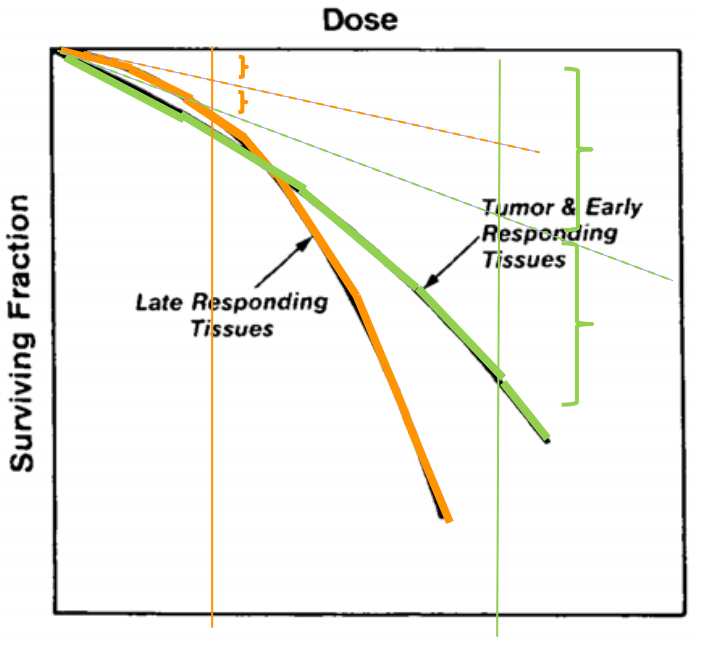
Small α/β ratio

- A relatively large β
- Means more SLD repair
- Corresponds to a large shoulder on the survival curve

Large α/β ratio

- A relatively small β
- Means less SLD repair
- Corresponds to a small shoulder

Single Dose Cell Survival for Normal vs. Cancer Cells

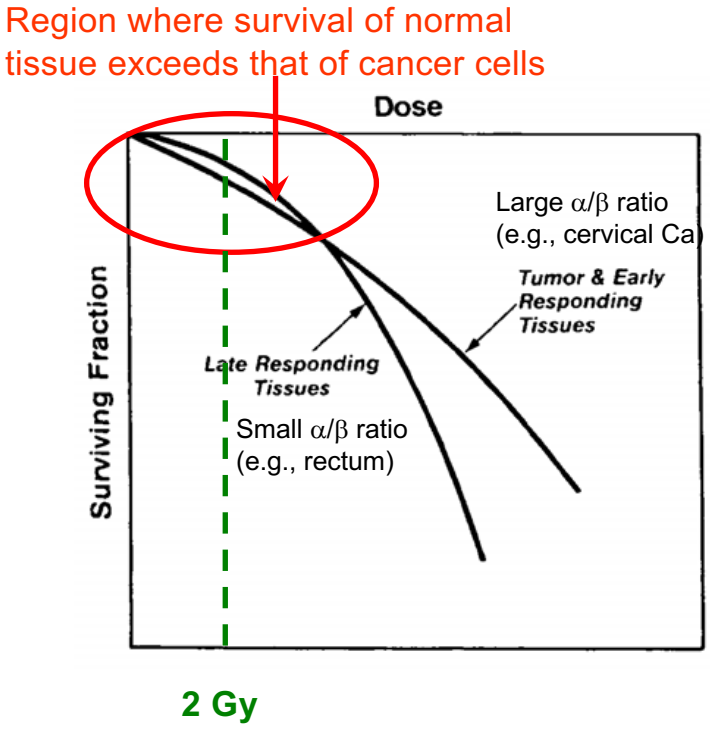


small α/β ratio **large α/β ratio**

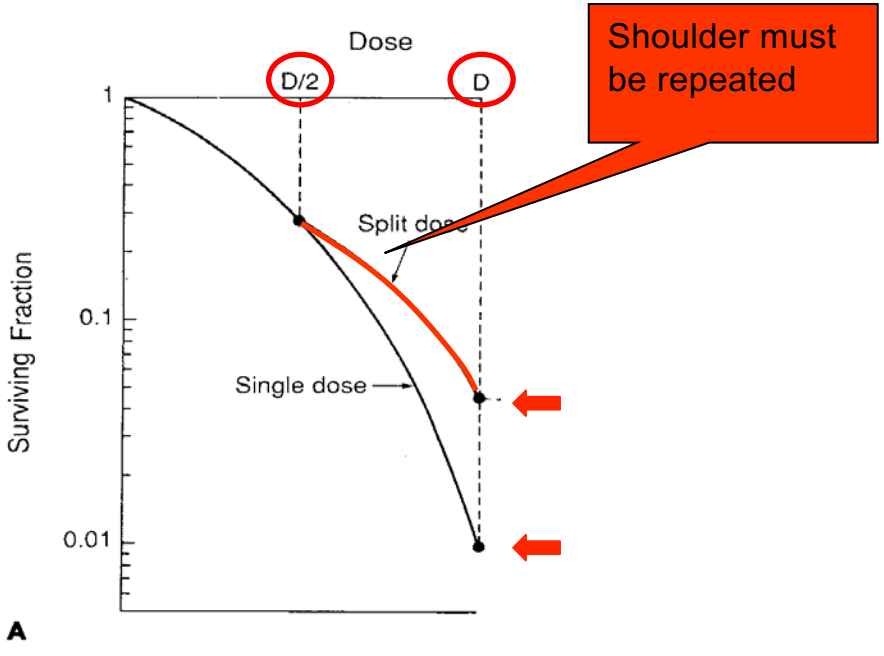
- In general, cells of late-reacting normal tissues (e.g., rectum) are better able to repair SLD than are cancer cells
- Cell-survival curves for late-reacting normal tissues are **"curvier"** than those for cancer cells (i.e., **broader initial shoulder**)
- In α/β model, late-reacting normal tissues have a **lower α/β ratio** than cancer cells

Single Dose Cell Survival for Normal vs. Cancer Cells

To take advantage of the differences in SLD repair (i.e., **α/β ratio)** b/w late normal tissue and cancer cells, we need to work within the region where survival of late-reacting normal tissue cells exceed that of cancer cells (the "window of opportunity").



Effect of Split-Dose (i.e., Fractionation)



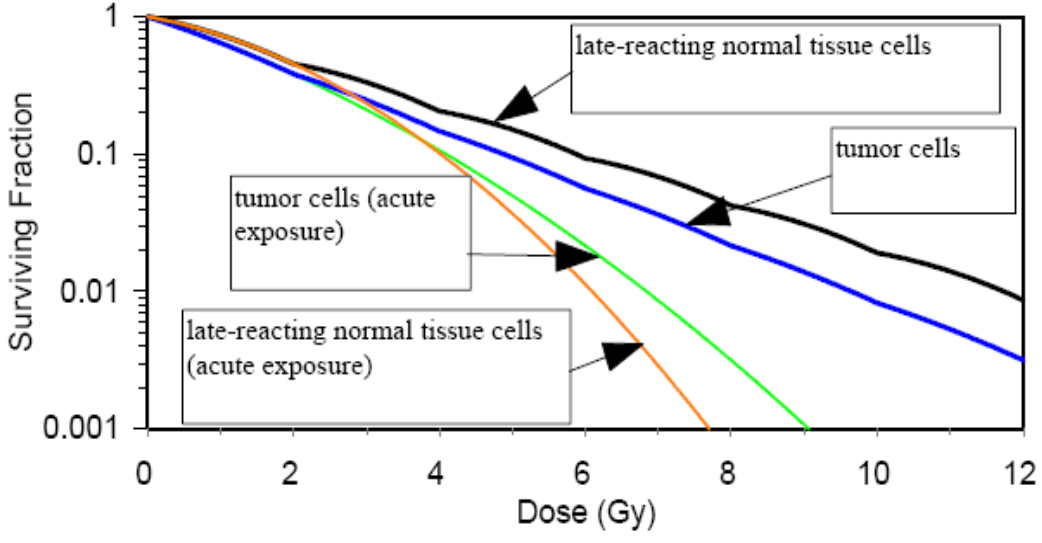
Shoulder must be repeated

It is the quadratic component (β) that causes the curve to bend and that results in the sparing effect of a split dose

In general, there is a good correlation b/w the extent of repair of SLD and size of the shoulder on the survival curve

Dose D is split into D/2 + D/2

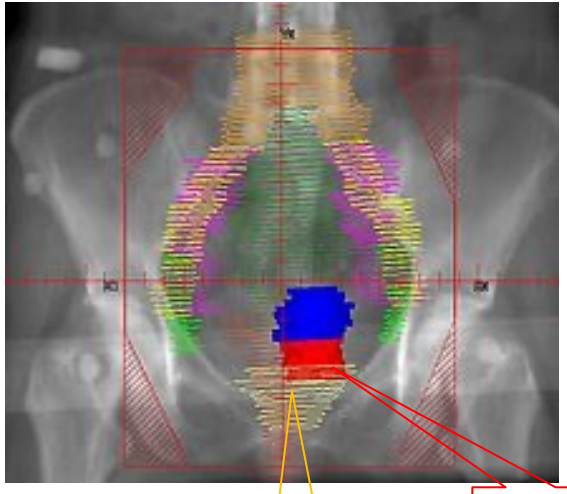
Multi-fraction Regimen

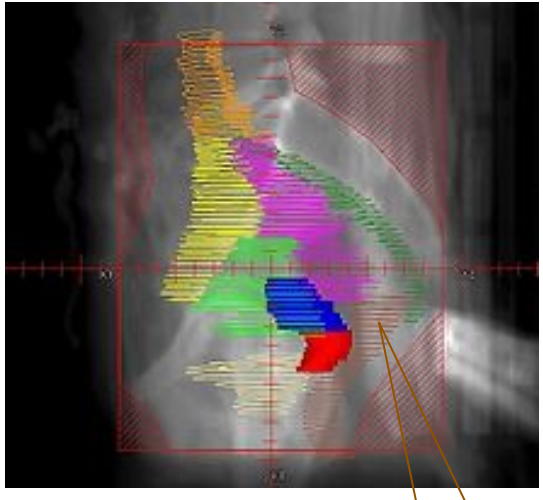


- Shoulder is repeated in multi-fractionation regimen
- Fractionate at doses/fraction within this window, i.e. typically around **2 Gy/fraction**

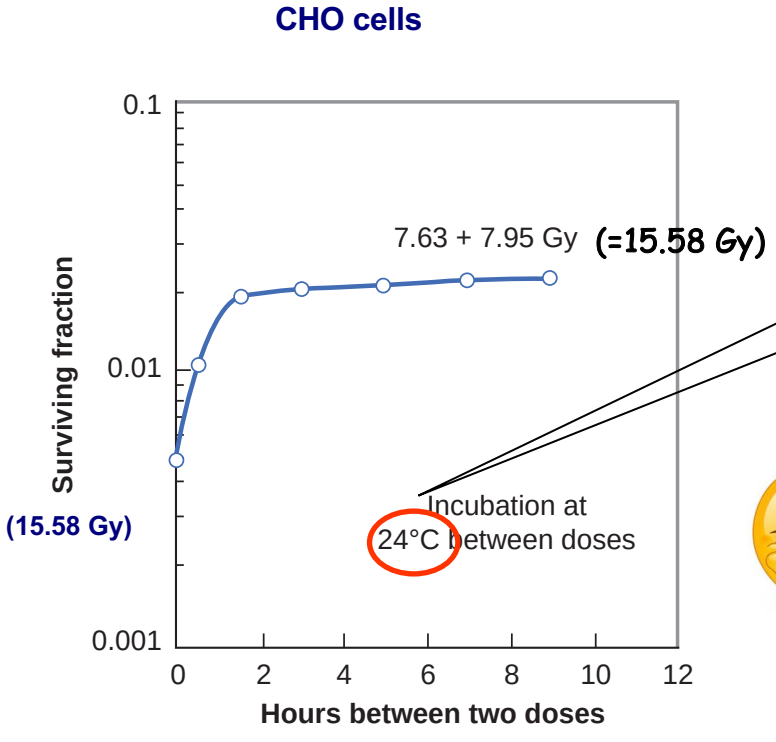
Late Responding Tissue vs. Tumor/Early Responding Tissue

Cervical cancer is typically treated to 45 Gy in 25 fractions @ 1.8 Gy per fraction





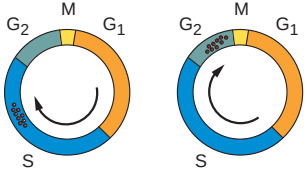
Split-Dose Experiment

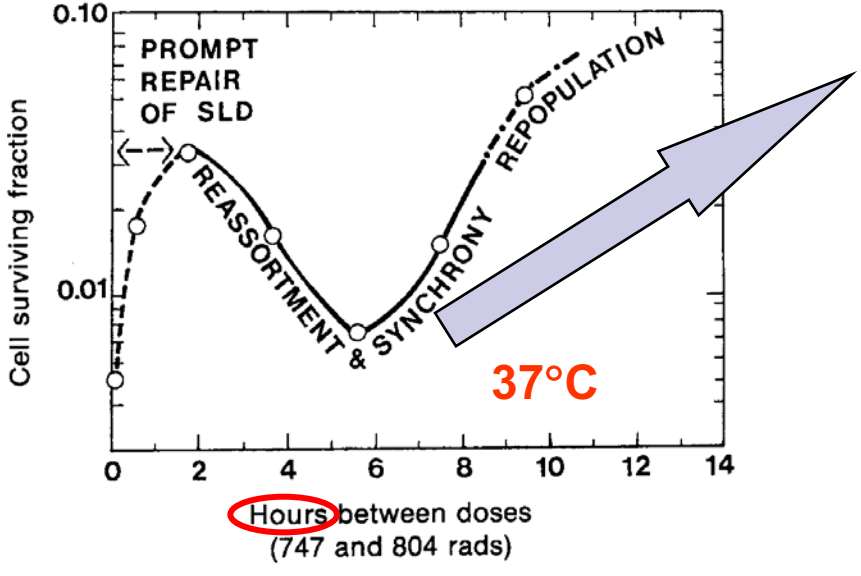


Note that cells are maintained at room temperature to prevent cycling

What would the survival curve look like if cells are cycling?

Split-Dose Experiment – Cells Maintained at 37°C





During the repair process, these cells will travel through the cell cycle

Cells that were in the late S phase of the cell cycle at the time of the 1st fraction will be most likely to survive and move towards mitosis

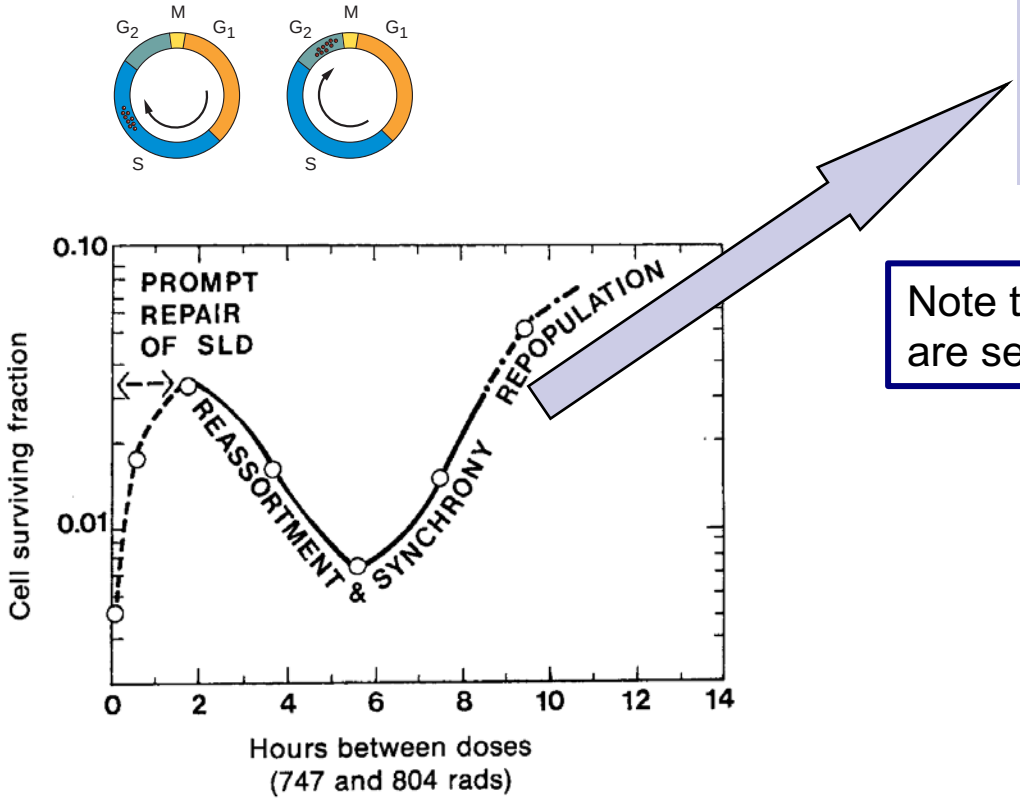
At the time of a 2nd fraction, these cells may have reached a sensitive phase, e.g., late G2/M

Cells survival for these cells will be reduced

Thus, due to cells reassorting themselves within the cell cycle after the 1st exposure, cell survival will decrease after reaching a maximum

This is termed ***reassortment*** or sometimes ***redistribution***

Split-Dose Experiment – Cells Maintained at 37°C



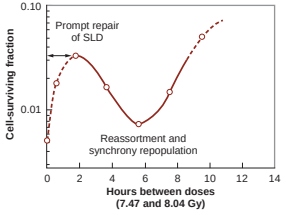
If the time interval between the split dose exceeds 10-12 hours (i.e, the length of the cell cycle), there is an increase of surviving fraction resulting from cell division, or **repopulation**

Note that reassortment & repopulation are seen only for rapidly growing cells

The four **R**s of radiobiolgy

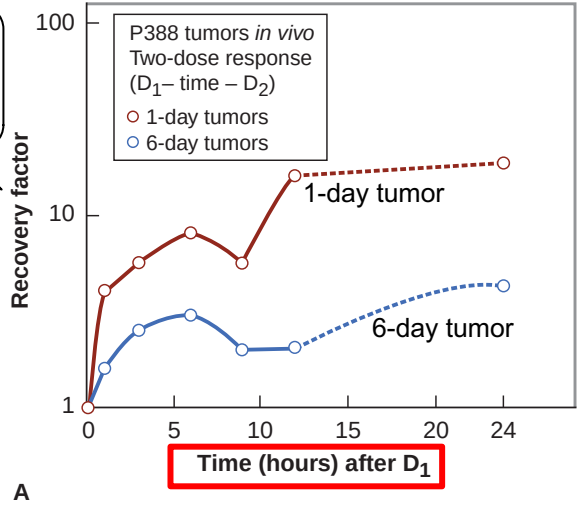
Repair
Reassortment
Repopulation
Reoxygenation

Repair of SLD *In Vivo*



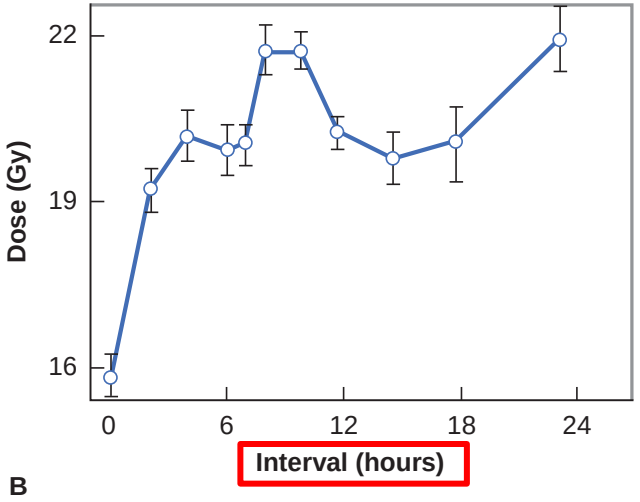
P388 mouse lymphocytic leukemia cells

Ratio of the surviving fraction resulting from 2-dose fractionation to the survival from a single equivalent dose



A

Mouse skin epithelial cells



B

Note that there is more repair in small 1-day tumors than in large hypoxic 6-day tumors – because repair is an active process requiring oxygen and nutrients

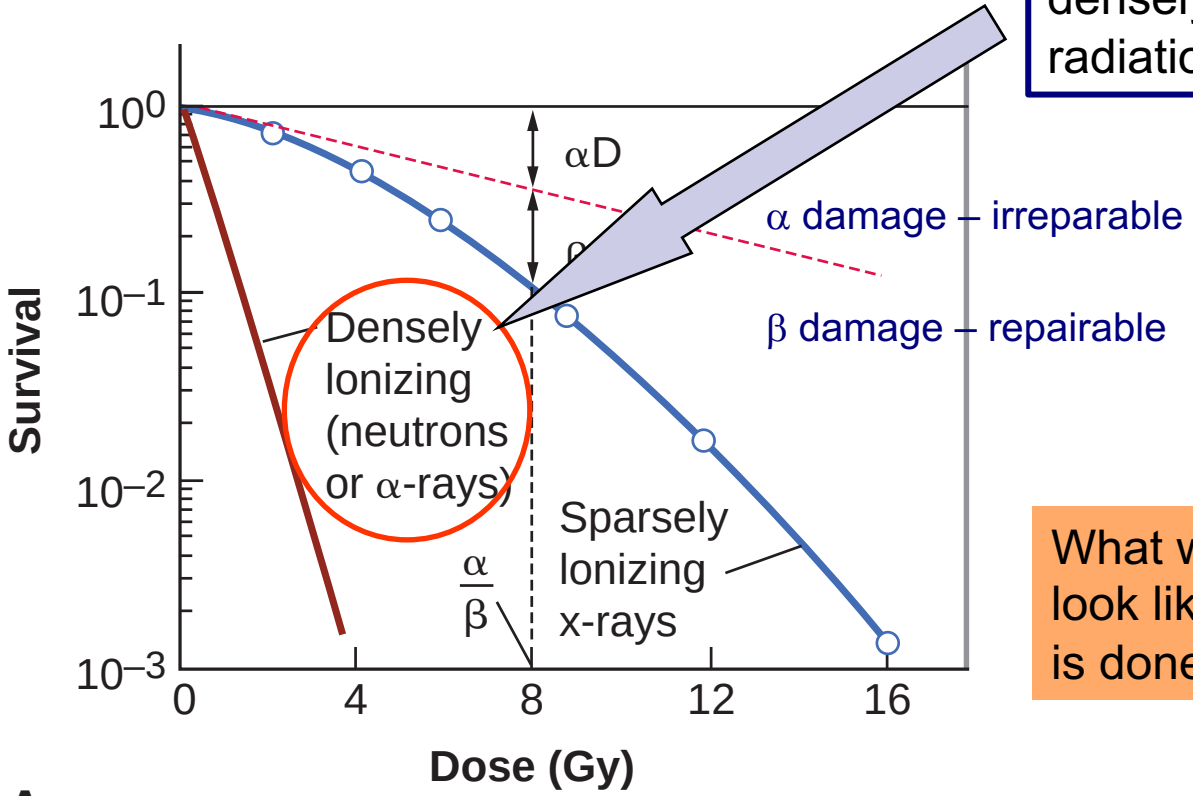
Note there is no dramatic dip at 6 hours – because the cell cycle is 10 days rather than 9 hours as in rapidly dividing CHO cells

Outline

- Operational Classifications of Radiation Damage
- **Repair and Radiation Quality**
- The Dose-Rate Effect
- The Inverse Dose-Rate Effect
- Brachytherapy
- Dose Rate and IMRT

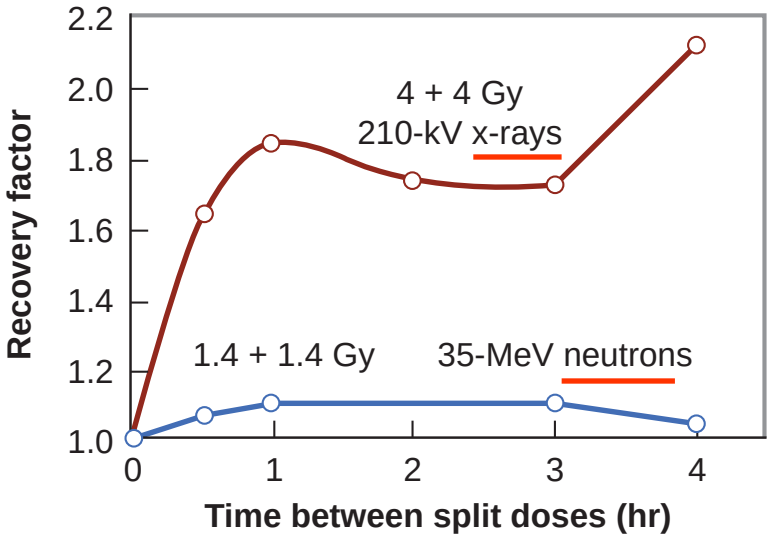
α/β Model Revisited – High LET Radiation

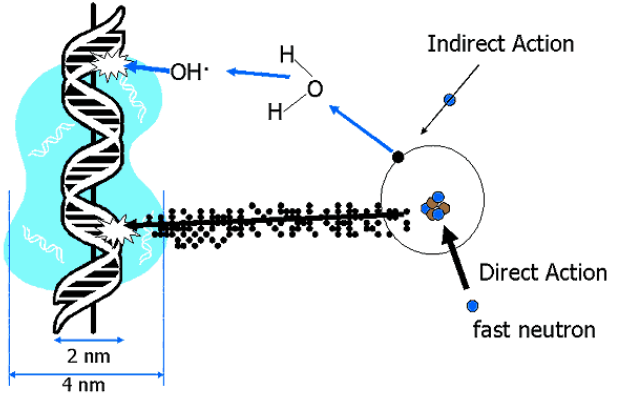
There is little SLD for densely ionizing radiation



What would the survival look like if split experiment is done with neutron?

Repair and Radiation Quality





High LET causes mostly "single-track damage"

There is virtually NO SLD repair following high LET radiations

In vitro studies also indicate that there is NO **PLDR** following high LET radiation

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- Operational Classifications of Radiation Damage
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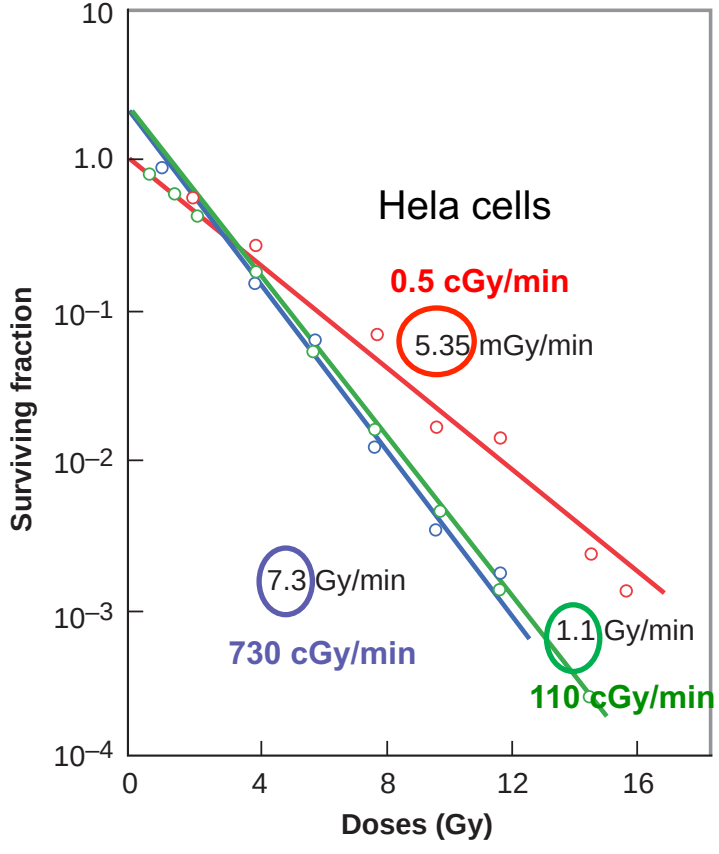
- The Inverse Dose-Rate Effect
- Brachytherapy
- Radiolabeled Immunoglobulin Therapy

Dose Rate Effect

- Radiation can be given at various dose rates
- Often expressed as Gy/hr, Gy/min, cGy/min etc

What is the dose rate for TBI for most of our protocols?

Dose-Rate Effect *In Vitro* – HeLa Cells



As the dose rate is reduced, the survival curve becomes shallower and the shoulder tends to disappear

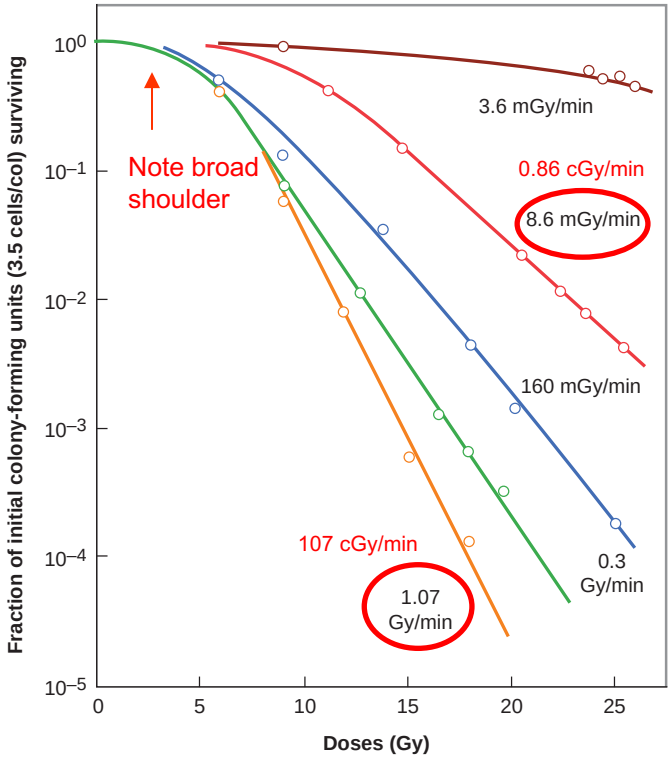
The dose-rate-effect caused by repair of SLD is most dramatic b/w **0.01 and 1 Gy/min (i.e., 1 cGy/min and 100 cGy/min)**; above and below this dose-rate range, the survival curve changes little, if at all, with dose rate

Dose-Rate Effect

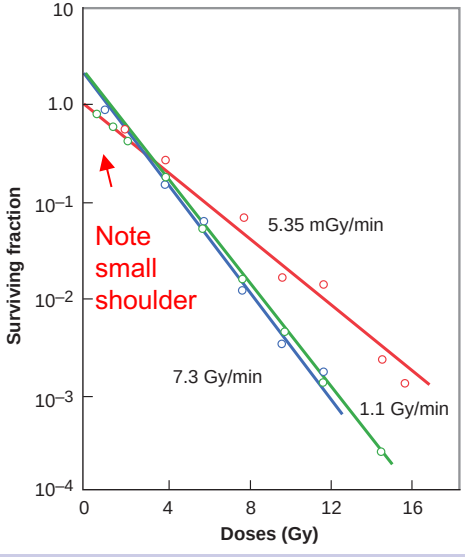
- Cell survival will ↑ due to SLD repair if
  - The irradiation is delivered in multiple fractions
  - The dose rate is reduced = **dose rate effect**
- Results from the repair of SLD that occurs during a long radiation exposure
- Important for **x- or γ-ray** therapy
  - As the dose rate is lowered and the exposure time extended, the biologic effect of a given dose generally is **reduced**

Dose-Rate-Effect *In Vitro* – CHO Cells

CHO cells



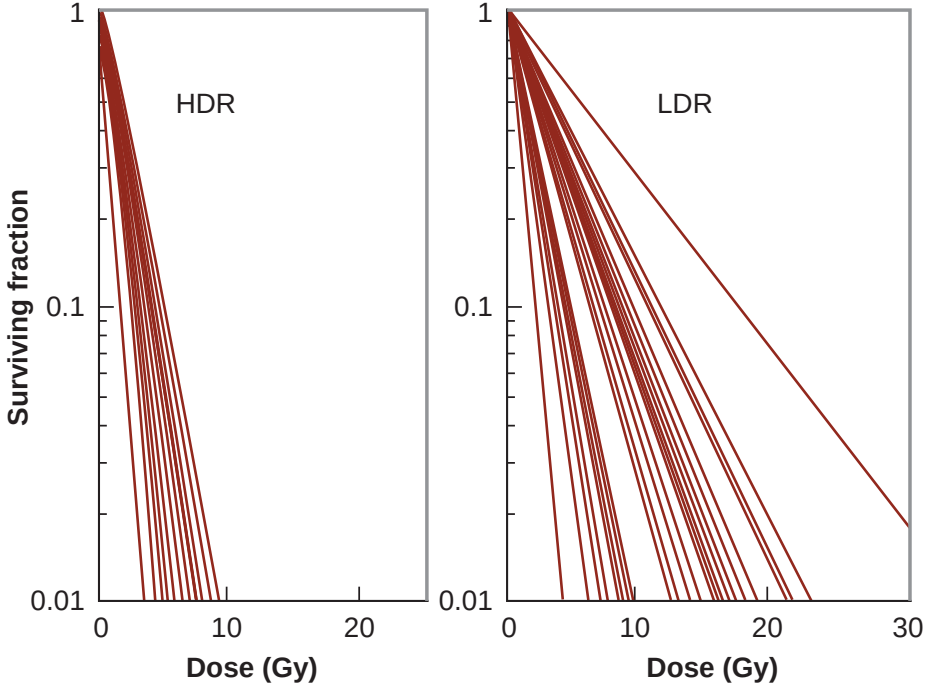
Hela cells



Dose rate effect is more dramatic in CHO than in HeLa Cells

Dose rate effect correlates with the extent of SLD repair

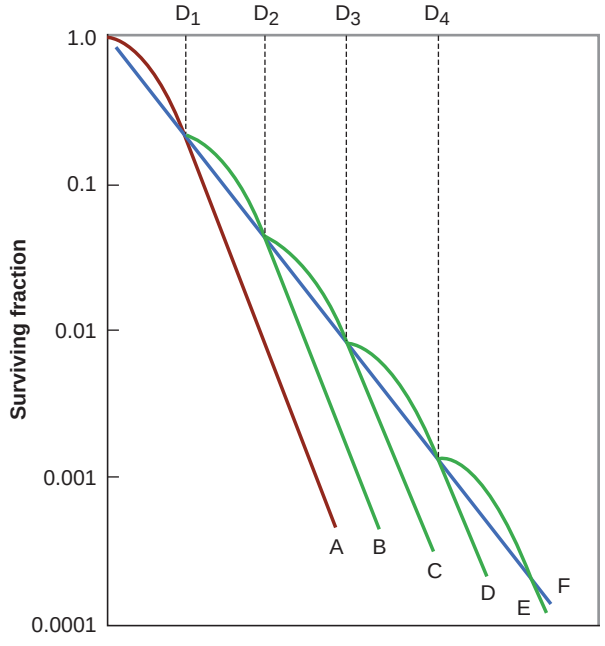
Dose-Rate-Effect *In Vitro* – HDR vs. LDR



Survival curves for 40 different cell lines of human origin

Note that survival curves fans out at LDR because in addition to a range of inherent radiosensitivities (evident in HDR), there is also a range of repair times of SLD

Idealized Fractionation Experiment



Experiment – radiation was delivered in a number of equal fractions of size D, with an interval b/w fractions sufficient for repair of SLD

Curve A – survival curve for a single acute exposures of x-rays

Curve B – survival curve for exposure to 2 fractions of size D

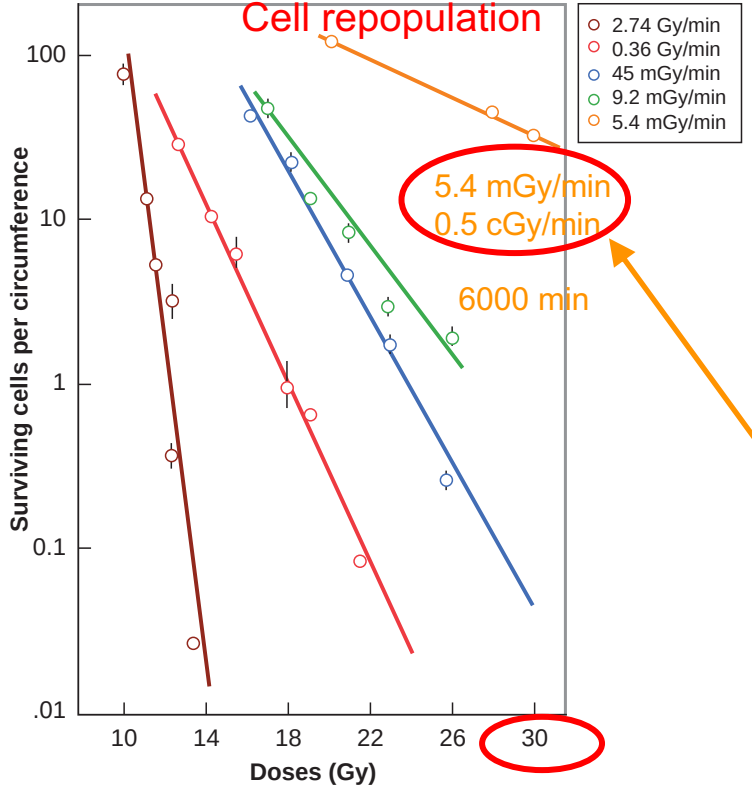
⋮

Curve F – overall survival curve with multiple equal fractions of size D
Note there is no shoulder

⋮

Continuous low-dose-rate (LDR) irradiation may be considered to be an **infinite number of infinitely small** fractions
Survival curve has **no shoulder** and is **shallower**

Dose-Rate-Effect *In Vivo*



Experiment – mouse were given total body irradiation over a wide range of dose rates; the proportion of surviving crypt cells was determined by the appearance of regenerating microcolonies in the crypts 3 days later

Note the dramatic dose-rate-effect due to SLD repair

Crypt cells are rapidly dividing cells; as the dose rate is lowered further, exposure time is longer than cell cycle time (i.e., **repopulation** takes over)

Mouse jejunal crypt cells

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- General Overview of DNA Repair Pathways
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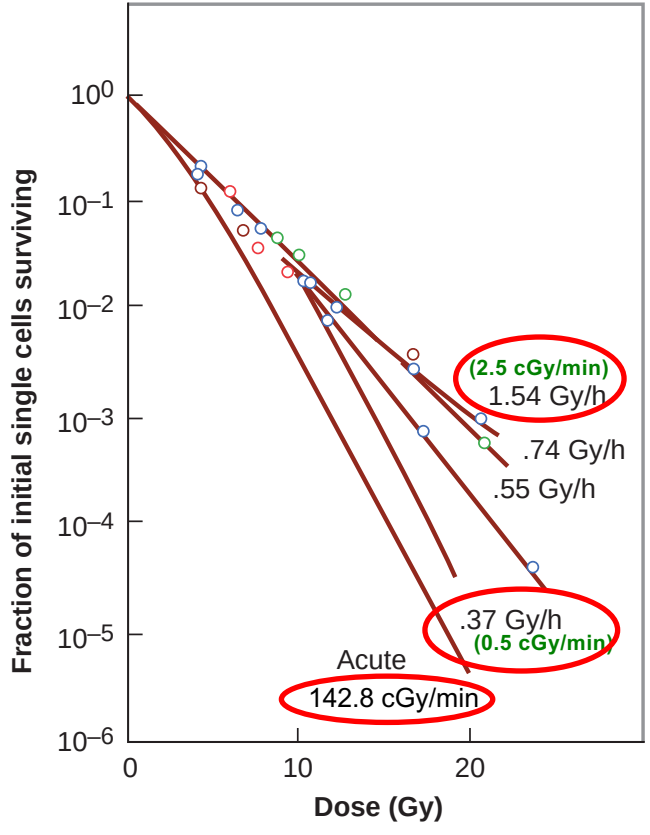
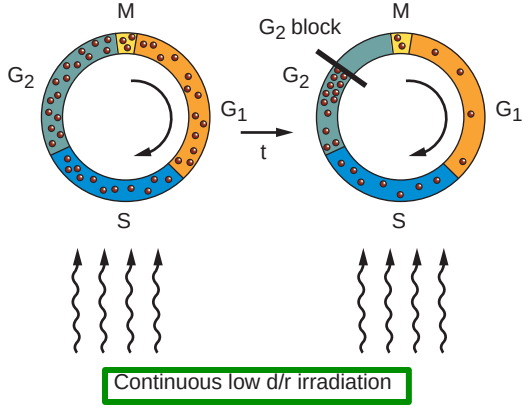
- **The Inverse Dose-Rate Effect**
- Brachytherapy
- Dose Rate and IMRT

The Inverse Dose-Rate-Effect

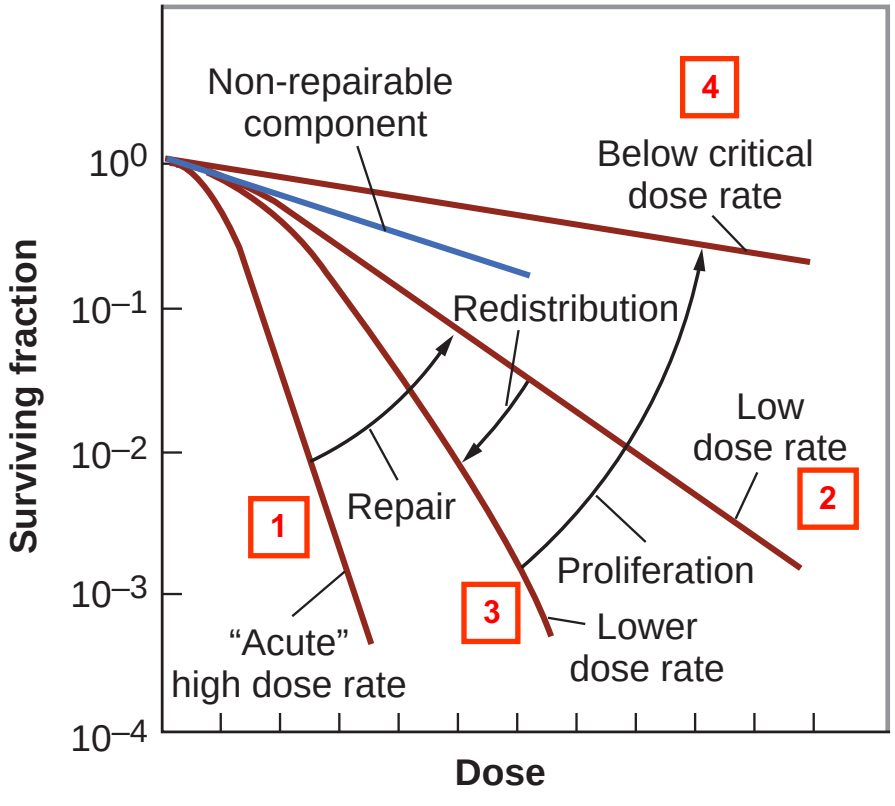


Inverse Dose-Rate-Effect – lowering the dose rate leads to more cell killing



Explanation – At higher dose rates, cells are "frozen" in the cell cycle; as dose rates are further lowered, cells continue to cycle during radiation and become arrested in the radiosensitive G2 phase

Dose-Rate-Effect Summarized



1 **Acute exposure** – note the initial shoulder width

2 **Dose-rate-effect** – note that survival curves becomes progressively shallower. Cells are "frozen" in their position and do not progress

3 **Inverse-dose-rate effect** – cells can progress through the cycle to be "trapped" in radiosensitive G_2 phase. Cells still cannot divide

4 **Repopulation** – below a critical dose rate, cells escape the G_2 block and divide; cell proliferation may occur

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- **Brachytherapy (Clinical Application of Dose-Rate Effect)**
- Dose Rate and IMRT

Brachytherapy

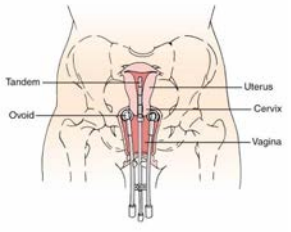
- **Brachy** – from the Greek word βραχυς *brachys*, meaning "short-distance"
- In 1901, Pierre Curie suggested to Henri-Alexandre Danlos that a radioactive source could be inserted into a tumor; it was found that the radiation caused the tumor to shrink
- In the early 20th century, techniques for the application of brachytherapy were pioneered at the Curie Institute in Paris by Danlos and at St Luke's and Memorial Hospital in New York by Robert Abbe

Henri-Alexandre Danlos (1844-1912)

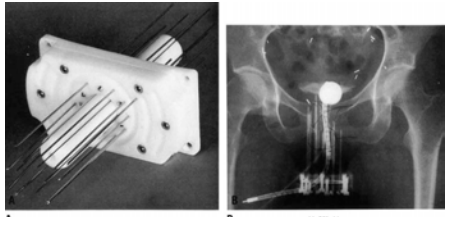
- **Henri-Alexandre Danlos** was a French physician and dermatologist born in Paris.
- With Danish dermatologist Edvard Ehlers , the Ehlers-Danlos syndrome was named, which is a group of inherited connective tissue disorders.
- Danlos was pioneer in the use of radium for treatment of lupus erythematosus of the skin, and in 1901 with phycisist Eugène Bloch, he was the first to apply radium on tuberculous skin lesions.

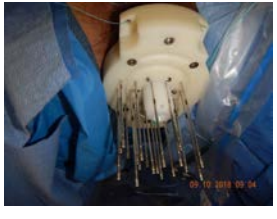
Brachytherapy

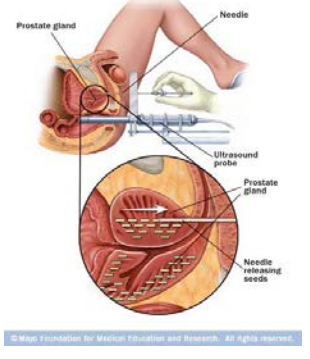
- 2 forms of brachytherapy
  - **Intracavitary** – radioactive sources placed in body cavities in close proximity to the tumor



  - **Interstitial** – radioactive wires or “seeds” implanted directly into the tumor volume
    - Temporary
    - Permanent







Radionuclides for Brachytherapy

TABLE 5.1. *Characteristics of Radionuclides for Intracavitary or Interstitial Brachytherapy*

Radionuclide	Photon Energy, KeV		Half-life	HVL, 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

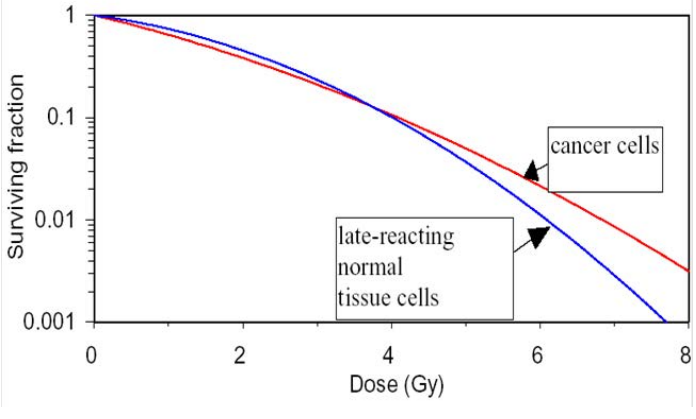
Data computed by Dr. Ravinder Nath, Yale University.

Clinical Applications of the Dose-Rate Effect

- Continuous LDR Teletherapy
- Pulsed LDR Teletherapy
- Brachytherapy
  - **Low dose rate (LDR)** – dose rate 0.5-2 cGy/min (30-120 cGy/hr)
  - Medium dose rate (MDR)
  - **High dose rate (HDR)** – dose rate $\geq$ 20 cGy/min (12 Gy/hr)
  - Pulsed dose rate (PDR)

Radiobiological Rationale of LDR Brachytherapy

- Cells which exhibit little repair (small shoulder on the acute-exposure cell survival curve) will also exhibit little dose-rate effect
- Conversely, cells with large shouldered (or very “curvy”) cell survival curves will demonstrate a significant dose-rate effect
- In general, **cancer cells will show less dose-rate effect than the cells of late-reacting normal tissue**

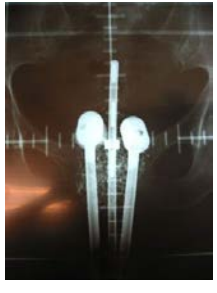


If we decrease the dose-rate, the late-reacting normal tissue will be spared to a greater extent compared to cancer cells = enhanced therapeutic ratio

Radiobiological Rationale for LDR Brachytherapy

- Since low dose rate benefits late-reacting normal tissues more than cancers, the lower the dose rate used in radiotherapy, the better
- However, too low a dose rate may allow cancer cells to proliferate during treatment (*repopulation*)

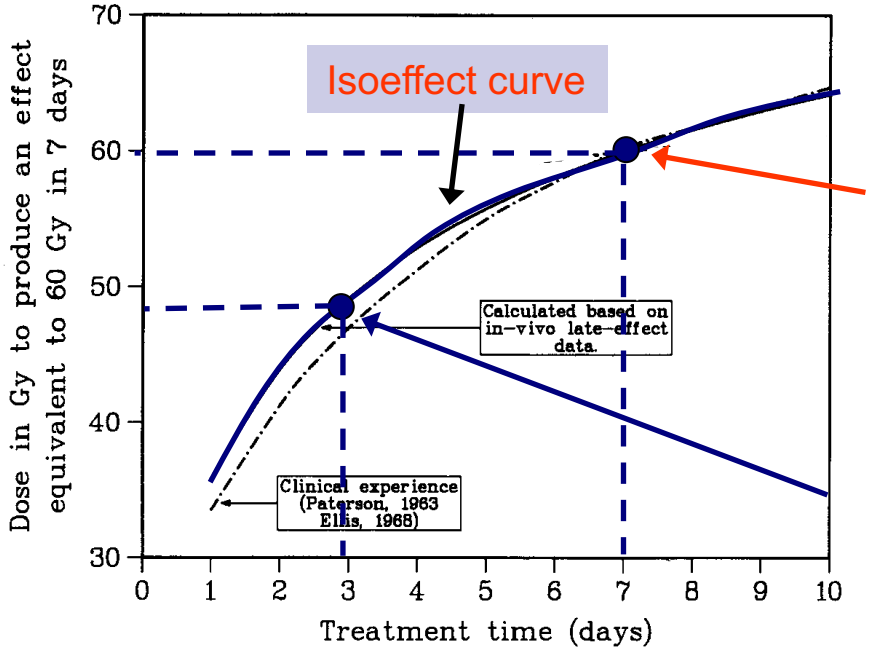
- The vast majority of interstitial and intracavitary brachytherapy experience has been with **LDR**
- Results have been excellent



Brachytherapy – Total Dose vs. Dose Rate

- The maximum dose that can be delivered without unacceptable damage to the surrounding normal tissue depends on
  - **Volume of tissue irradiated**
  - **Dose rate** – to achieve a consistent biologic response, the total dose used should be varied according to the dose rate employed

Dose-Rate Correction – the Manchester Experience



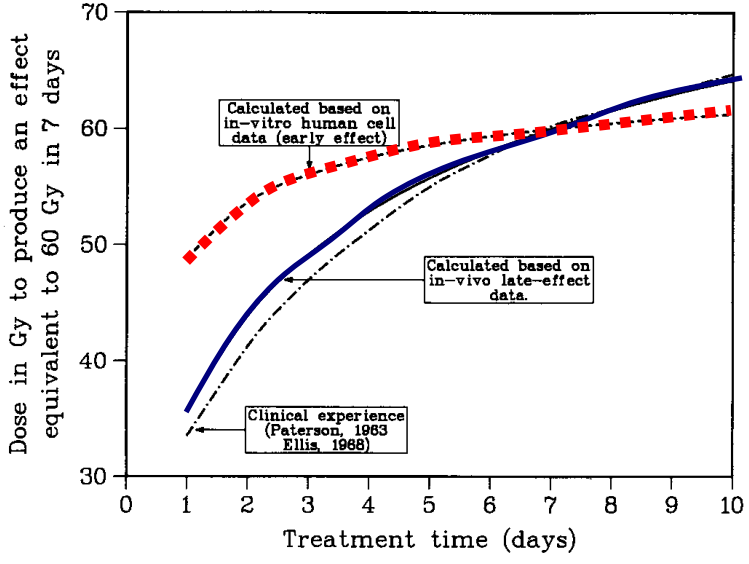
Standard = 60 Gy/7days
Dose rate = 0.357 Gy/hr

Equivalent biologic effect

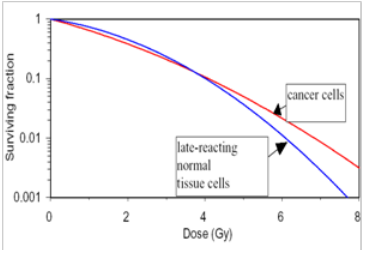
Dose rate = 0.64 Gy/hr
Total dose = 46 Gy (in 3 days)

Note that the calculated curve (from radiobiologic data) agrees closely with clinical experience

Isoeffect Curves – Early- vs. Late-Responding Tissues



The variation of total dose with dose-rate is much larger for late-than for early-responding tissues (more in Chapter 23)



Late-responding Tissue

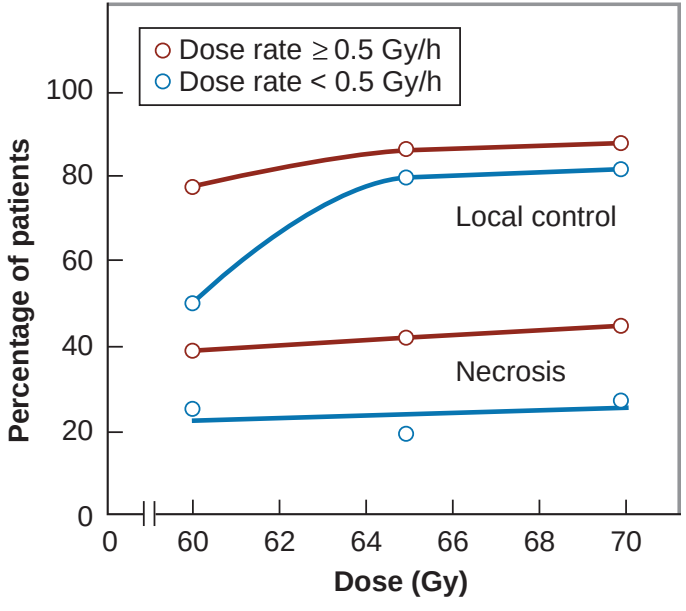
Example – spinal cord
Large shoulder
Small α/β
Large dose-rate effect
Large variation of total dose with dose-rate

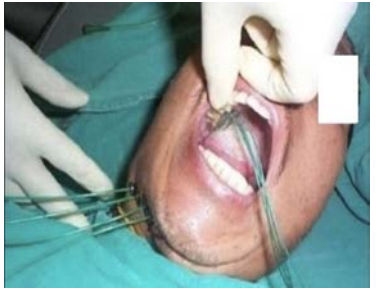
Early-responding Tissue

Example – cancer cells
Small shoulder
Large α/β
Little dose-rate effect
Little variation of total dose with dose-rate

Dose-Rate Effect – Clinical Data

T1-2 SCC of oral tongue and floor of mouth
Treated with interstitial Ir-192 implants

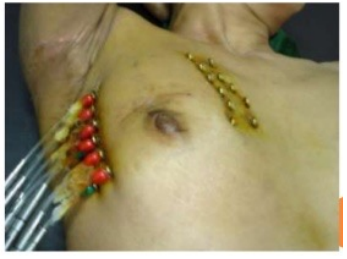




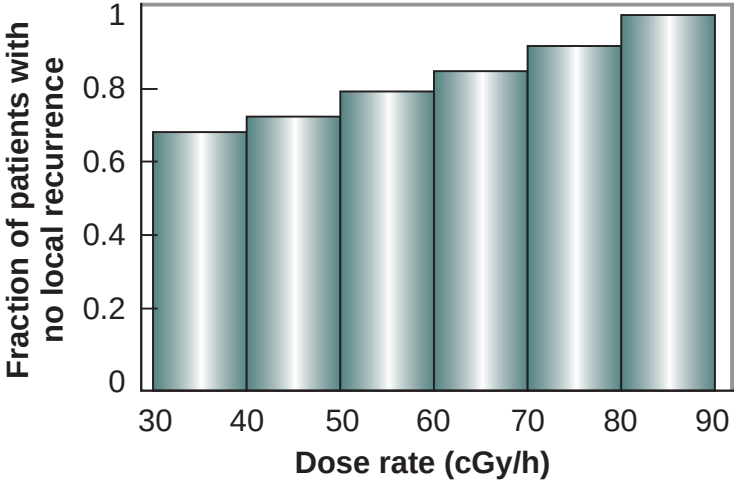
Local tumor control depends less on dose-rate, provided the total dose was sufficiently large (**early-responding**)

Necrosis rate was substantially higher in patients treated with higher dose-rates (**late-responding**)

Dose-Rate Effect – Clinical Data



Breast Ca Treated with EBRT + interstitial Ir-192 boost



Interstitial Ir-192 as a boost to EBRT

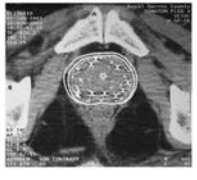
A fixed standard dose was used

Conclusion – for a given total dose, there were markedly fewer recurrences if the radiation was delivered at a higher dose rate rather than a lower dose rate

Clinical implication – because of the short $t_{1/2}$ of Ir-192, dose rates decrease over time $\rightarrow$ important to correct the total dose for the dose rate

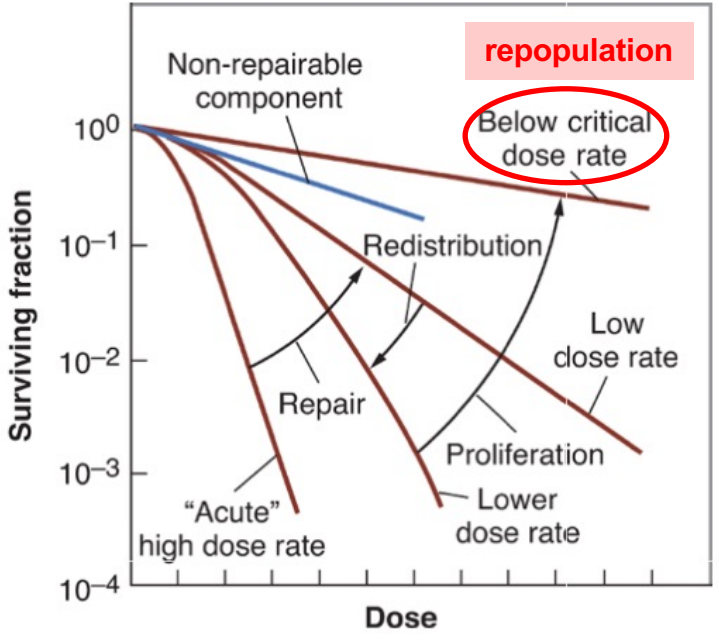
Permanent Interstitial Implants

- Permanent implants have the advantage that only a single insertion is required
- The dose-rate effect is complicated due to the gradually decreasing dose rate
  - The initial dose rate is high and falls off as the implanted sources decay
- I-125 ($t_{1/2}$ = 60 days) and Pd-103 ($t_{1/2}$ = 17 days) are the most common sources



Permanent Implant – I-125

- Average photon energy ~ 28 eV
  - Simplifies radiation protection
  - Rapid dose fall-off
- $T_{1/2}$ = 60 days – means that dose spreads over several months
  - A problem for rapidly growing tumors b/c repopulation compensates for cell killing
  - Not a concern for slow growing tumors (e.g., prostate)

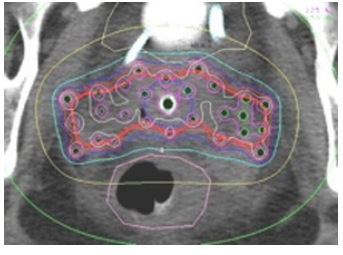


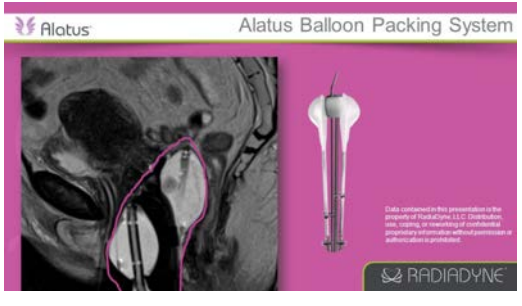
Brachytherapy – HDR

- HDR brachytherapy, to a large extent, is replacing the traditional LDR brachytherapy
- High-dose rate gives up much of the radiobiological advantage and the sparing of late-responding normal tissues
- However, the physical advantages of HDR offsets the radiobiological disadvantages

Brachytherapy – HDR

- HDR is attractive because it can be performed on an outpatient basis
- Remote afterloading technology eliminates exposure to medical personnel
- Computer planning allows greater control over dose distribution
- Special retractors are available to shield dose-limiting normal tissues





Physical Advantage

Brachytherapy – HDR

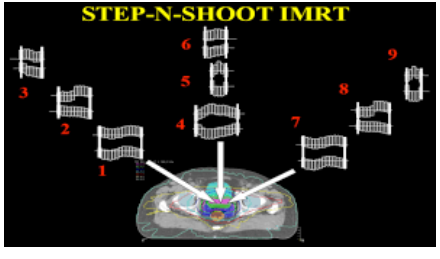
- HDR should be fractionated to allow for repair (typically 3-12 fractions)
- The time between fractions must be adequate for repair
- Clinical data indicate that properly fractionated HDR can be at least as good as LDR

Outline

- General Overview of DNA Repair Pathways
- Operational Classifications of Radiation Damage
- The Dose Rate Effect
- The Inverse Dose-Rate Effect
- Brachytherapy
- **Dose Rate and IMRT**

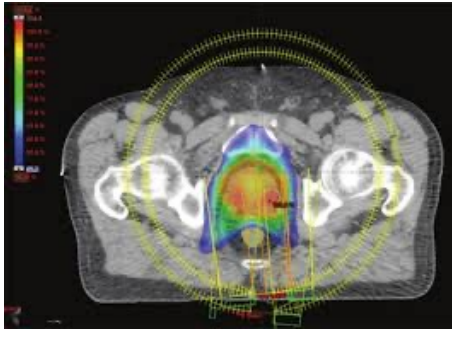
IMRT and Dose Rate

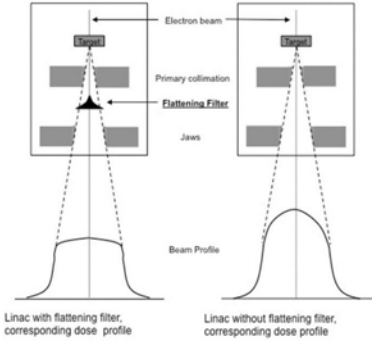
- Initial implementation of IMRT requires a high number of separate segments and often longer delivery time of 20-30 minutes per fraction
- Part of the biological effect may be lost by repair during treatment
- It was shown that cell kill may decrease by up to 20% for treatment times of 20-30 minutes *in vitro*
- *In vivo,* the the loss of cell kill may be compensated by rapid reoxygenation



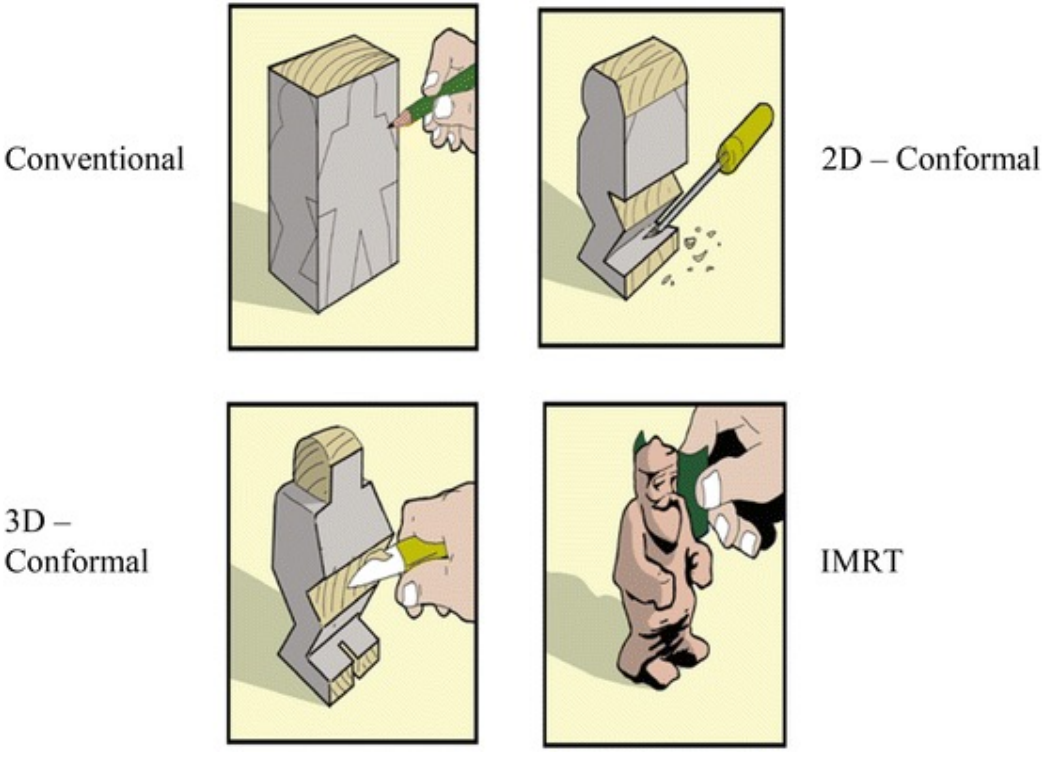
VMAT

- Volumetric modulated arc therapy (VMAT) allows delivery of dose fractions typically in less than 10 minutes
- New treatment units now offers flattening-filter free (FFF) beams which can result in higher average dose rates and hence also allow faster treatment delivery





Happy Studying!



https://radiologykey.com/computer-assisted-treatment-planning-approaches-for-imrt/

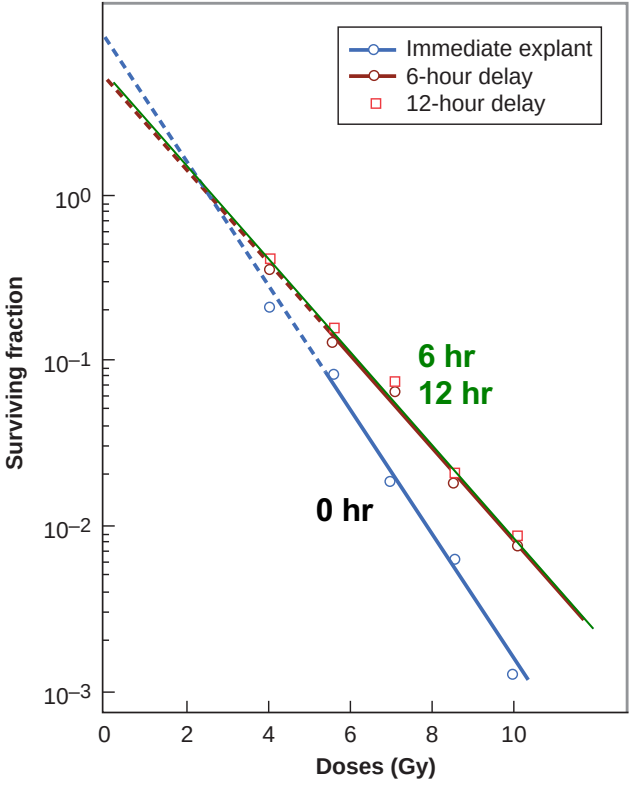
Review Questions

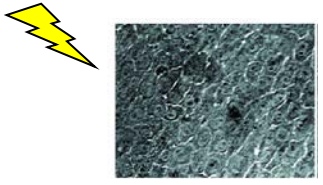
Question 1

When cells are held under suboptimal growth conditions for 6 hours after a single dose of X-rays, the cell surviving fraction is noted to increase. This is evidence for the:

A. repair of sublethal damage
B. redistribution of cells around the cell cycle
C. repair of potentially lethal damage
D. repair of base damages
E. inverse dose rate effect

PLD – Density-Inhibited Stationary-Phase Cells





Experiment – ***density arrested cells*** are irradiated, and either plated immediately or **maintained in density-inhibited stationary phase for 6-12 hours** before plating out for survival curve

Observation – survival enhanced if cells are left for 6-12h in density-inhibited state

Interpretation – if mitosis are delayed by **suboptimal growth conditions**, PLD (complex as opposed to simple DSBs) can be repaired

Potentially Lethal Damage (PLD)

- This is the component of radiation damage that can be modified by **post-irradiation environmental conditions**
- Under normal conditions, PLD is lethal
- By *manipulation* of the post-irradiation **environment**, PLD can be repaired
- PLD is believed to be complex DSBs that are repaired slowly as compared to simple DSBs

Question 2

An 8 Gy X-ray dose delivered at 1 Gy/hr is less toxic than the same dose delivered at 1 Gy/min primarily because:

A. fewer free radicals are generated

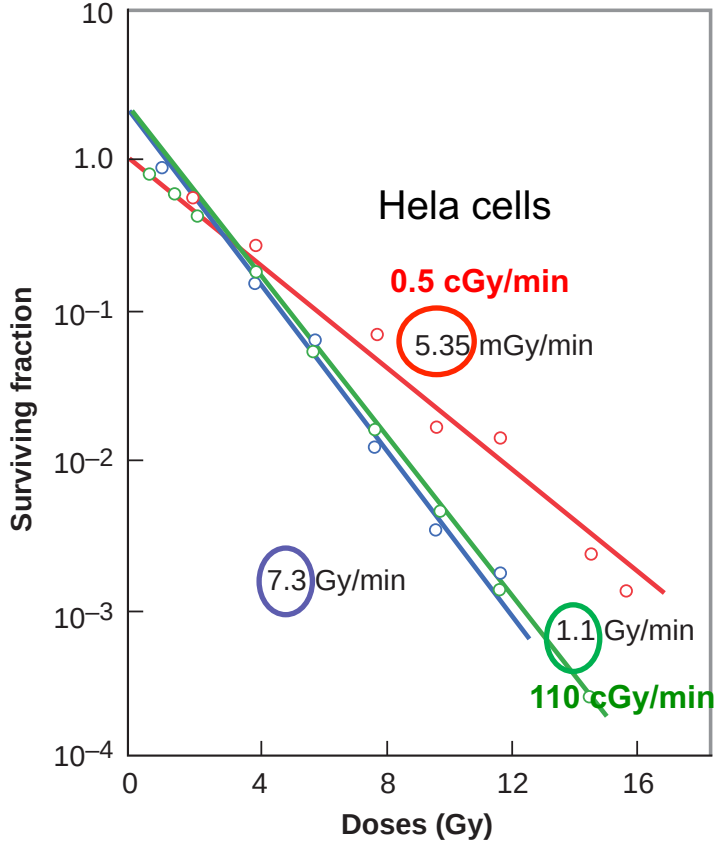
B. cell division occurs during exposure

C. free radical scavenging takes place

D. sublethal damage repair occurs during the irradiation

E. chemical restitution is permitted

Dose-Rate Effect *In Vitro* – HeLa Cells



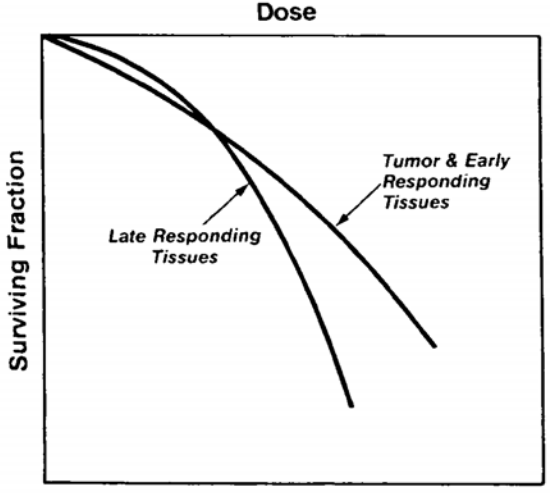
As the dose rate is reduced, the survival curve becomes shallower and the shoulder tends to disappear

The dose-rate-effect caused by repair of SLD is most dramatic b/w **0.01 and 1 Gy/min (i.e., 1 cGy/min and 100 cGy/min)**; above and below this dose-rate range, the survival curve changes little, if at all, with dose rate

Question 3

Which one of the following normal tissues would be expected to show the least amount of sparing when irradiated with X-rays at a low versus high dose rate?

A. kidney
B. lung
C. spinal cord
D. breast epithelium
E. bone marrow

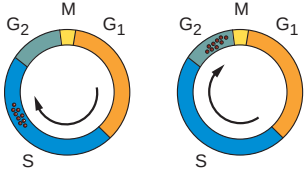


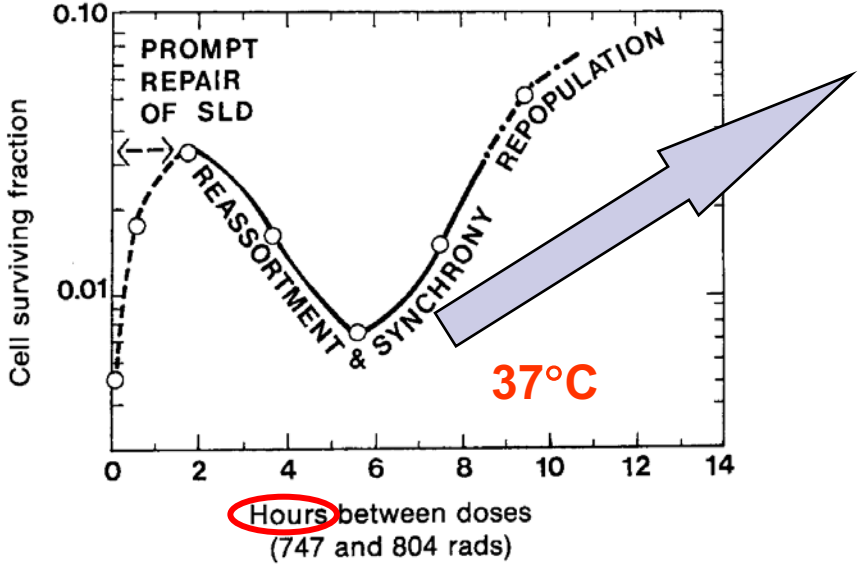
Question 4

Generally, the sparing effect of dose fractionation increases with increasing time between fractions. Under certain irradiation conditions however, an increase in the interval between fractions results in *decreased* cell survival. This occurs because of:

A. reassortment
B. repopulation
C. repair
D. reoxygenation
E. adaptive response

Split-Dose Experiment – Cells Maintained at 37°C





During the repair process, these cells will travel through the cell cycle

Cells that were in the late S phase of the cell cycle at the time of the 1st fraction will be most likely to survive and move towards mitosis

At the time of a 2nd fraction, these cells may have reached a sensitive phase, e.g., late G2/M

Cells survival for these cells will be reduced

Thus, due to cells reassorting themselves within the cell cycle after the 1st exposure, cell survival will decrease after reaching a maximum

This is termed ***reassortment*** or sometimes ***redistribution***

Question 5

The dose rate range over which SLDR most contributes to the dose rate effect for X-rays is:

A. 0.001 - 0.01 Gy/min

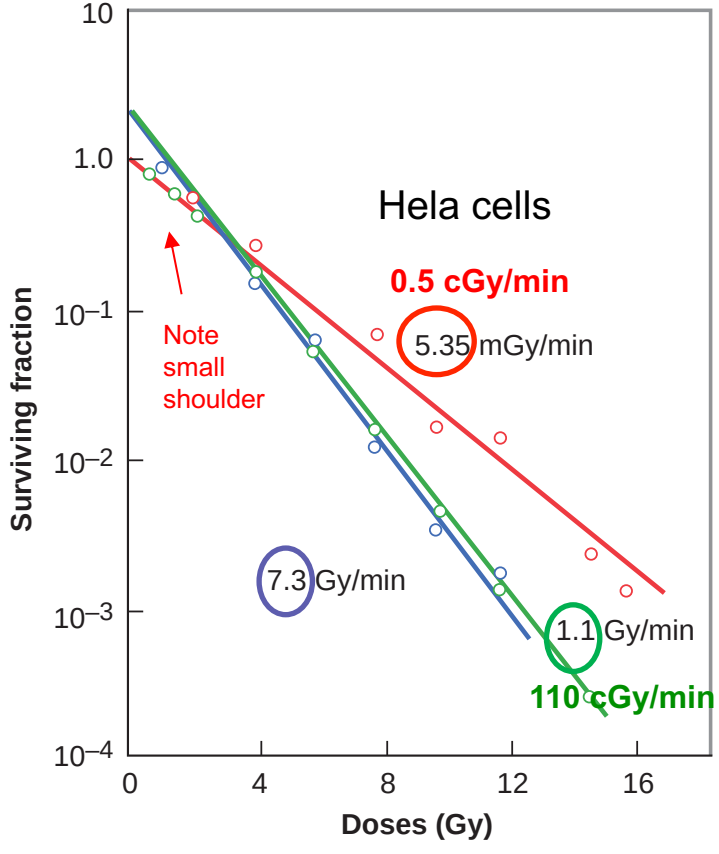
B. 0.01 – 1 Gy/min

C. 1 - 5 Gy/min

D. 5 - 10 Gy/min

E. 10 - 20 Gy/min

Dose-Rate Effect *In Vitro* – HeLa Cells



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The dose-rate-effect caused by repair of SLD is most dramatic b/w **0.01 and 1 Gy/min (i.e., 1 cGy/min and 100 cGy/min)**; above and below this dose-rate range, the survival curve changes little, if at all, with dose rate

Question 6

The inverse dose rate effect occurs due to inhibition of cell cycle progression during which phase of the cell cycle?

A. G_0

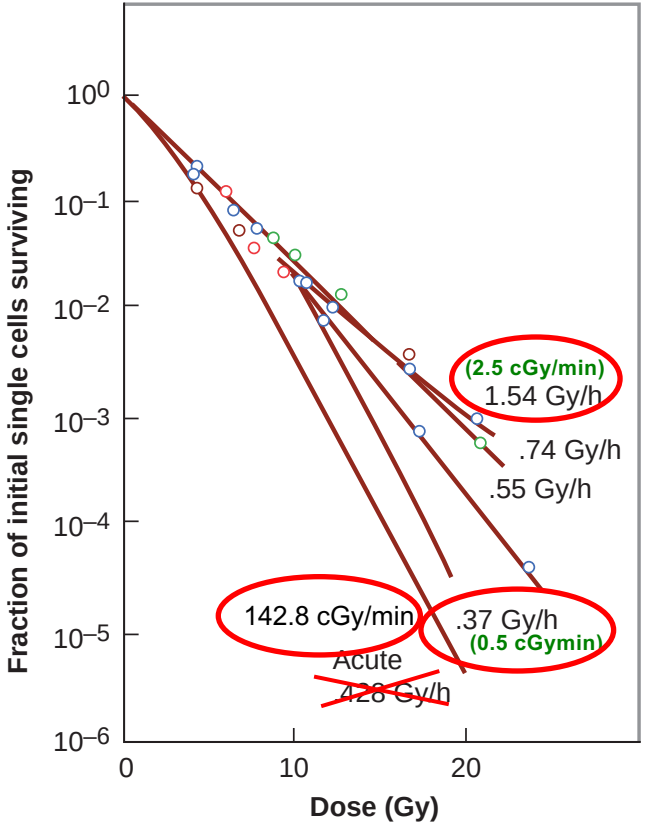
B. G_1

C. S

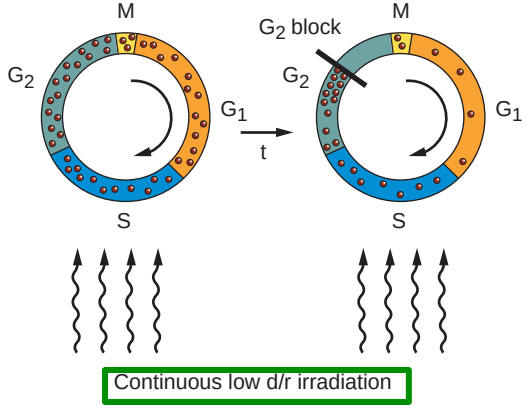
D. G_2

E. M

The Inverse Dose-Rate-Effect

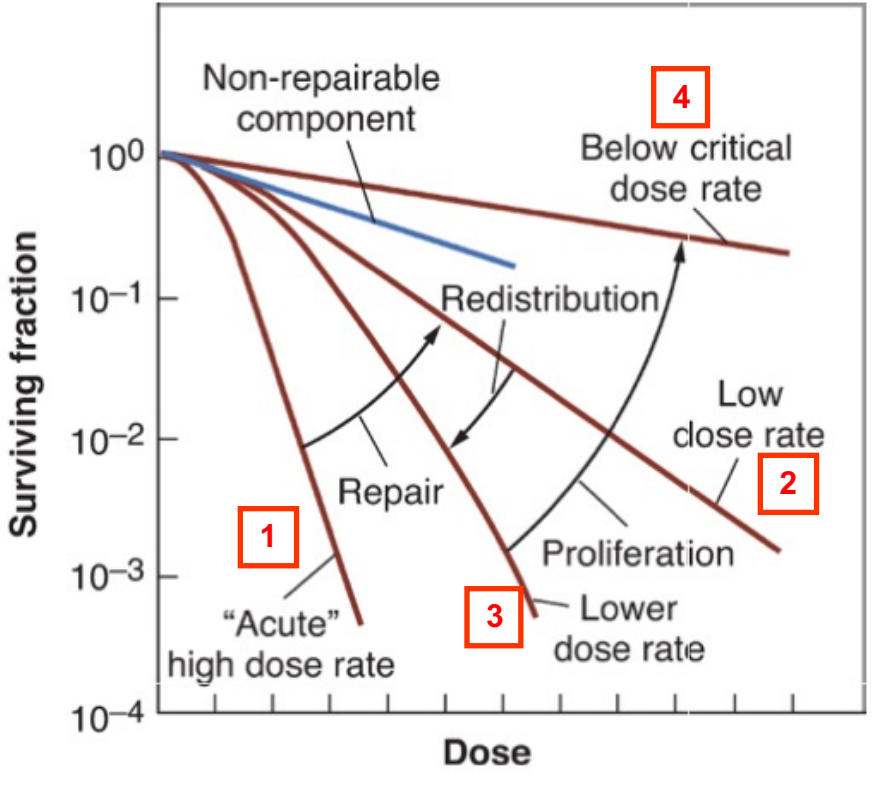


Inverse Dose-Rate-Effect – lowering the dose rate leads to more cell killing



Explanation – At higher dose rates, cells are "frozen" in the cell cycle; as dose rates are further lowered, cells continue to cycle during radiation and become arrested in the radiosensitive G2 phase

Dose-Rate-Effect Summarized



1 **Acute exposure** – note the initial shoulder width

2 **Dose-rate-effect** – note that survival curves becomes progressively shallower. Cells are "frozen" in their position and do not progress

3 **Inverse-dose-rate effect** – cells can progress through the cycle to be "trapped" in radiosensitive G_2 phase. Cells still cannot divide

4 **Repopulation** – below a critical dose rate, cells escape the G_2 block and divide; cell proliferation may occur