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Radiation Biology for Radiology Residents

Kathryn D. Held, Ph.D.
Massachusetts General Hospital/Harvard Medical School
National Council on Radiation Protection and Measurements

Sequences in the Development of Radiobiological Effects

Time	Event
10^{-18} s	Absorption of Ionizing Radiation
10^{-16} s	Physical Events
	Ionization
	Excitation
10^{-12} s	Physicochemical Events
	Free radical formation
	Breakage of chemical bonds
$10^{-12} - 10^{-6}$ s	Chemical Events
	Reactions of radicals
Minutes to hours	Biochemical/Cellular Processes
	Repair
	Division delay
	Chromosome damage
	Loss of reproductive capacity
Days to months	Tissue Damage
	CNS, GI, Bone marrow syndromes
	Late tissue damage
	Birth defects from in utero exposure
Years	Late Somatic Effects
	Cataracts
	Carcinogenesis
Generations	Genetic Effects

Radiation Biology for Radiology Residents

- Molecular and cellular effects of radiation
- Modification of radiation response

- Systems effects of radiation
- Radiation mutagenesis and carcinogenesis
- Risk and risk models

Last year, next year

References:

Bushberg *et al*., Chapter 20, Radiation Biology and Protection in ***Essential Physics of Medical Imaging***, 2012.

Hall and Giaccia, Radiobiology for the Radiologist, 7th Ed., 2012

Martin *et al*., J. Radiol. Prot. 2009.

Radiation Biology for Radiology Residents

- Molecular and cellular effects of radiation
  - Radiation chemistry
  - Effects on DNA and chromosomes
  - Cell survival/cell death
- Modification of radiation response

All biological effects produced by ionizing radiation result from the chemical events that occur shortly after the initial deposition of radiation energy.

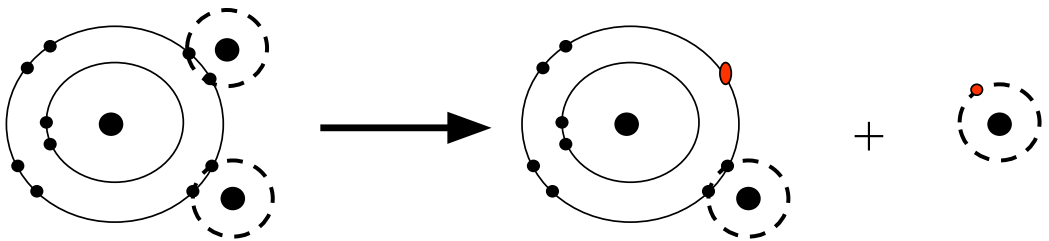
Physics		Chemistry		Biochemistry/Biology
10^{-18} s	→	10^{-12}-10^{-6} s	→	minutes-generations

Ionizing Radiation

Free radicals - atoms or molecules that have one or more unpaired electron

- designated by "•"
- may be formed by division of a covalent bond

  $R{:}S \rightarrow R^{\bullet} + S^{\bullet}$
- may be charged or neutral
- are generally very reactive
- name often ends in "yl"

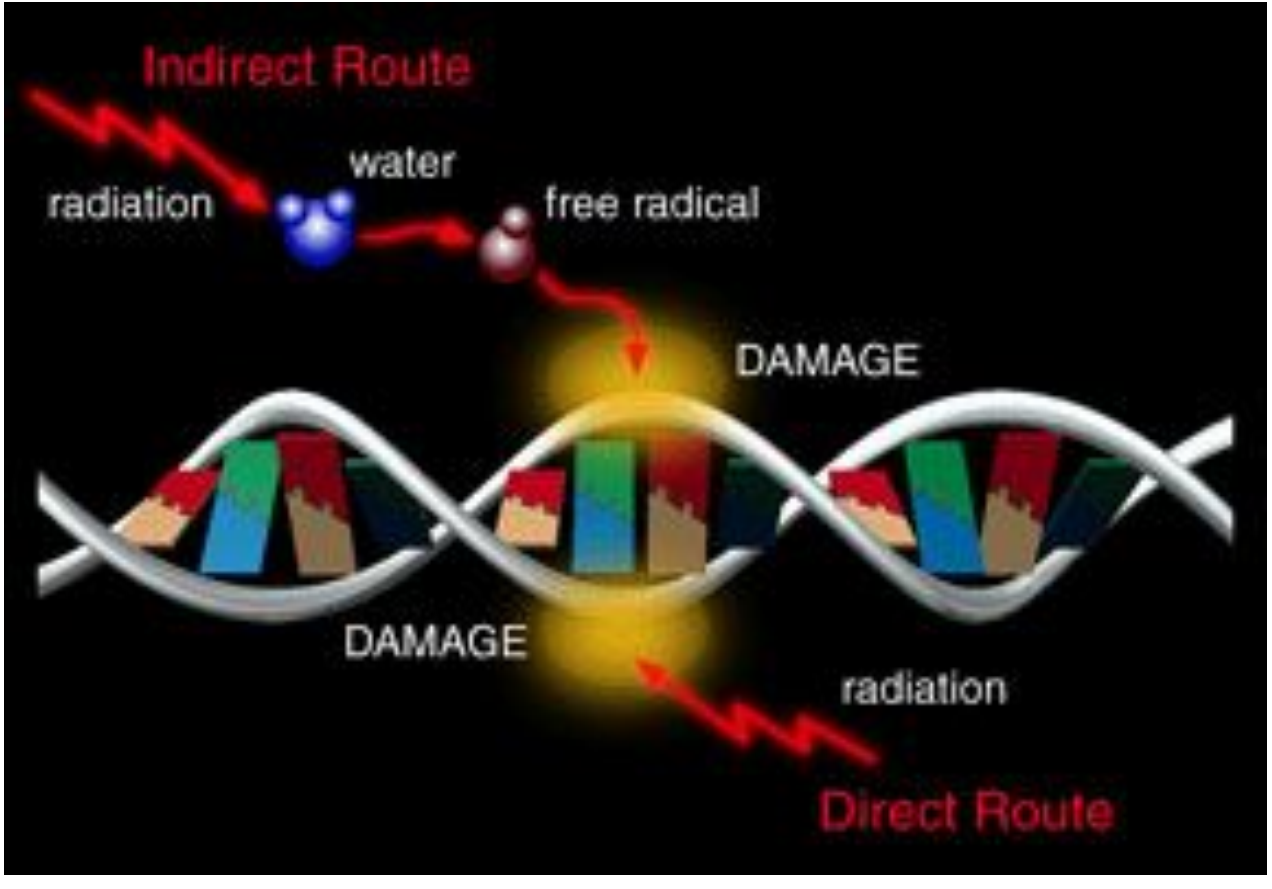


Water molecule

Hydroxyl ($^{\cdot}OH$) radical

H-atom

Direct and Indirect Actions of Ionizing Radiation



Low LET

70%

30%

(Diagram from S Wallace)

Water Radiolysis Summary

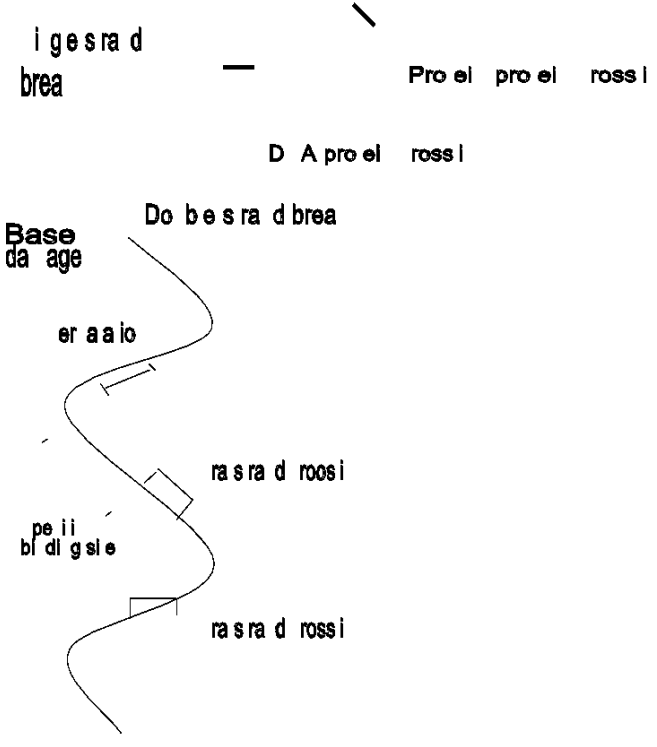
$$H_2O \rightarrow {}^{\bullet}OH,\ {}^{\bullet}H,\ e^-_{aq},\ H_2,\ H_2O_2$$

${}^{\bullet}OH$ is the most important biologically.
(a very strong oxidizing species)

DNA is a Primary Target

- Microbeam experiments show cell nucleus to be more sensitive than cytoplasm.
- Halogenated base analogues sensitize cells and DNA.
- Radioisotopes in DNA are more lethal than when in RNA or protein.
- DNA repair deficient cells are radiation sensitive; drugs that inhibit DNA repair usually are radiosensitizers.
- Oxygen and LET modify survival, cytogenetic damage and biological activity of DNA in similar manner.

Types of DNA Lesions from IR



Breaks

- SSB
- DSB

Base damages

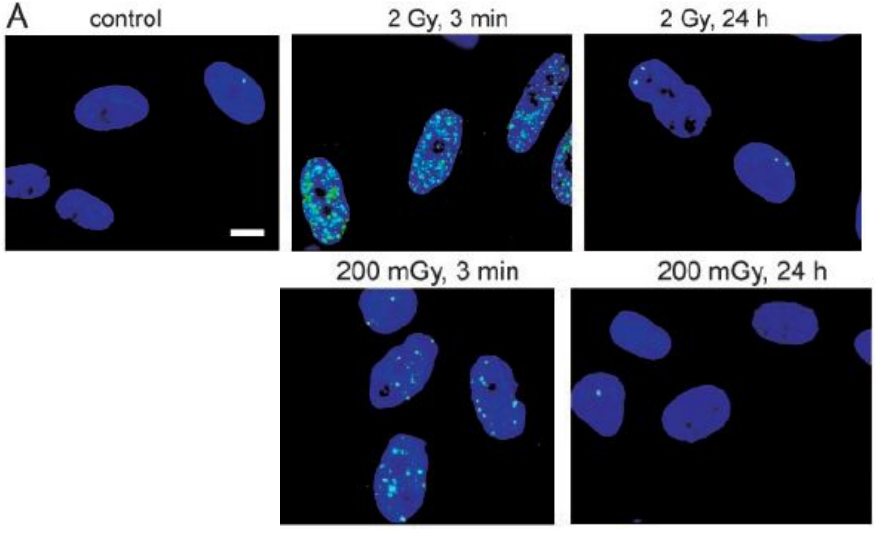
- Change
- Loss (abasic sites)

Crosslinks

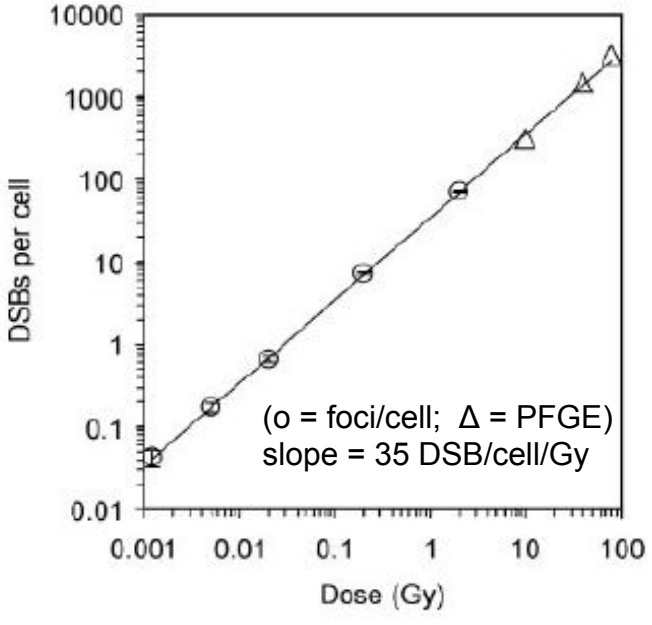
- DNA-DNA
- DNA-protein

Of these lesions, DSBs are most important for biological effects.

Foci of DNA Repair-Related Proteins (e.g., γ-H2AX) as Measure of DNA DSBs



(from Rothkamm and Löbrich 2003)



γ-H2AX – phosphorylated histone H2A variant X
Foci – fluorescent "blobs" representing aggregates of protein recognized by antibodies

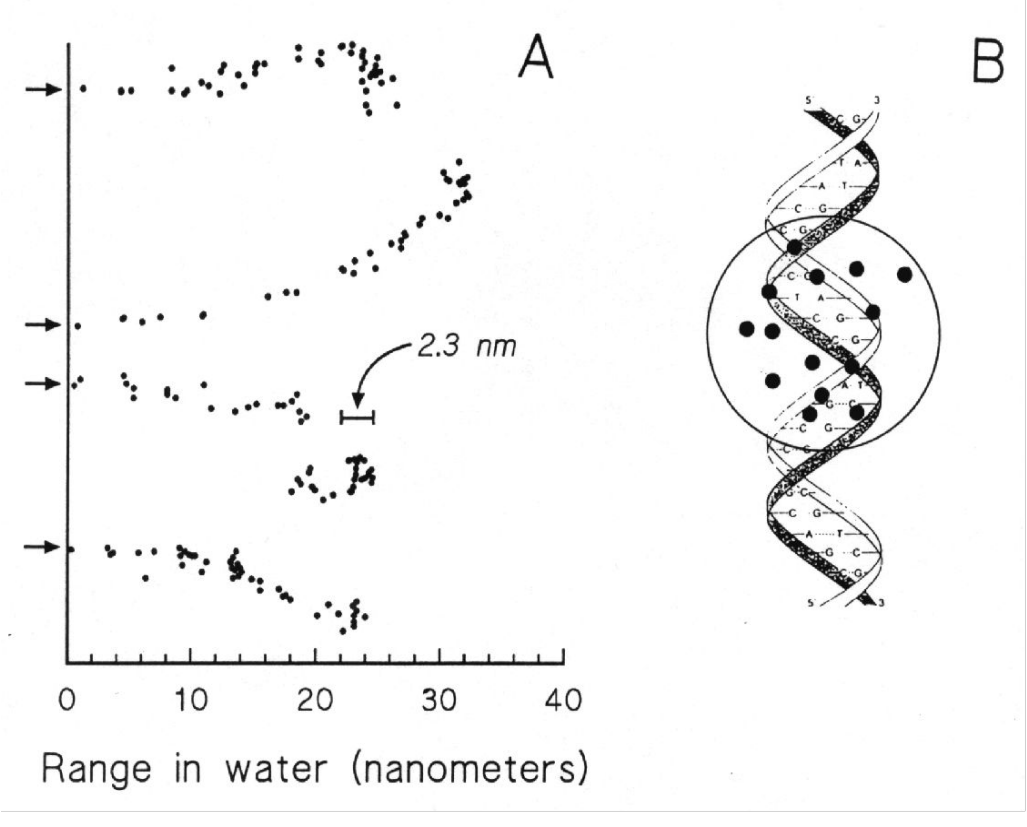
- Number of foci increases linearly with dose, with same slope as DSBs measured by PFGE.
- Even after very low doses, some foci remain at 24 h.

Number of Radiation-Induced Lesions

Type of Lesion	Number per cell per Gy
Ionizations	100,000
Double strand breaks	25-40
Single strand breaks	1000
Base damages	>2000
Sugar damages	800-1000
DNA-DNA crosslinks	30
DNA-protein crosslinks	150
Alkali-labile sites	200-300

Number of **Clustered Lesions** not well quantified.

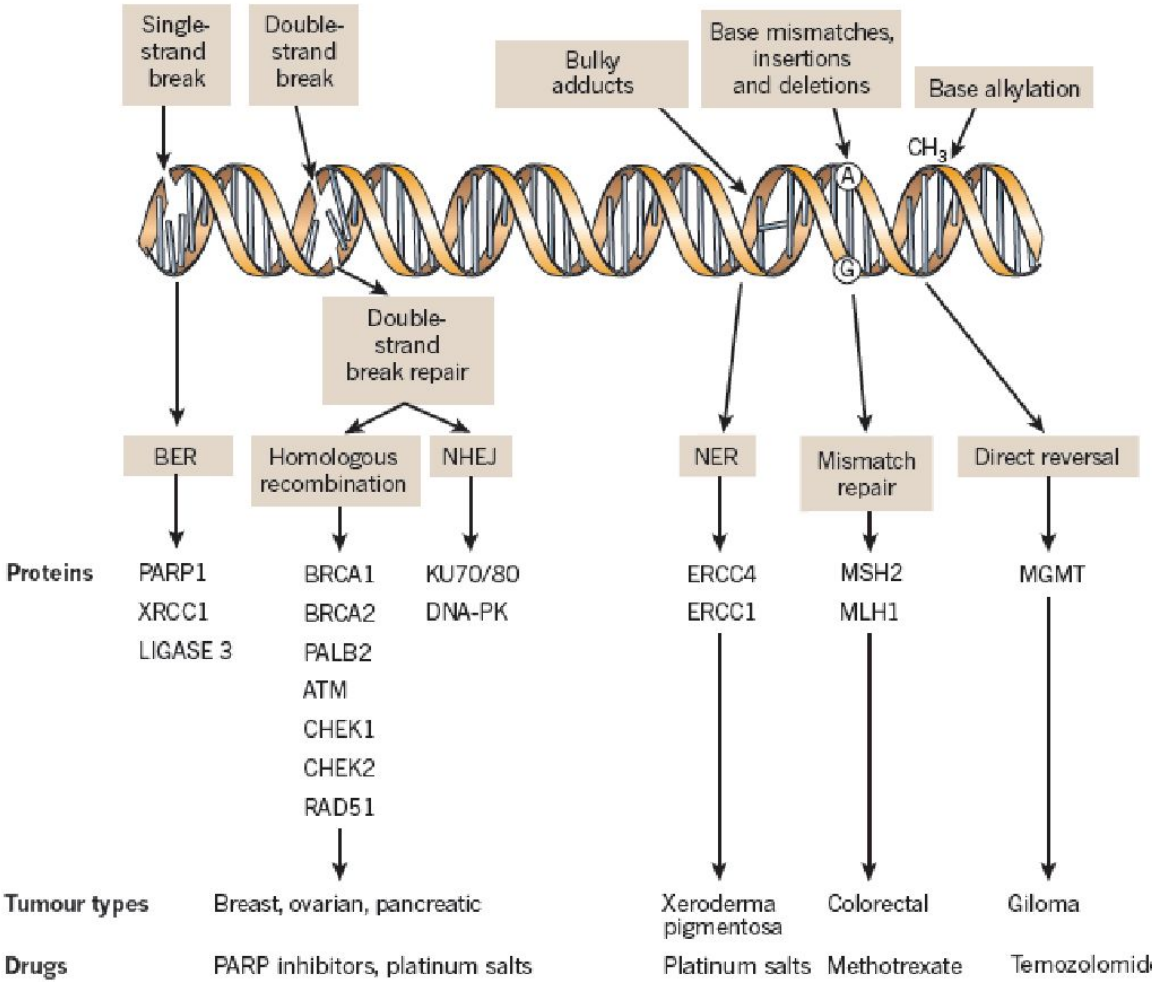
Clustered Lesions (Multiply Damaged Sites) (from Steel 1993)



Biological Consequences of Clustered Lesions (MDS)

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

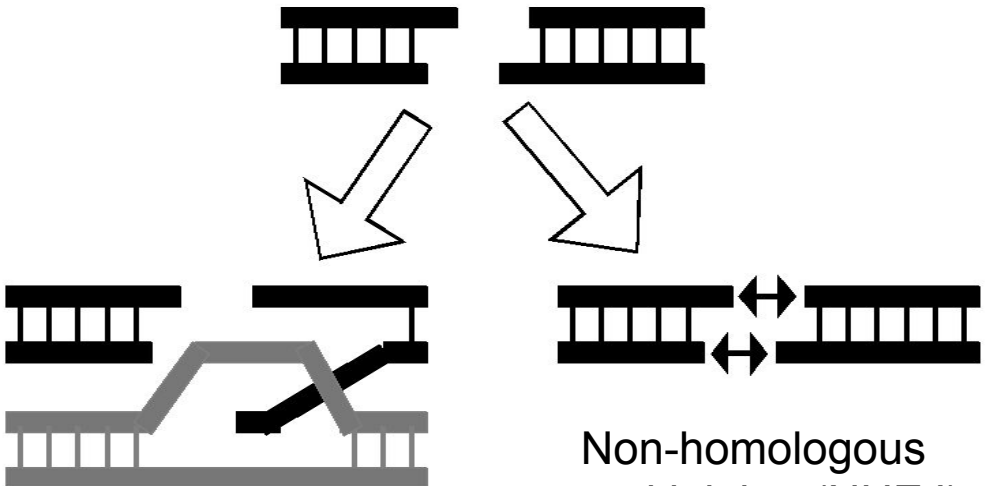
Summary of DNA Repair Mechanisms



(from Lord and Ashworth 2012)

Double Strand Break (DSB) Repair

- Breaks from IR are “dirty”, so at a minimum one base could be lost
- Fidelity of rejoining can be questioned
- Two main pathways of DSB repair



DNA Damage Response & Human Disease

(modified from S. Powell)

Mre11-rad50-nbs1 → (MRN)

Ataxia Telangiectasia → (ATM)

Nijmegen Breakage → Syndrome (NBS)

Li-Fraumeni → Syndrome (LFS)

Immune Deficiency → Syndromes (incl. SCID)

Sensor

Signaling

Mediator/Regulator

Effector

NHR / HR

← Fanconi Anemia (FA)

← Familial Breast and Ovarian Cancer

← Bloom's & Werner Syndromes

← Sporadic Tumors

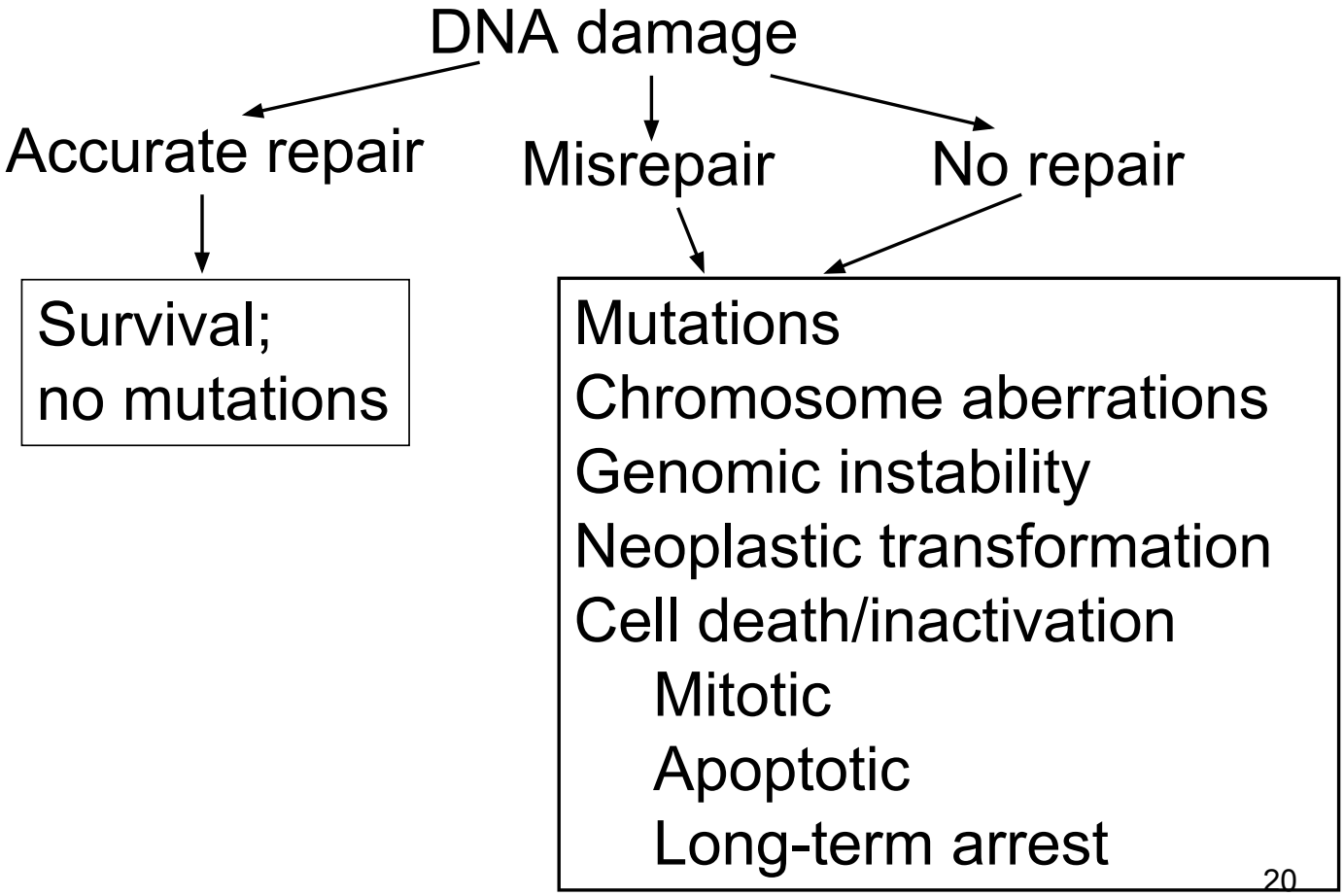
Human Chromosomal Instability Syndromes

Syndrome	Gene(s)	DSB repair defect	IR sensitive
AT	ATM	signaling?	+++
NBS	Nbs1	processing?	+
ATLD	Mre11	processing?	+
Li-Fraumeni	p53/Chk2	HR↑ ?	+/-
Fanconi's Anemia	FA A-G; BRCA2	ICLs↓, HR↓ ?	+/-
Familial Breast Ca	BRCA1/2; Chk2	ICLs↓, HR↓	+
Bloom's	BLM helicase	HR↑	-
Werner's	WRN helicase	HR/NHR?	-
LIG4	Ligase IV	NHR↓	+
SCID	Artemis	NHR↓	+
Seckel's syndrome	ATR	---	---

Other Human Inherited Cancer Syndromes: DNA Repair Genes

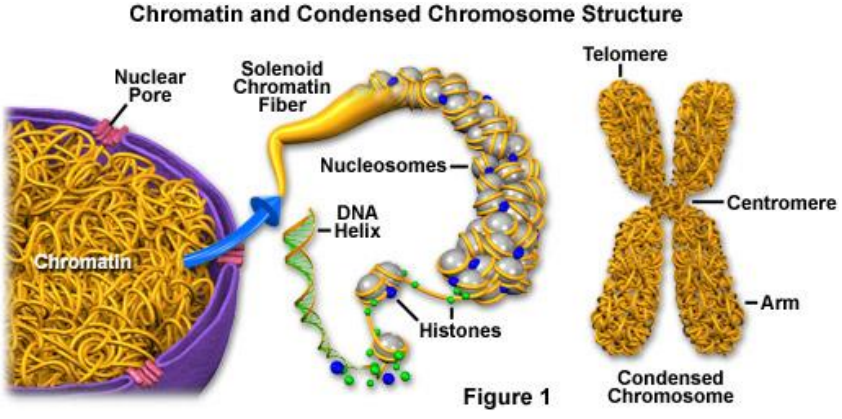
Syndrome	Gene(s)	DNA repair defect	Sensitive
XP	XPA-G	NER	UV
CS	CS	TCR	UV
HNPCC	MLH1, MSH2/6	Mismatch	-

Biological Consequences



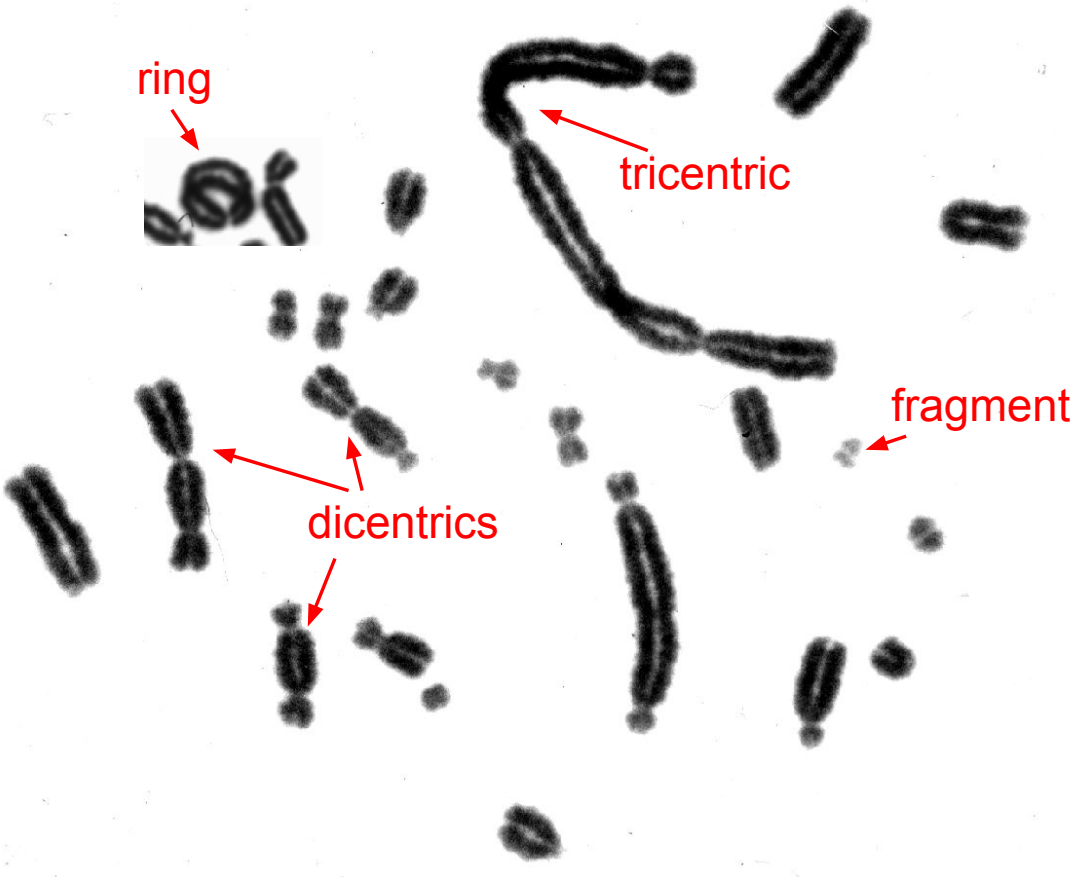
Chromosome Aberrations

- Visible defects in mitotic chromosomes
- Reflect
  - initial DNA damage
  - its repair
    (or non/misrepair)
- Two general types
  - Chromosome aberrations
    - G1 irradiation
    - Both sister chromatids involved
  - Chromatid aberrations
    - S or G2 irradiation
    - Usually only one chromatid involved

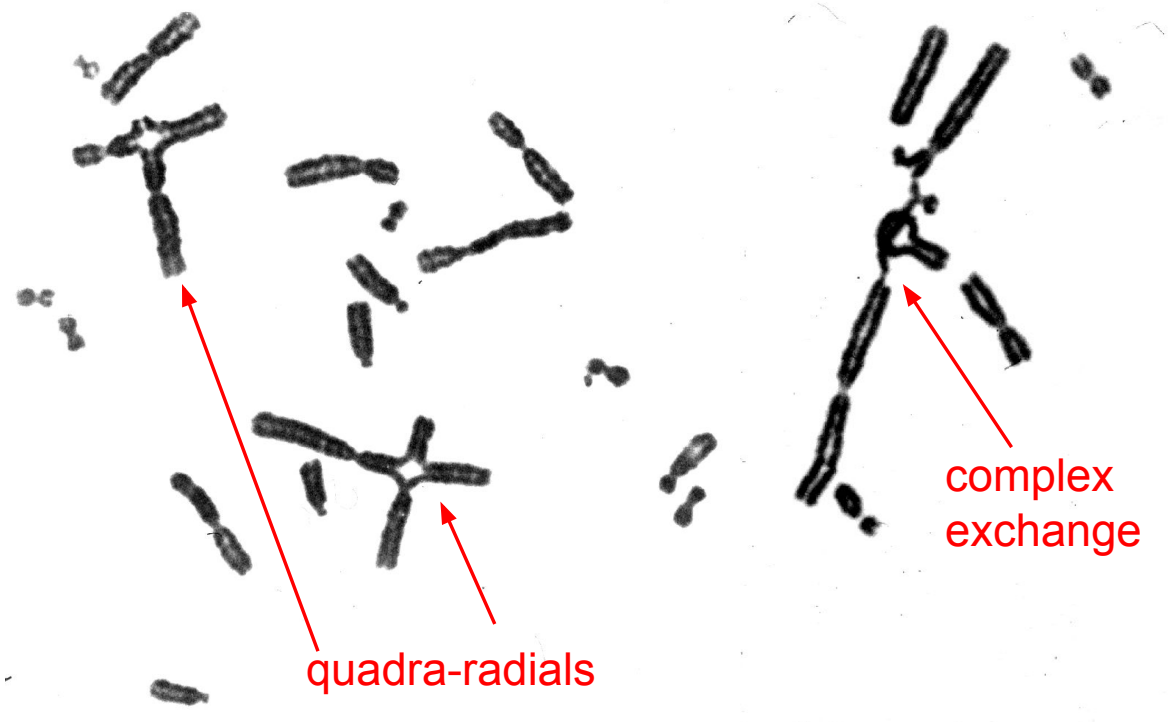


Examples of Chromosome Aberrations

(results of mis-rejoining after irradiation in G1 phase)



Examples of Chromatid Aberrations



Chromosome Aberrations

- Principal aberrations produced by radiation:
  - Dicentrics
  - Rings
  - Acentric fragments
  - Translocations
  - Anaphase bridges
- Exchange-type aberrations can be symmetric or asymmetric.
- Aberrations can be stable or unstable.
- Dicentrics (e.g., in lymphocytes) are a good biomarker of radiation exposure.

Dose Response Curve for Chromosome Aberrations is Linear-Quadratic

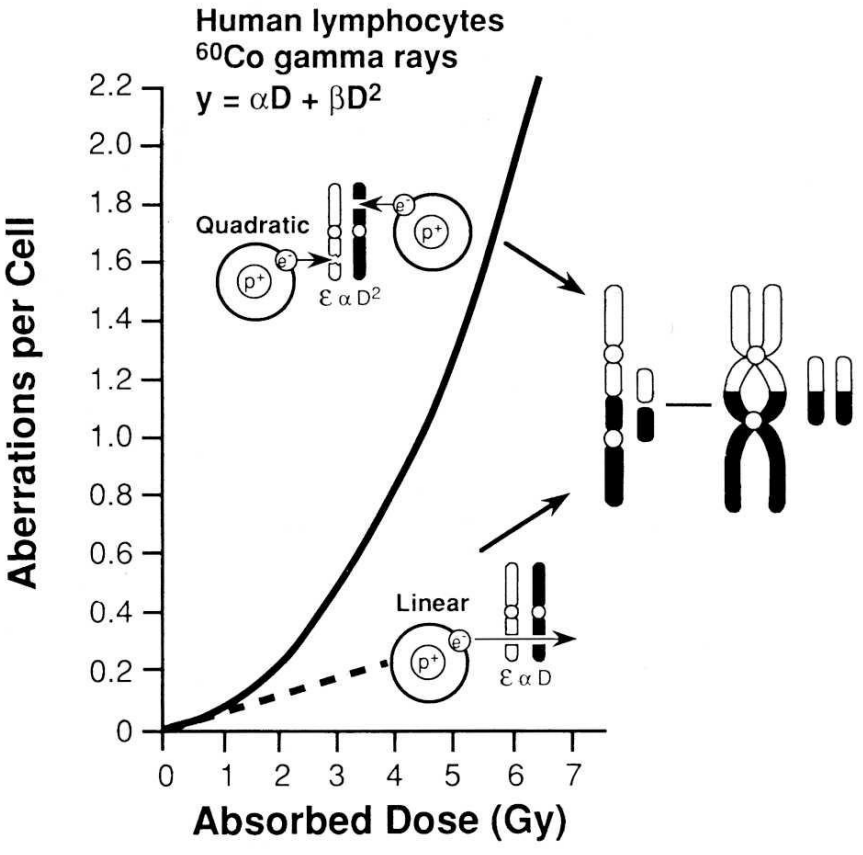
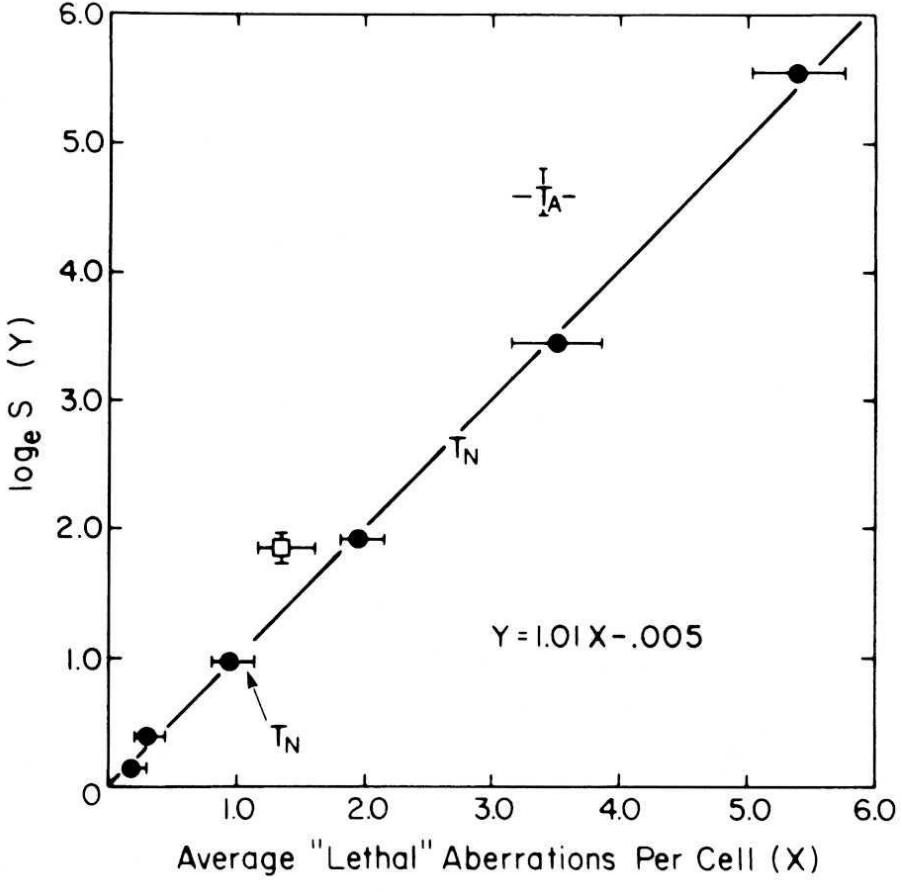


Figure 2.11. The frequency of chromosomal aberrations (dicentrics and rings) is a linear-quadratic function of dose because the aberrations are the consequence of the interaction of two separate breaks. At low doses, both breaks may be caused by the same electron; the probability of an exchange aberration 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).

(from Hall 2000)

Good Correlation Between Chromosome Aberrations and Loss of Clonogenicity



(from Hall 2000)

Take Home Messages - 1

- Indirect action produces most damage from low LET radiation; $^{\bullet}OH$ is the most critical water radiolysis species for causing biological damage.
- A plethora of DNA damages are produced by IR.
  - Cells have multiple pathways to repair DNA damage.
- IR produces clustered lesions (multiply damaged sites) that are probably most important biologically.
- Induction of chromosome aberrations can correlate with loss of clonogenic survival.
- The biological consequences of misrepair or no repair include mutations, aberrations, genomic instability, cell death/inactivation.

Dose-Response (Dose-Effect) Curves

- Characterization of effects as a function of radiation dose
  - DNA damage
  - Chromosome aberrations
  - Mutations
  - Cell survival curves
  - etc.
- Slopes of curves indicate yields of product/damage or radiosensitivity
- Ratios of slopes (or of isoeffect doses) are used as measures for comparison of modifiers or treatments

Clonogenic Cell Survival Curves

- Cell death – loss of reproductive capacity; loss of ability to form a colony
- Cell survival curve – quantitative relationship between radiation dose and the proportion of cells that survive (form a colony) the dose

Cell Survival Curves

- Plot log surviving fraction versus dose on a linear scale.

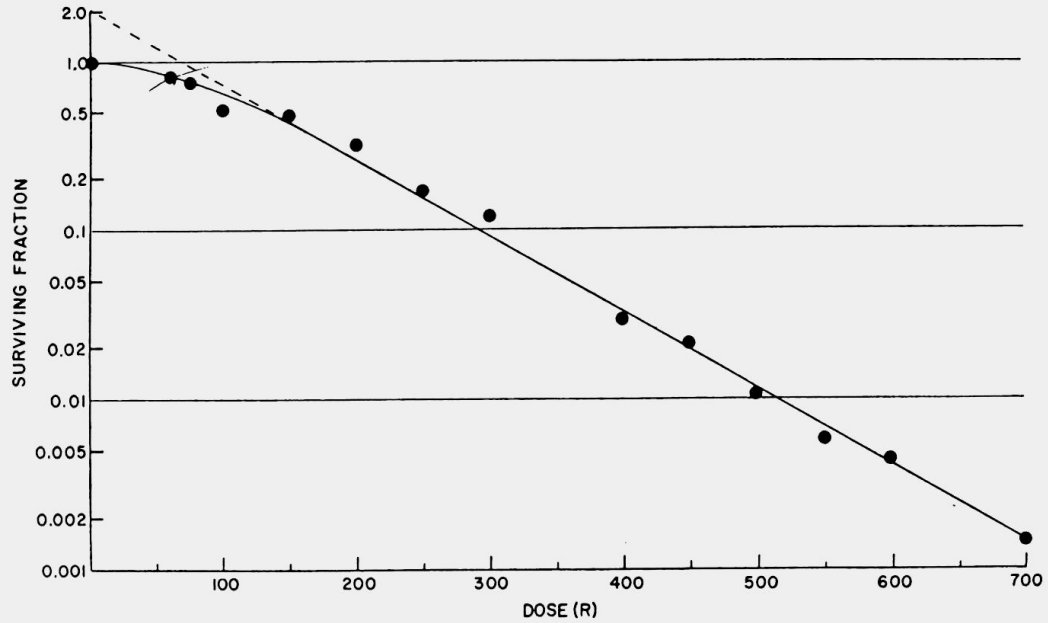
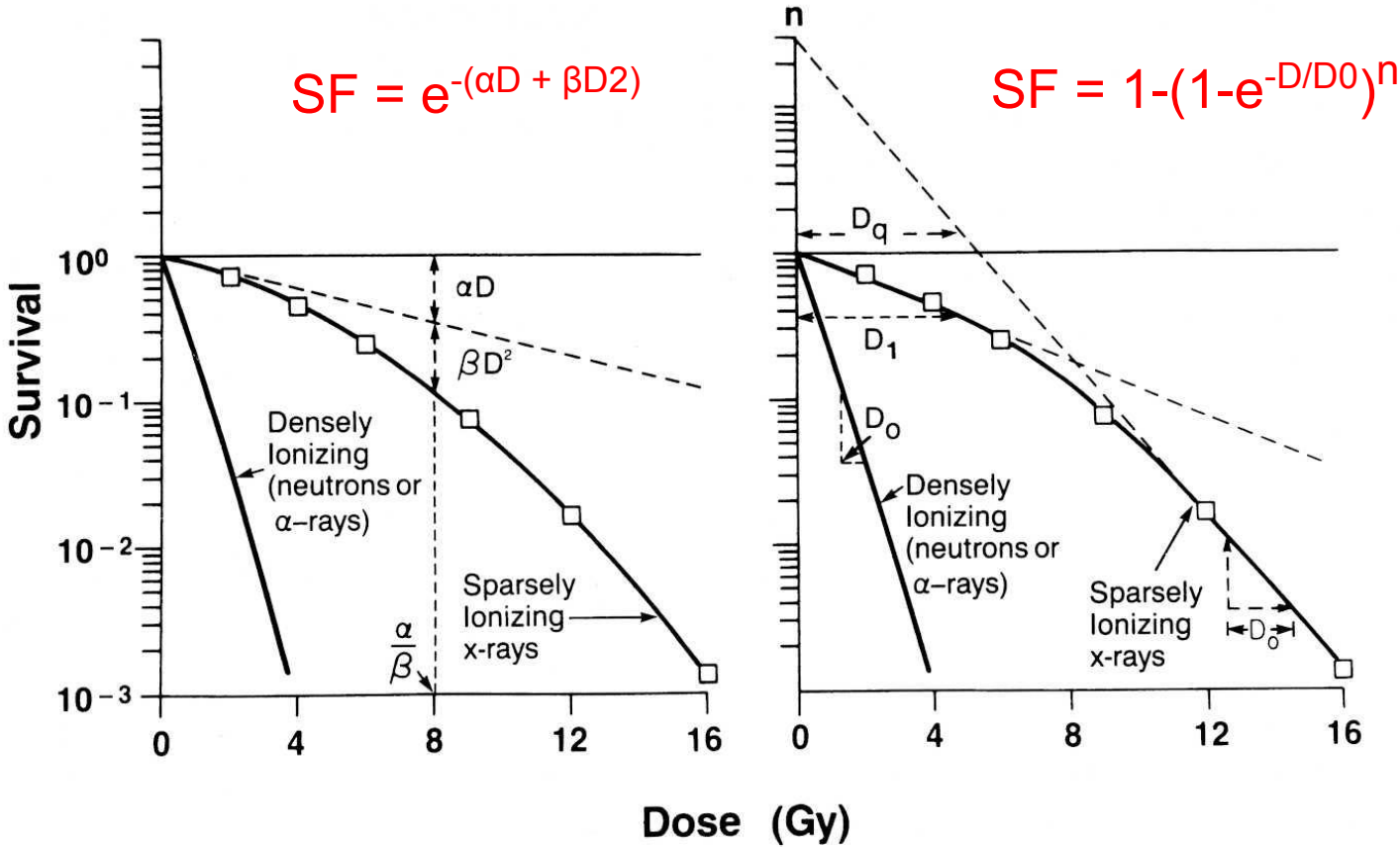


Figure 3.7. Survival curve for HeLa cells in culture exposed to x-rays. Characteristically, this cell line has a small initial shoulder. (From Puck TT, Markus PI: Action of x-rays on mammalian cells. J Exp Med 103:653–666, 1956, with permission.)

(from Hall 2000)

Cell Survival Curves

Different shapes; different biophysical models



(from Hall 2000)

Survival Curves for Some Normal Tissues

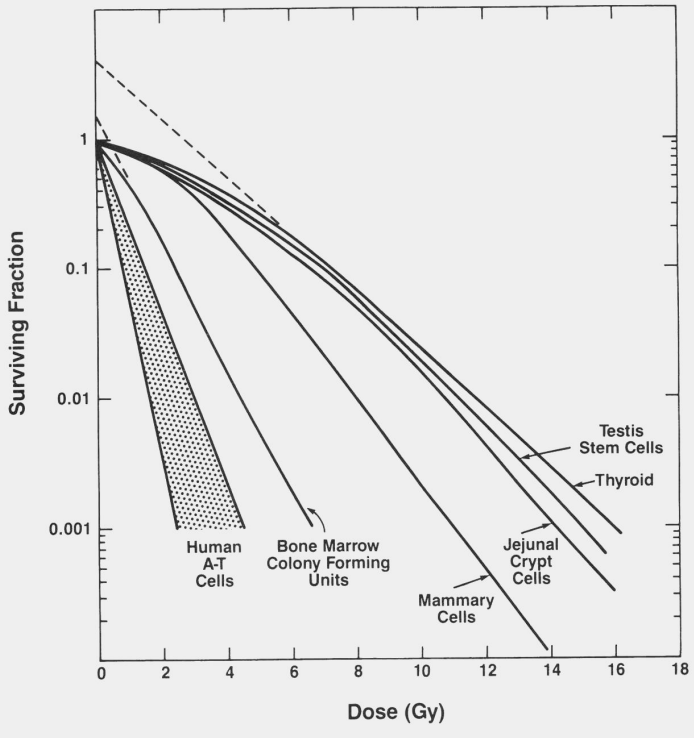


Figure 18.18. Summary of survival curves for clonogenic assays of cells from normal tissues. The human ataxia telangiectasia cells are included because they are the most sensitive mammalian cells. The bone-marrow colony-forming units, together with the mammary and thyroid cells, represent systems in which cells are irradiated and assayed by transplantation into a different tissue in recipient animals. The jejunal crypt and testis stem cells are examples of systems in which cells are assayed for regrowth *in situ* after irradiation.

(from Hall 2000)

Various Processes Can Contribute to Loss of Colony Formation After Irradiation

Cell Death

- Mitotic-linked death (mitotic catastrophe) – in most cases, the primary mode of cell death after radiation
- Apoptosis
- Necrosis/Necroptosis
- Autophagy

Also loss of proliferative ability due to:

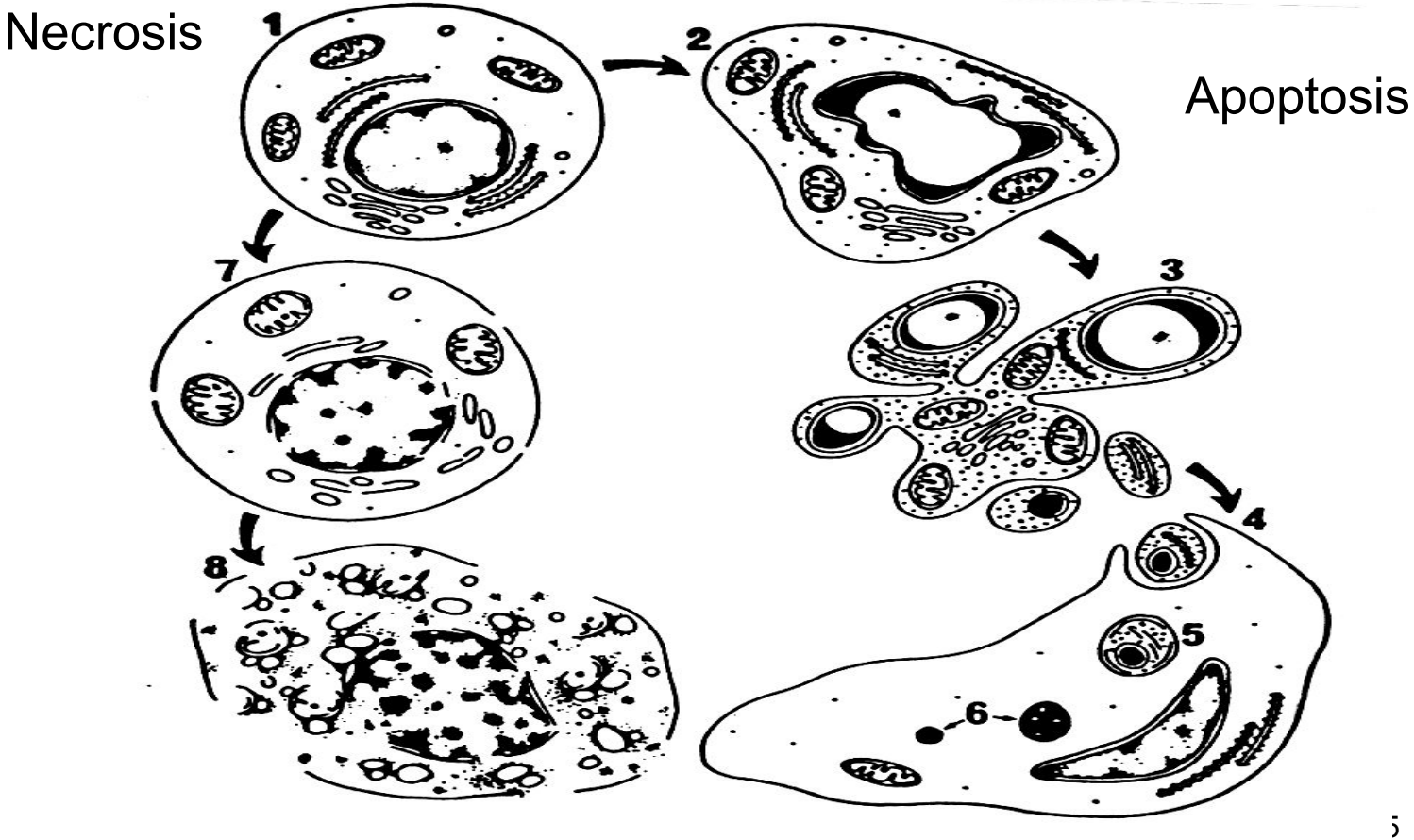
- Cell cycle arrest
- Senescence
- Terminal differentiation

Mitotic Death/Catastrophe

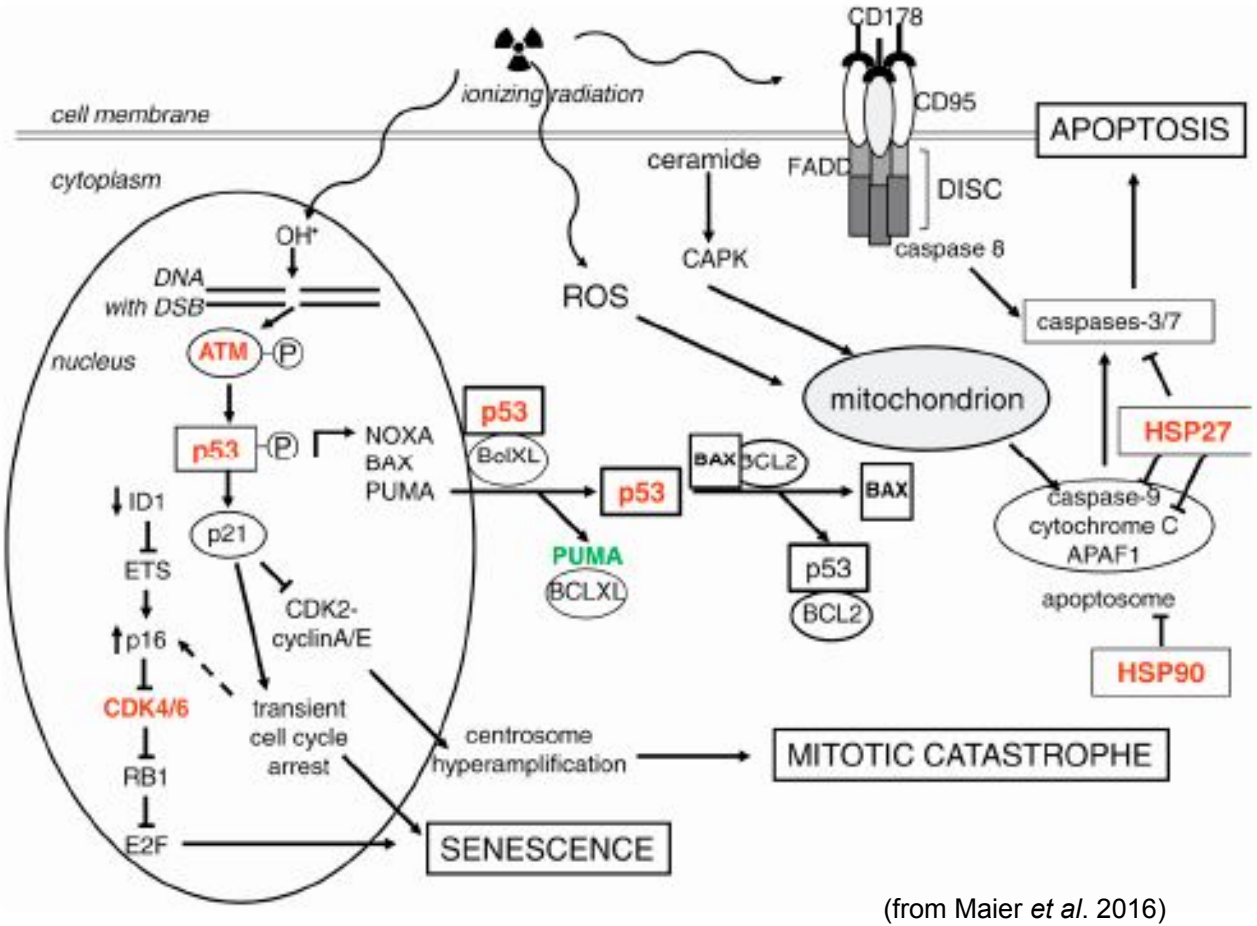
- A major form of radiation-induced cell death
- Cells die when they are unable to go through mitosis
- Can result from:
  - Chromosome loss/damage
  - Problem with spindle formation
    - Formation of giant cells with multiple nuclei
- Is often delayed (days, not hours), since cells have to go through cell cycle
- Can occur after several cell divisions

Necrosis and Apoptosis

(from Kerr *et al*.)



Multiple Modes of Cell Death after Irradiation



(from Maier *et al*. 2016)

Mechanisms of Cell Death - Summary

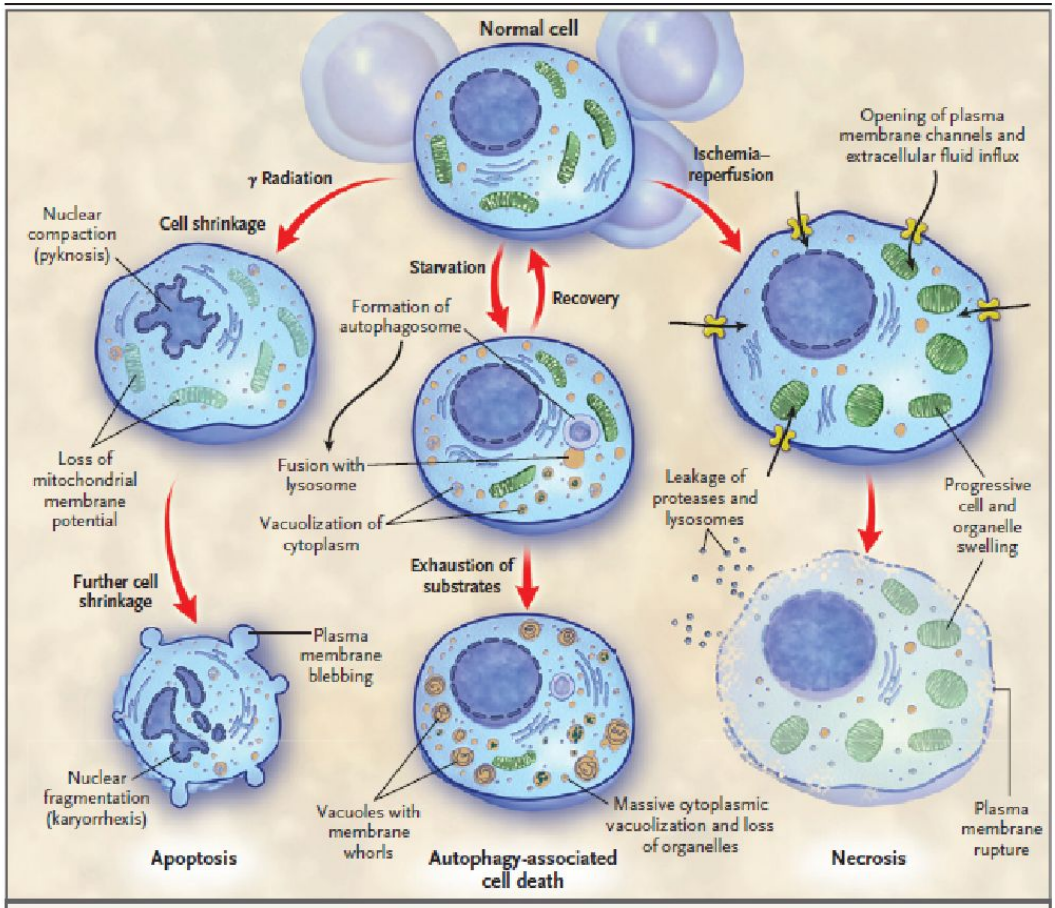


Figure 1. Three Pathways of Cell Death.

Among the three major pathways of cell death — apoptosis, autophagy, and necrosis — a particular mode of cell death may predominate, depending on the injury and the type of cell. Cross-talk among the different types of cell-death pathways exists at multiple levels and is not shown.

Remember: after radiation, mitotic-linked cell death is a major player, and mitotic damage often precedes these modes of cell death

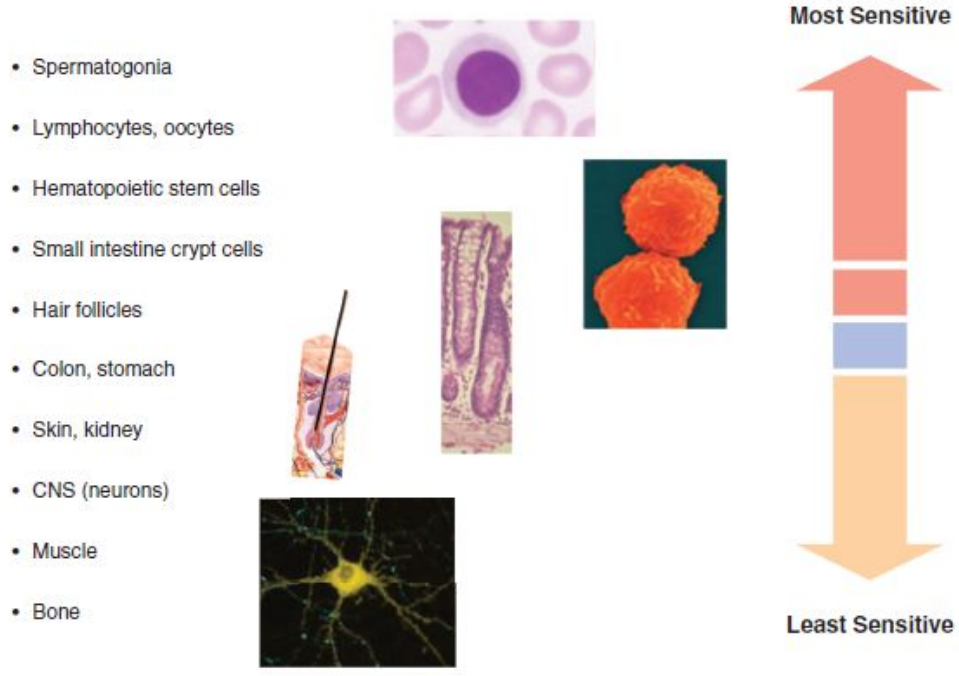
(from Hotchkiss *et al*. 2009)

Relative Radiosensitivities of Tissues

"Law" of Bergonie and Tribondeau that highest radiosensitivity in cells/tissues with:

- high mitotic rate
- long mitotic future
- more differentiation

But tissues are much more complex than just a collection of cells and many cells in mature tissues do not divide, both characteristics that impact radiation sensitivity – more on that next year



■ FIGURE 20-14 Relative radiosensitivity of tissues.

(from Bushberg et al., 2012)

Take Home Messages – 2

- Cell survival curves - reflect loss of cell reproductive ability; are a major assay used in radiation effects studies
- Several different mathematical models can be used to describe cell survival-dose relationships, but the LQ model is most widely used currently.

$$SF = e^{-(\alpha D + \beta D2)}$$

- Various modes of cell death or disruption of proliferative capacity can cause loss of colony formation from radiation.

Radiation Biology for Radiology Residents

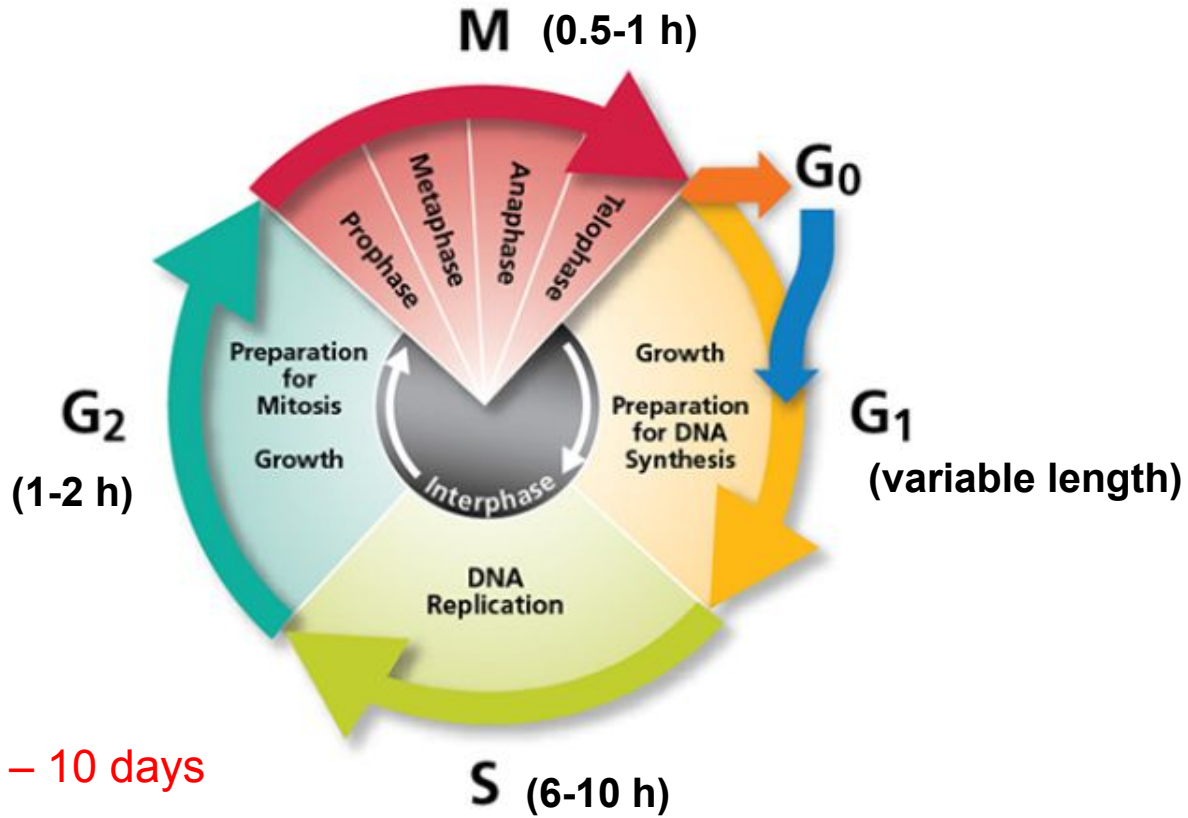
- Molecular and cellular effects of radiation
  - Radiation chemistry
  - Effects on DNA and chromosomes
  - Cell survival
- Modification of radiation response
  - Biological
  - Chemical/pharmacologic
  - Physical (radiation quality)

References:
Bushberg *et al*., Chapter 20, Radiation Biology and Protection in ***Essential Physics of Medical Imaging***, 2012.
Hall and Giaccia, Radiobiology for the Radiologist, 7th Ed., 2012

Modification of Radiation Response

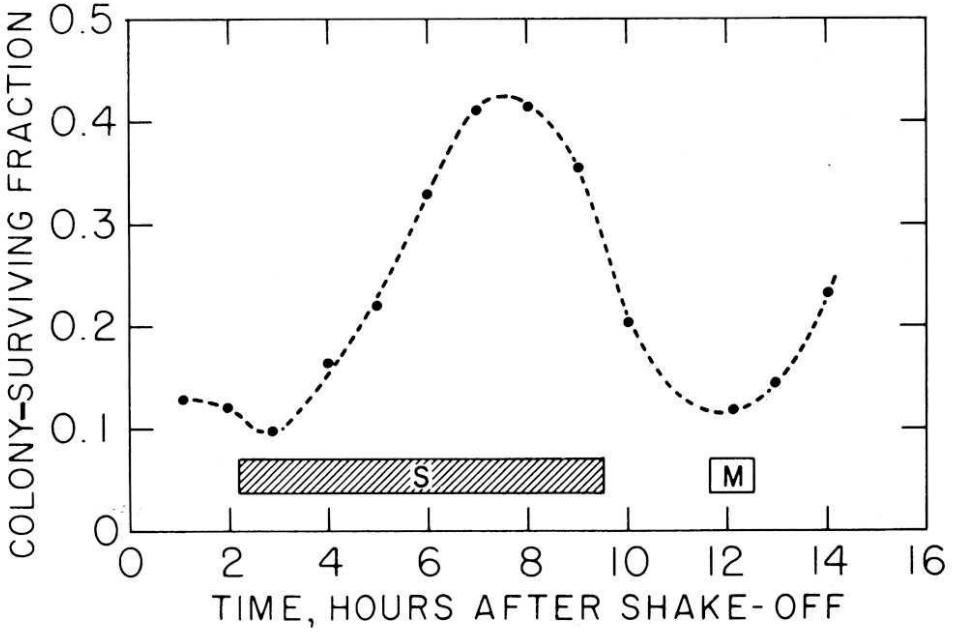
- Biological Modification
  - Cell cycle (cell age) response
  - SLDR
  - Dose rate effects
- Chemical/pharmacologic Modification
  - Oxygen
  - Sensitizers
  - Protectors/mitigators
- Physical Modification

Stages of the Cell Cycle



T_C = 10 h – 10 days

Age Response in Rapidly Growing Cells

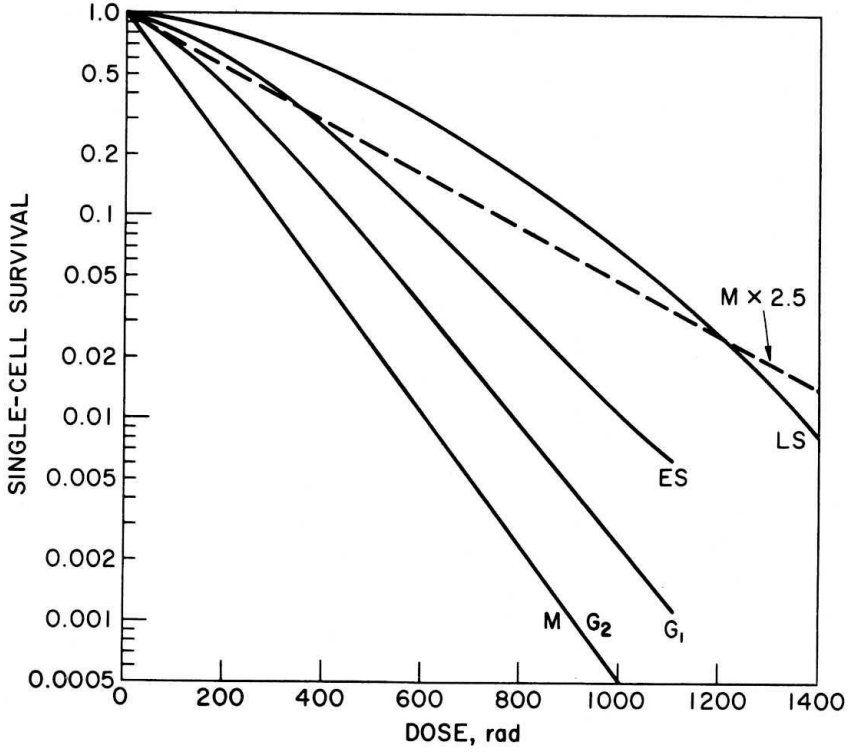


(from Hall 2000)

Figure 4.7. Fraction of Chinese hamster cells surviving a dose of 6.6 Gy (660 rad) of x-rays as a function of time. Time zero corresponds to the harvesting of mitotic cells. The cell-surviving fraction increases to a maximum late in S phase. (Adapted from Sinclair WK, Morton RA: X-ray sensitivity during the cell generation cycle of cultured Chinese hamster cells. Radiat Res 29:450–474, 1966, with permission.)

Cells most sensitive in G2/M.
Cells most resistant in late S.

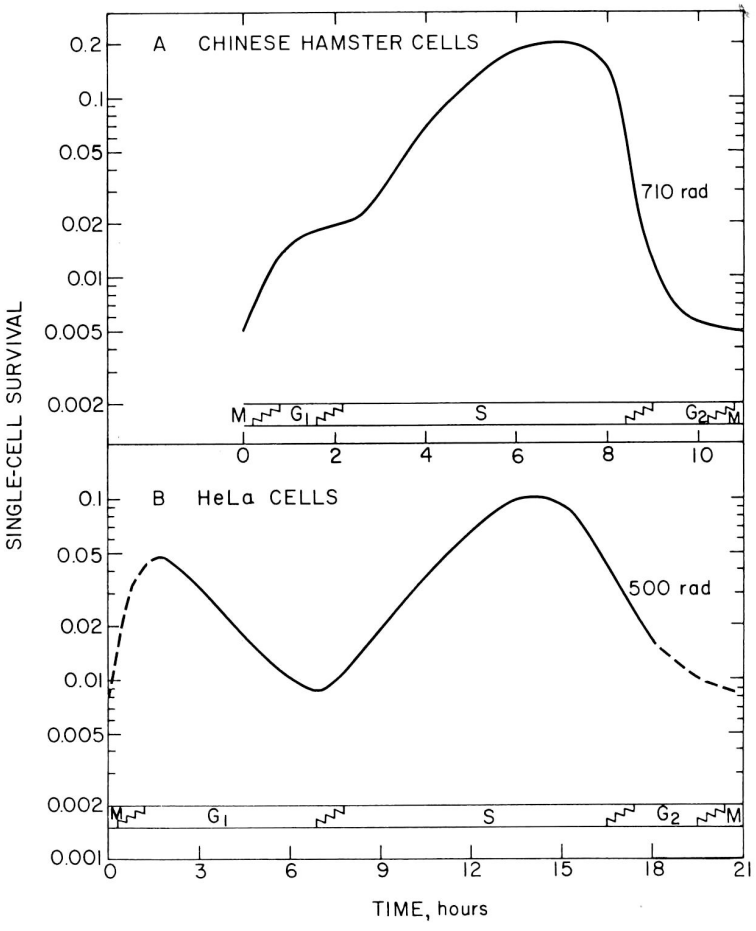
Shape of Survival Curve Depends on Cell Cycle Phase at Time of Irradiation



(from Hall 2000)

Figure 4.8. Cell-survival curves for Chinese hamster cells at various stages of the cell cycle. The survival curve for cells in mitosis is steep and has no shoulder. The curve for cells late in S phase is shallower and has a large initial shoulder. G_1 and early S phases are intermediate in sensitivity. The *broken line* is a calculated curve expected to apply to mitotic cells under hypoxia. (From Sinclair WK: Radiat Res 33:620–643, 1968, with permission.)

Cell Cycle Response in Slower Growing Cells

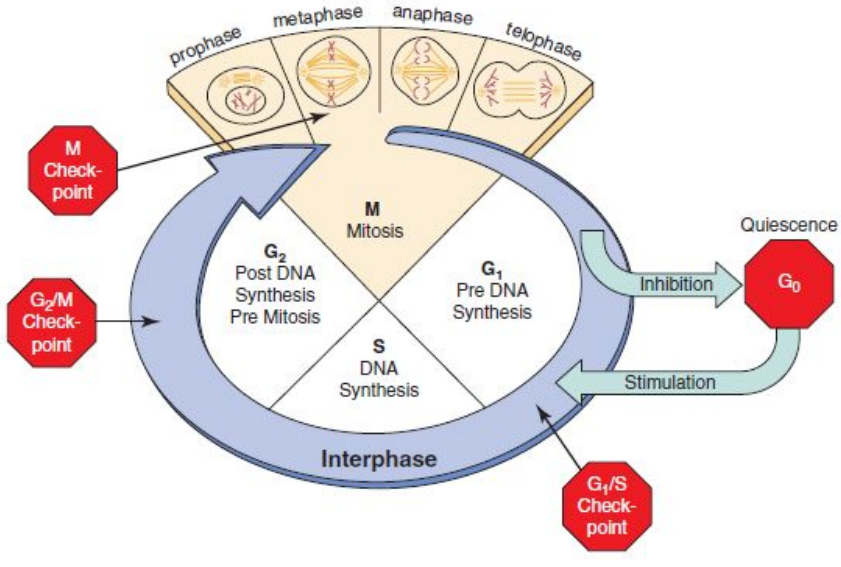


- Cells still most sensitive in G2/M.
- Cells still most resistant in late S.
- Additional peak of resistance in G1.

(from Hall 2000)

Cell Cycle Checkpoints

- Checkpoints - Points where cells make sure all components are ready for cell to progress to next stage of cycle
- IR causes temporary arrest in G1, S and/or G2 phases of the cell cycle
  - Dose dependent
  - G1 arrest is p53-dependent



(from Bushberg et al., 2012)

Modification of Radiation Response

- Biological Modification
  - Cell cycle response
  - Sublethal Damage Repair (SLDR)
  - Dose rate effects
- Chemical Modification
  - Oxygen
  - Sensitizers
  - Protectors/mitigators
- Physical Modification

SLDR Occurs When Dose is Split into More than One Fraction

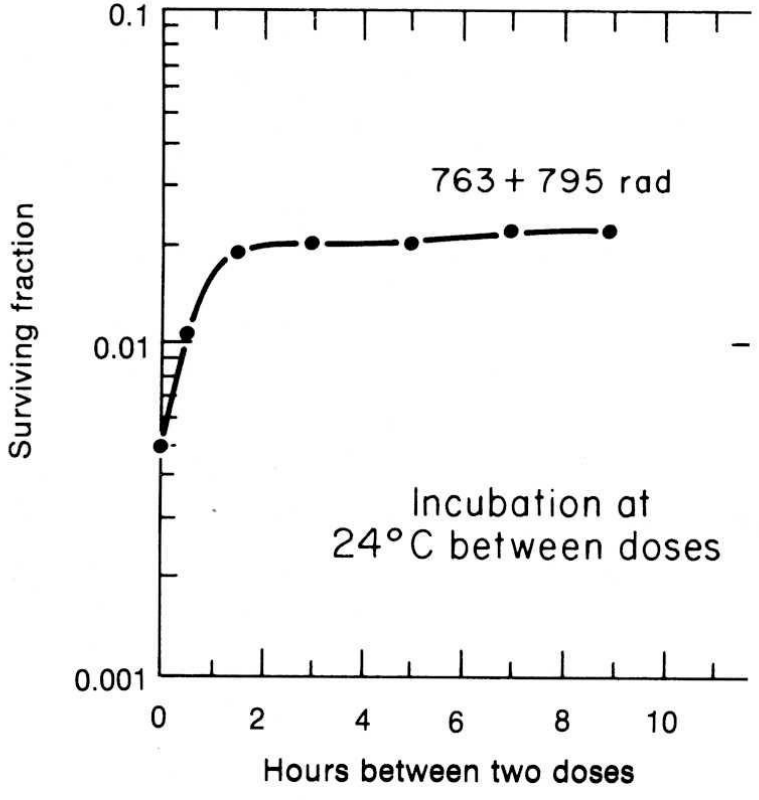
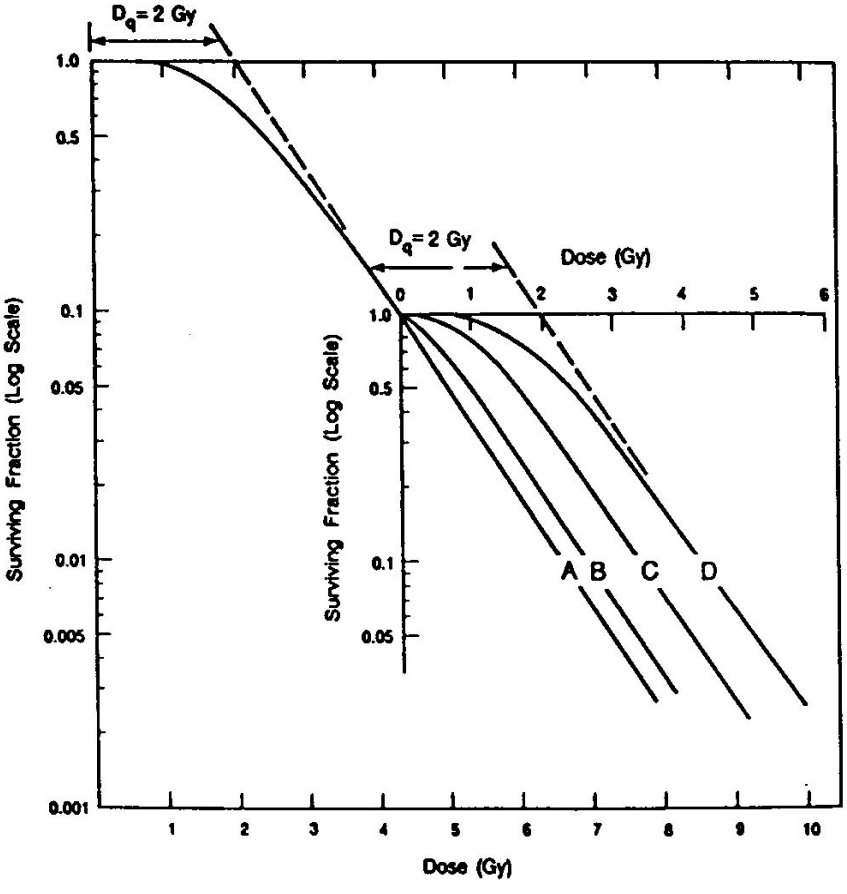


Figure 5.3. Survival of Chinese hamster cells exposed to two fractions of x-rays and incubated at room temperature for various time intervals between the two exposures. (From Elkind MM, Sutton-Gilbert H, Moses WB, Alescio T, Swain RB: Radiation response of mammalian cells in culture: V. Temperature dependence of the repair of x-ray damage in surviving cells (aerobic and hypoxic). (Radiat Res 25:359–376, 1965, with permission.)

(from Hall 2000)

SLDR - Reappearance of the Shoulder



(from Alpen 1998)

SLDR is Temperature Dependent

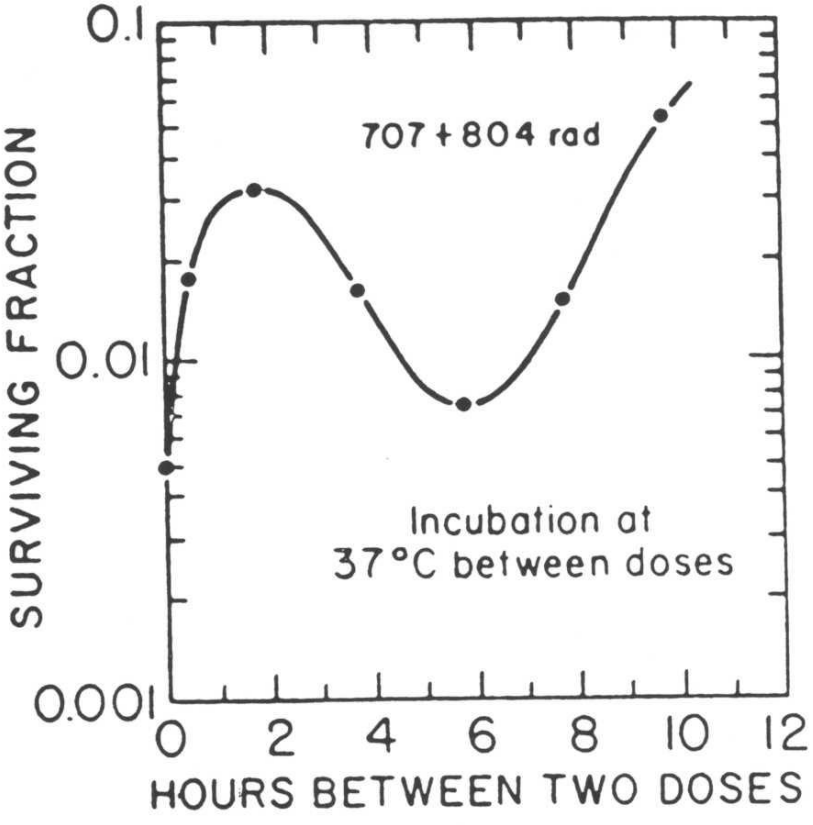


FIG. 8–5. Survival of Chinese hamster cells exposed to two fractions of x-rays and incubated at 37°C for various time intervals between the two doses. (From Elkind MM, Sutton-Gilbert H, Moses WB, Alescio T, Swain RW: Radiat Res 25:359, 1965)

(from Hall 1978)

SLDR + Age Response

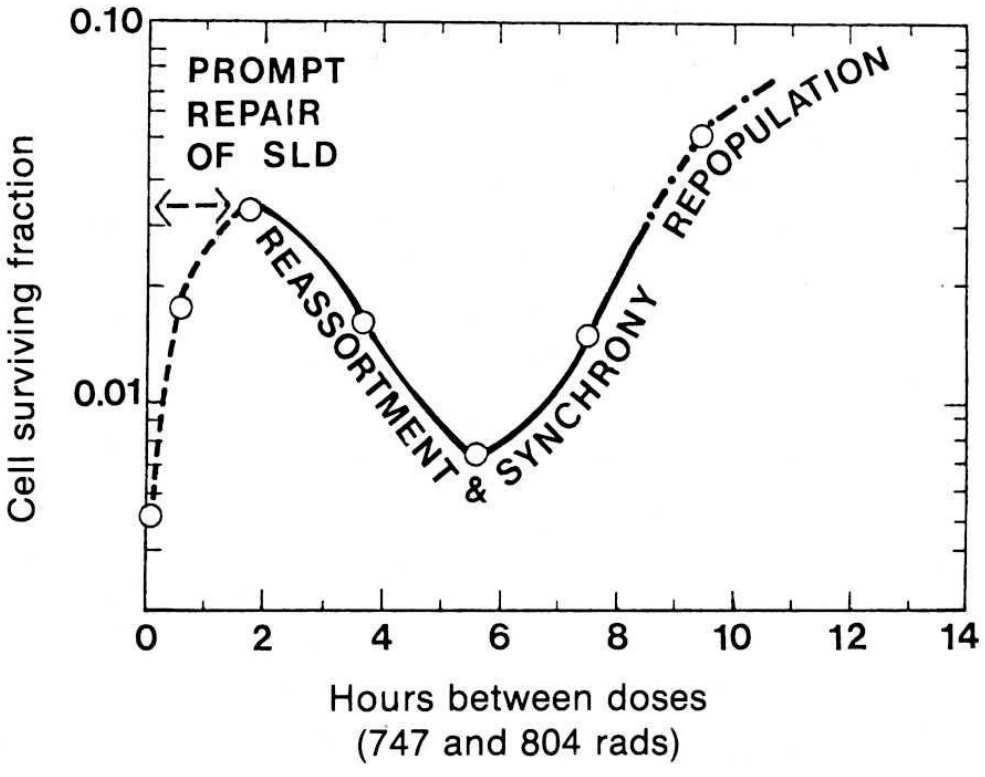


Figure 5.4. Survival of Chinese hamster cells exposed to two fractions of x-rays and incubated at 37°C for various time intervals between the two doses. The survivors of the first dose are predominantly in a resistant phase of the cycle (late S). If the interval between doses is about 6 hours, these resistant cells have moved to the G2-M phase, which is sensitive. (Adapted from Elkind MM, Sutton-Gilbert H, Moses WB, Alescio T, Swain RB: Radiation response of mammalian cells in culture: V. Temperature dependence of the repair of x-ray damage in surviving cells (aerobic and hypoxic). Radiat Res 25:359–376, 1965, with permission.)

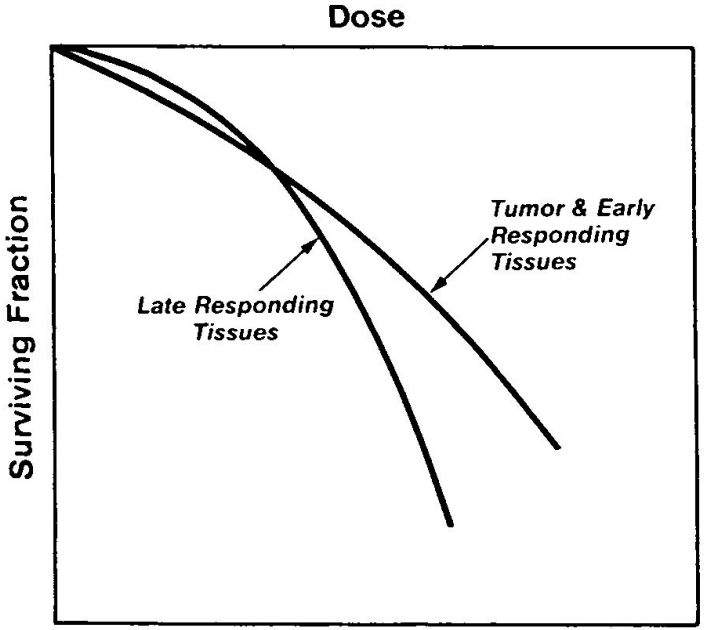
(from Hall 2000)

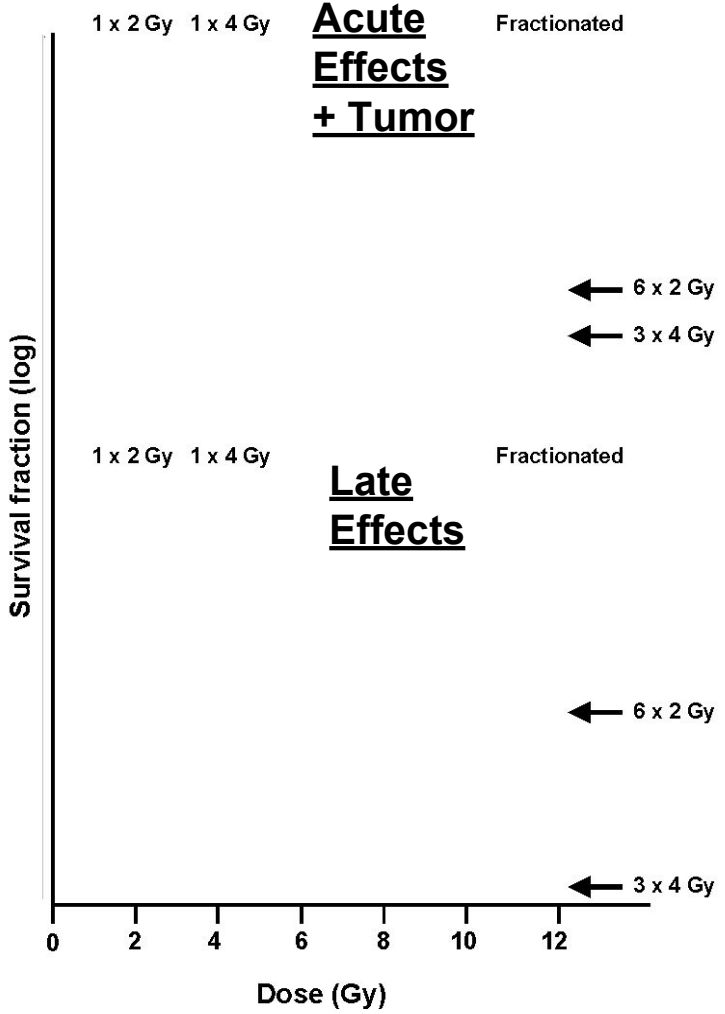
Importance of SLDR

- Occurs both *in vitro* and *in vivo*
- One factor involved in the sparing effect of dose fractionation
- Large shoulder, or small α/β ratio, more repair of SLD - characteristic of late-responding tissues
  - More sparing with fractionation than in early-responding tissues

Fractionation in Radiation Therapy

- Radiation therapy takes advantage of greater "sparing" of late responding normal tissues by fractionation (more SLDR) than responding tissues of tumors and early

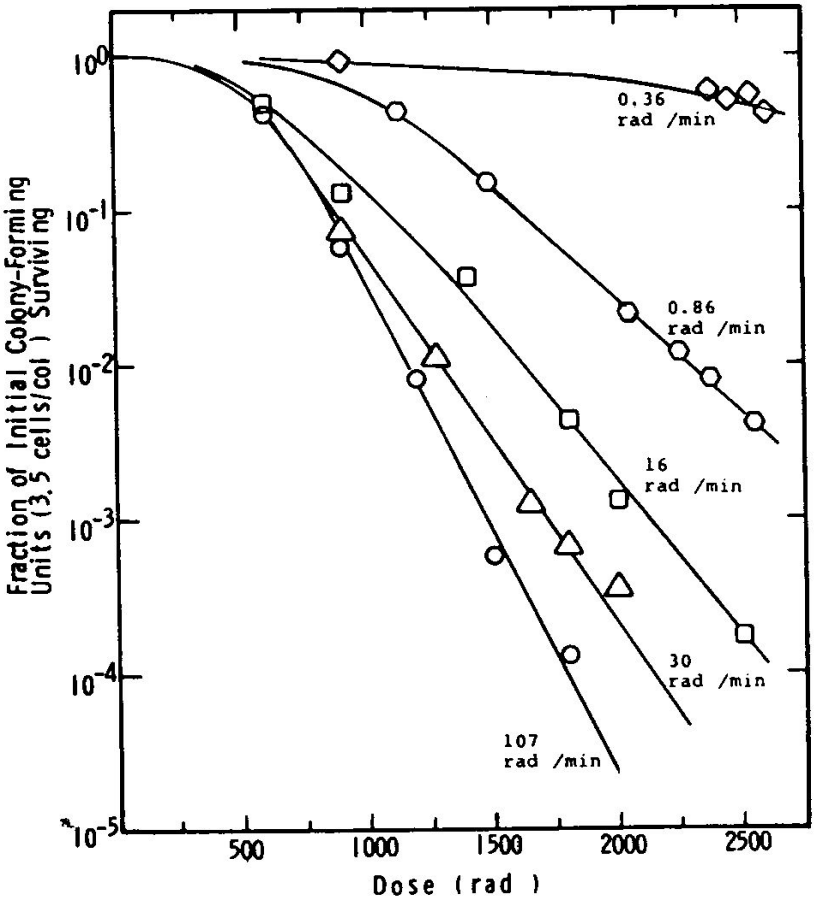




Modification of Radiation Response

- Biological Modification
  - Cell cycle response
  - SLDR
  - Dose rate effects
- Chemical Modification
  - Oxygen
  - Sensitizers
  - Protectors/mitigators
- Physical Modification

Dose Rate Effect



(from Hall 2000)

As dose rate is reduced:

- slope of survival curve decreases (D_0 increases)
- shoulder decreases (n goes to 1)

At very low dose rates:

- all SLD is repaired during exposure
- repopulation may increase survival

Dose Rate Effect in Normal Tissues

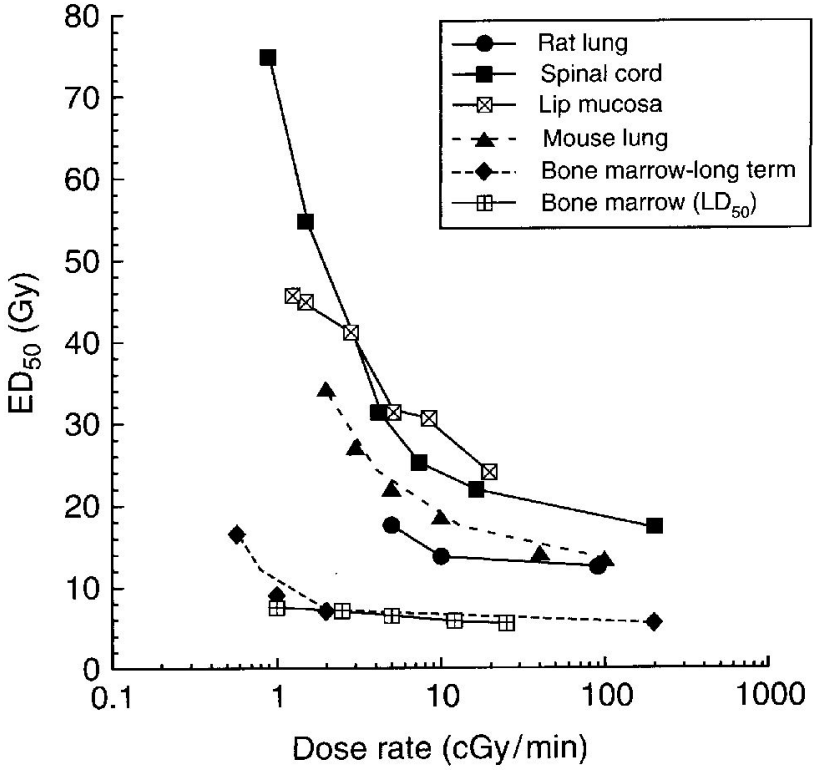
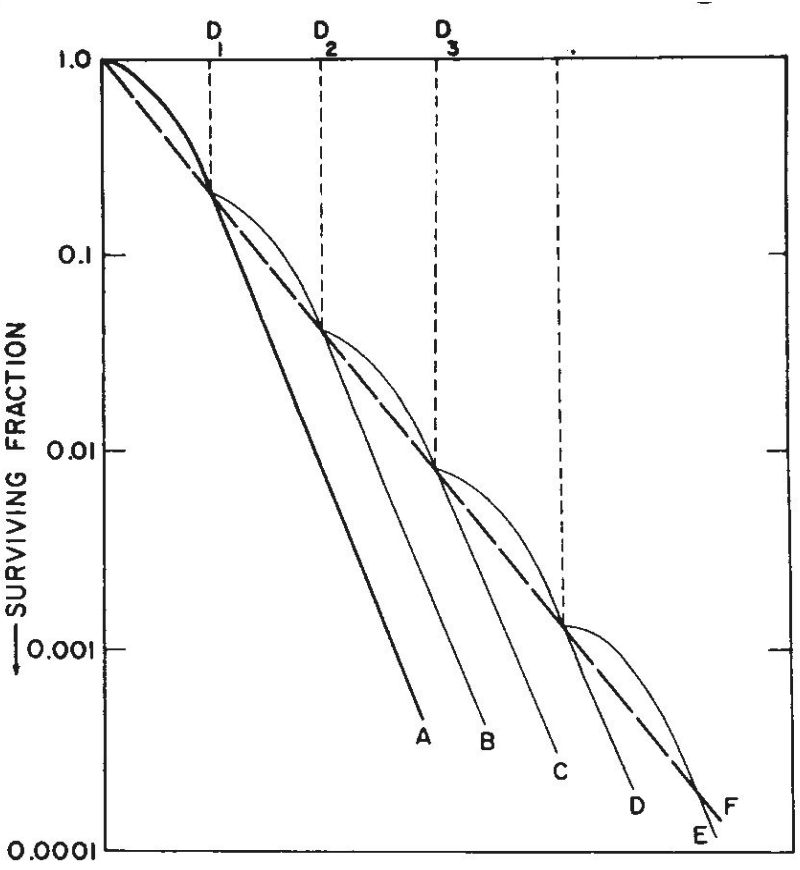


Figure 12.6 The dose-rate effect in various rodent normal tissues: lung, spinal cord, lip mucosa and bone marrow.

Greater dose rate effect in late responding normal tissues

(from Joiner and van der Kogel 2009)

Continuous Low Dose Rate Irradiation



Like multiple fractions

Biological response depends on:

- cellular sensitivity
- duration of the cell cycle
- ability of cells to adapt

(from Hall 2000)

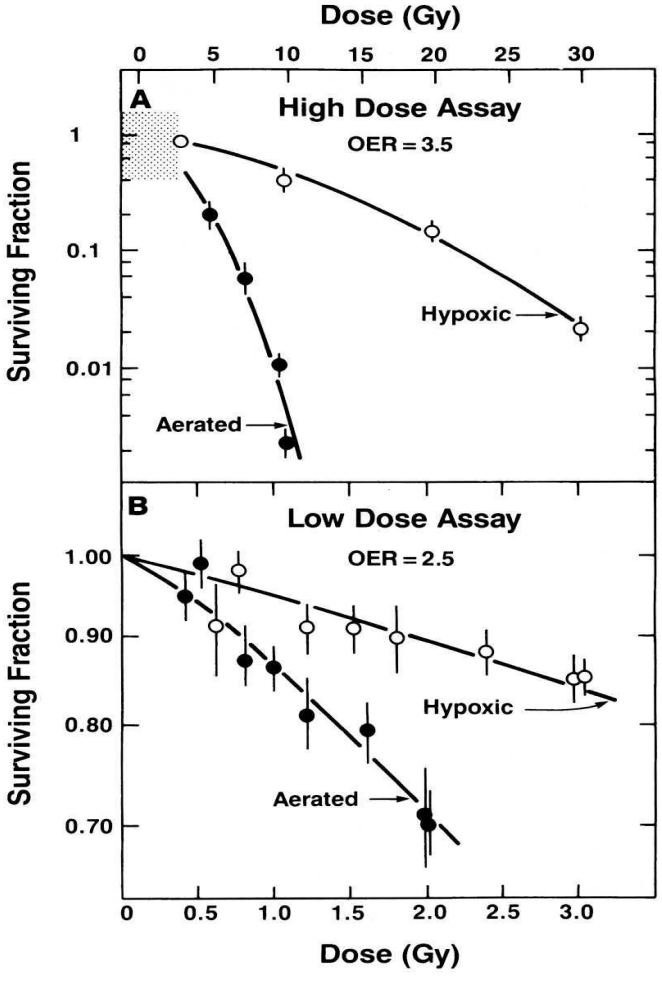
Take Home Messages – Biological Modification

- Radiation sensitivity varies through the cell cycle
  - G2/M phase cells are most sensitive
  - Late S phase cells are most resistant.
  - If G1 phase is long, there is another peak of radiation resistance.
- Sublethal damage repair (SLDR) occurs between fractions in a fractionated dose exposure.
  - SLDR accounts, at least in part, for the sparing of late responding normal tissues by dose fractionation.
- Low dose rate irradiation is less effective at causing damage from low LET radiation than high dose rate radiation.

Modification of Radiation Response

- Biological Modification
  - Age response
  - SLDR
  - Dose rate effects
- Chemical/pharmacologic Modification
  - Oxygen effect
  - Radiation sensitizers
  - Radiation protectors/mitigators
- Physical Modification

Oxygen Effect



Oxygen is the best known and most general radiation sensitizer.

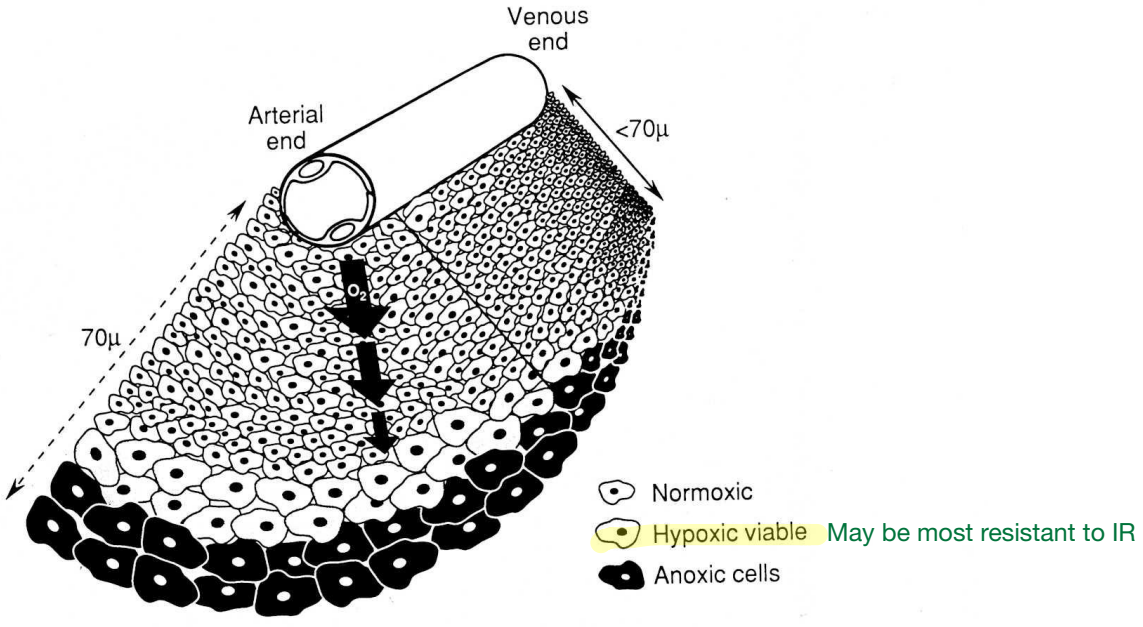
$$OER = \frac{\text{Dose(hypoxia)}}{\text{Dose(oxygenated)}}$$

Oxygen enhancement ratio

OER is usually about 3 at high radiation doses, but can be lower at low doses.

(from Hall 2000)

Importance of the Oxygen Effect

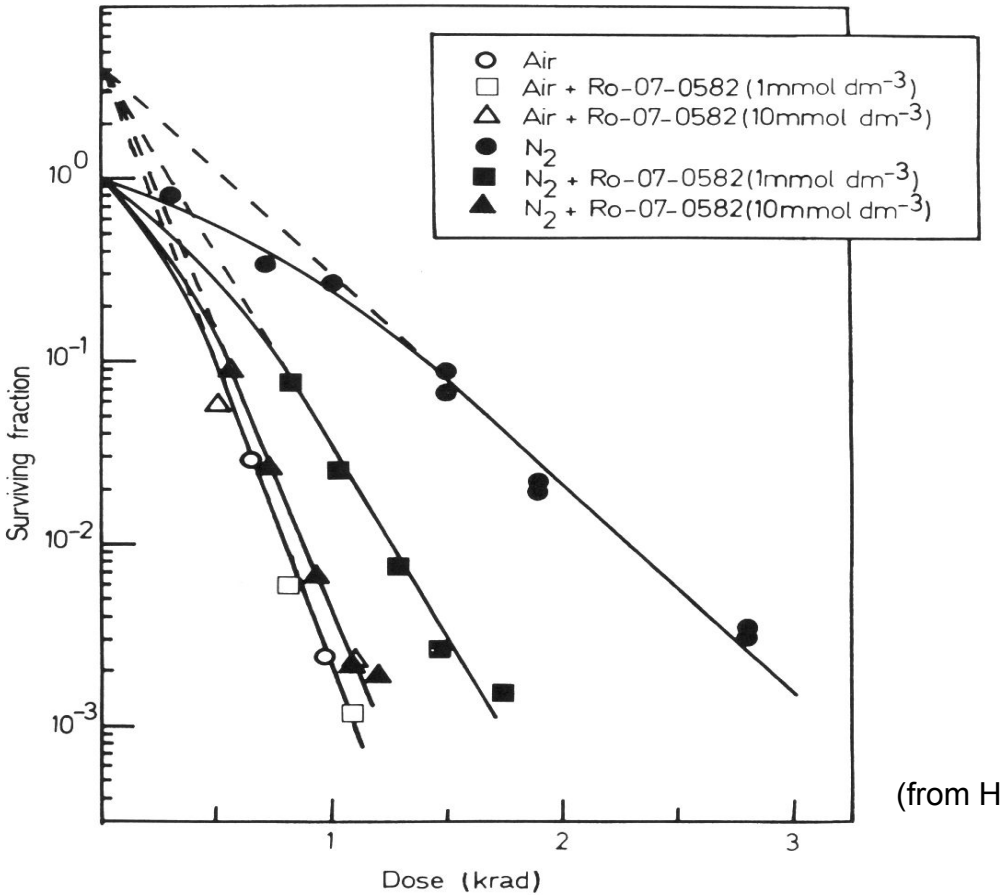


May be most resistant to IR

Figure 6.8. The diffusion of oxygen from a capillary through tumor tissue. The distance to which oxygen can diffuse is limited largely by the rapid rate at which it is metabolized by respiring tumor cells. For some distance from a capillary, cells are well oxygenated (*white*). At greater distances oxygen is depleted, and tumor cells become necrotic (*black*). Hypoxic tumor cells form a layer, perhaps one or two cells thick, in between (*gray*). In this region the oxygen concentration is high enough for the cells to be viable but low enough for them to be relatively protected from the effects of x-rays. These cells may limit the radiocurability of the tumor. The distance to which oxygen can diffuse is about 70 μm at the arterial end of a capillary and less at the venous end.

(from Hall 2000)

Hypoxic Cell Sensitizers: Radiation Sensitization by Misonidazole



SER = D_0(-drug)/D_0(+drug)

(from Hall 2000)

Many Chemotherapy Agents Are Radiosensitizers

Radiation sensitizers/enhancers typically used in the clinic:

GBM + temozolomide

Head and neck + cisplatin

NSCLC + carboplatin/paclitaxel

NSCLC + cisplatin/etoposide (systemically active)

Esophageal + cisplatin/5FU

GI cancers + 5FU

GYN + cisplatin

Anal cancer + MMC/5FU

(slide modified from H Willers)

Many New Chemo Agents Target Specific Molecular Signaling Pathways and Radiosensitize

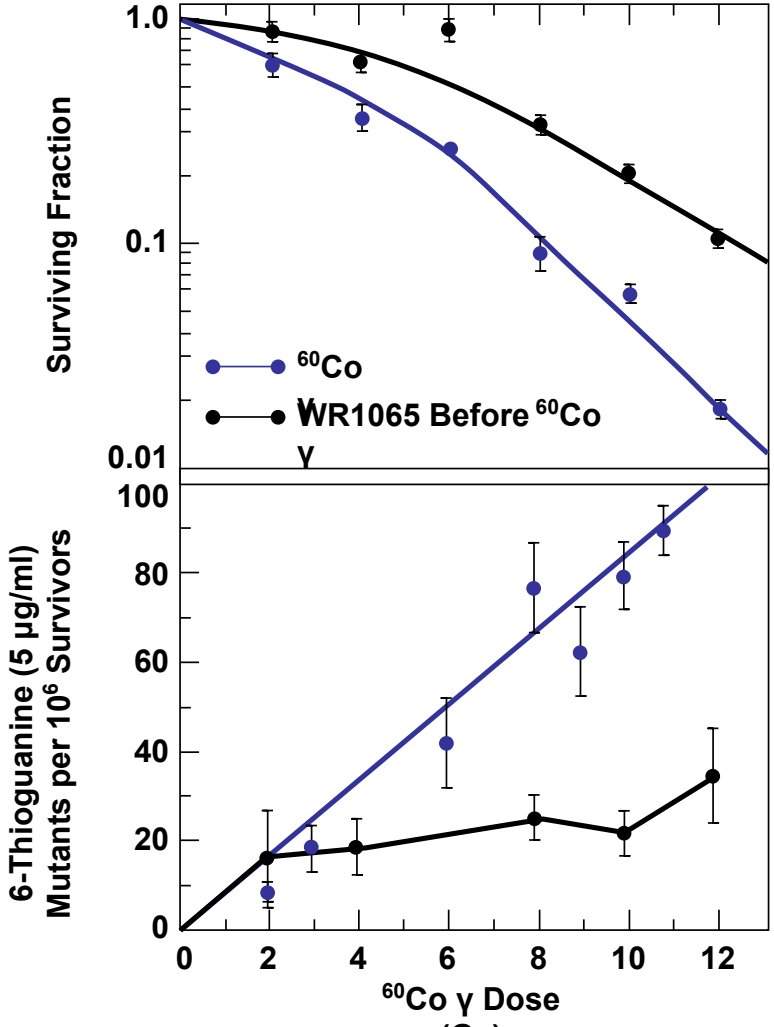
Radiosensitizer	Target	Clinical Testing
olaparib, ABT-888, others	PARP1/2	various
erlotinib, cetuximab	EGFR	HNSCC, NSCLC, colorectal
bevacizumab	VEGF	colorectal, brain tumors
MK-0646	IGF-1R	?
tipifarnib, lonafarnib, BMS-214662	farnesyl transferase (RAS)	various
valproic acid	HDAC	various
IPI-504	HSP90	?

(slide from H. Willers)

Radiation Protectors

- Agents that decrease the response of cells to radiation
- The best radioprotectors are thiols
- PF = DRF = D_0(+drug)/D_0(-drug)

Protection by WR1065 (4 mM)



WR1065 is the active form of amifostine.

Too much side effect

Grdina et al. 1985

Radiation Protectors/Mitigators

- New classes of radioprotectors/mitigators being developed
  - Growth factors/cytokines
    - Keratinocyte growth factor
    - G-CSF
    - IL-11
  - Antioxidants (SOD or catalase mimetics) and/or anti-inflammatory agents

- Currently, much interest in chemical countermeasures against radiation that could be used in a radiation incident.

Take Home Messages – Chemical Modification

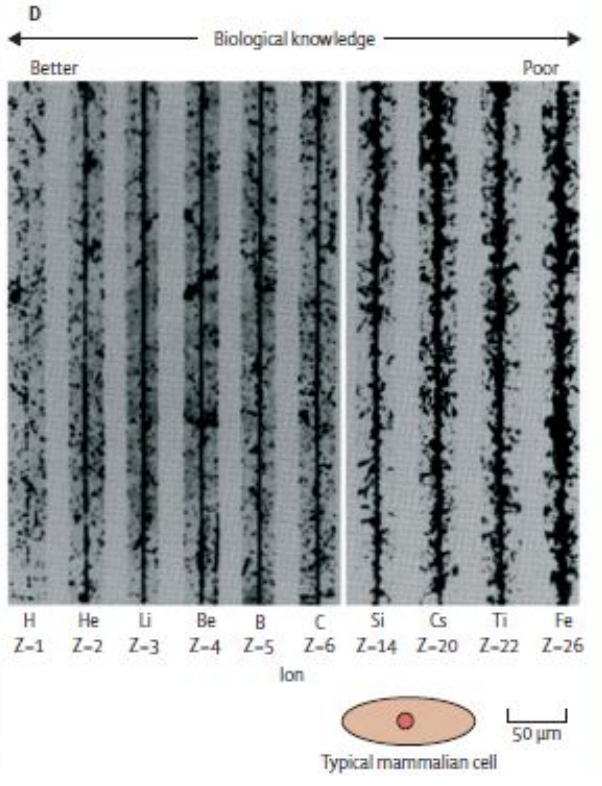
- Oxygen is the most effective radiation sensitizer (i.e., hypoxia is radioprotective).
- Hypoxic cell radiosensitizers demonstrated role of hypoxia in tumors, but were too toxic to be useful clinically.
- Many chemotherapy agents, including new drugs that target specific intracellular signaling pathways in cancer cells, are radiosensitizers.
- Thiol-containing radioprotectors have limited clinical usefulness due to toxicity.
- Increasing research effort is being put into development of novel radiation protectors, mitigators and agents for treatment of radiation damage to normal tissues.

Modification of Radiation Response

- Biological Modification
  - Cell cycle response
  - Sublethal Damage Repair (SLDR)
  - Dose rate effects
- Chemical/pharmacologic Modification
  - Oxygen effect
  - Radiation sensitizers
  - Radiation protectors/mitigators
- Physical Modification (Radiation quality)

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)

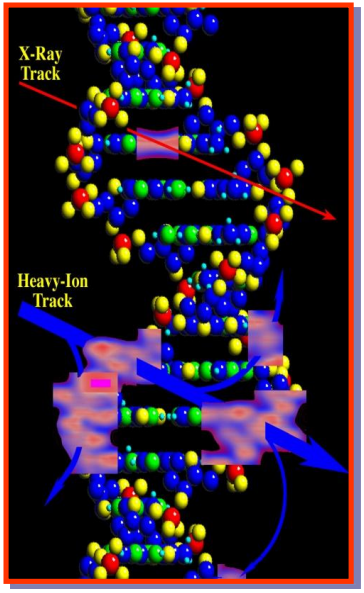


(from Cucinotta and Durante 2006)

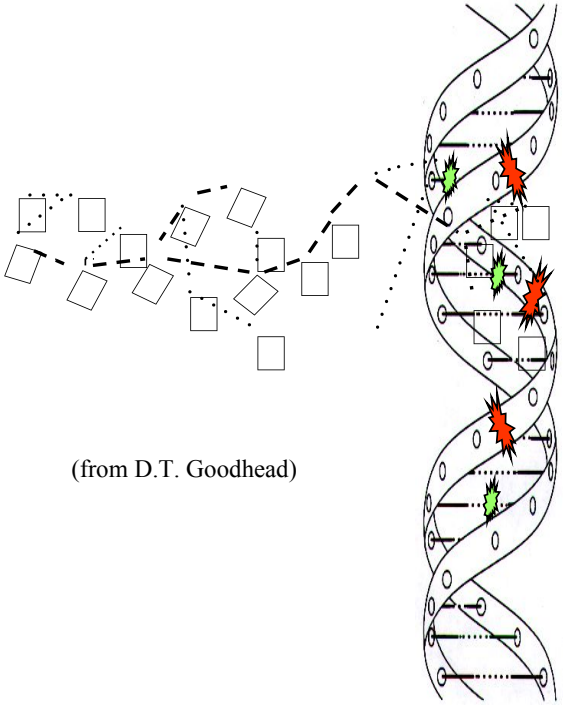
Typical LET Values

Radiation	LET (keV/μm)
Cobalt-60 γ-rays	0.2
250 kVp X-rays	2.0
“diagnostic” X-rays	3
10 MeV protons	4.7
150 MeV protons	0.5
14 MeV neutrons	12
2.5 MeV α-particles	166

Clustered Lesions: Complexity of DNA Damage Increases with LET Due to Particle Track Structure

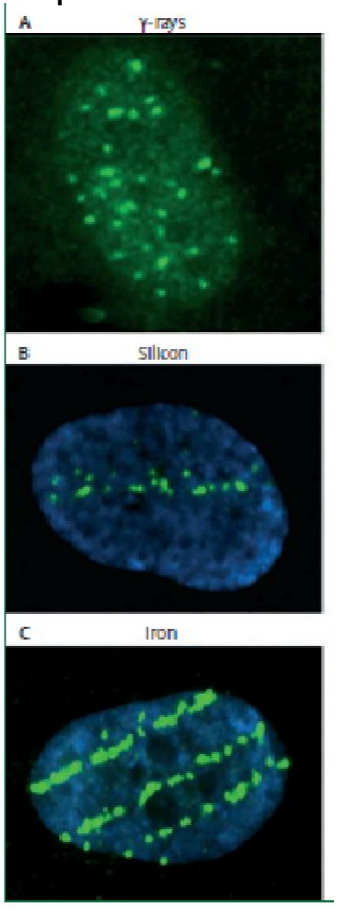


(from NASA website)



(from D.T. Goodhead)

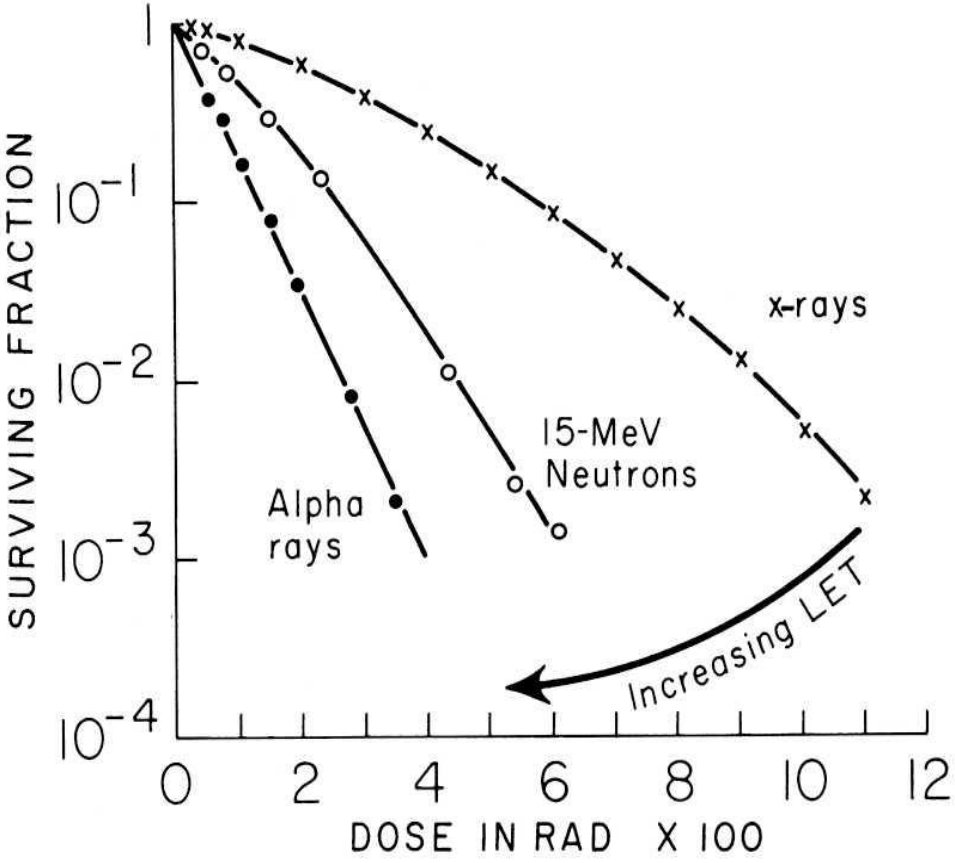
γ-H2AX foci



(from Cucinotta and Durante 2006)

More complex DNA lesions, less repair (and less accurate repair), greater lethality.

Cell Response Depends on LET



With increasing LET:

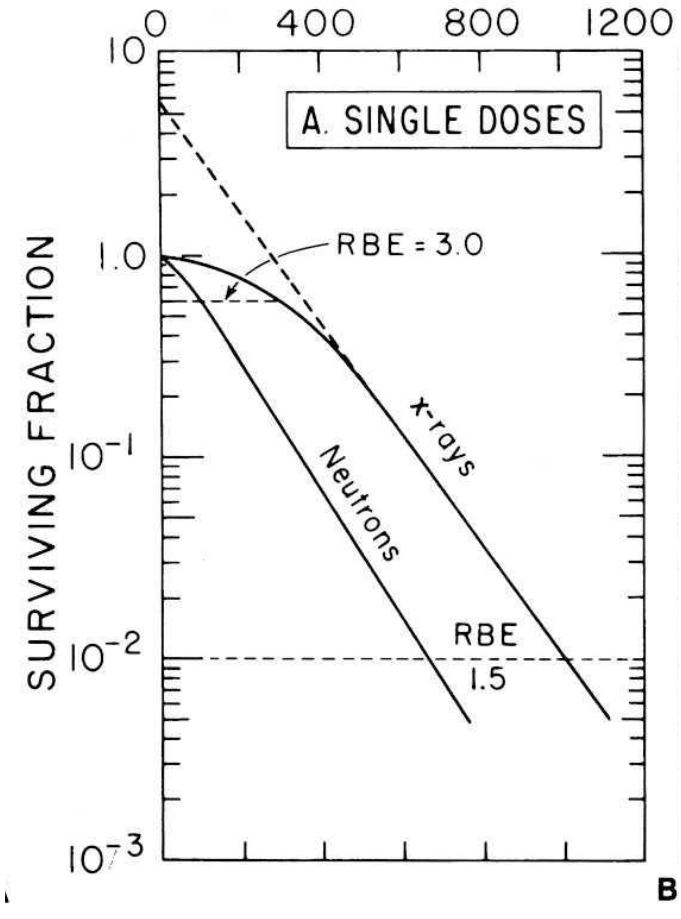
- curves become steeper
- shoulder becomes smaller

At high LET:

$SF=e^{-\alpha D}$

(from Hall 2000)

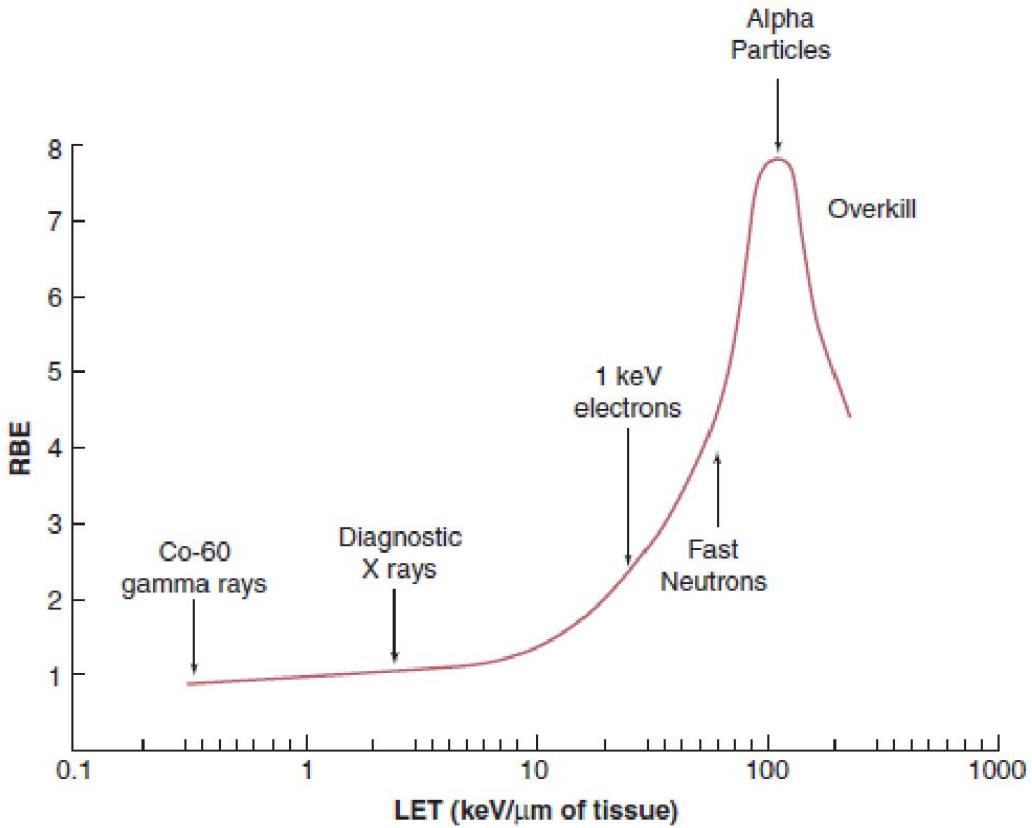
Relative Biological Effectiveness



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

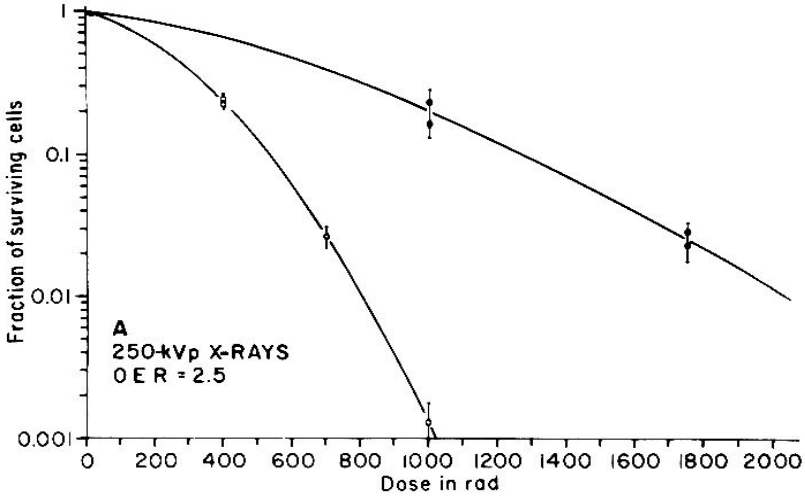
RBE is larger at higher survival.

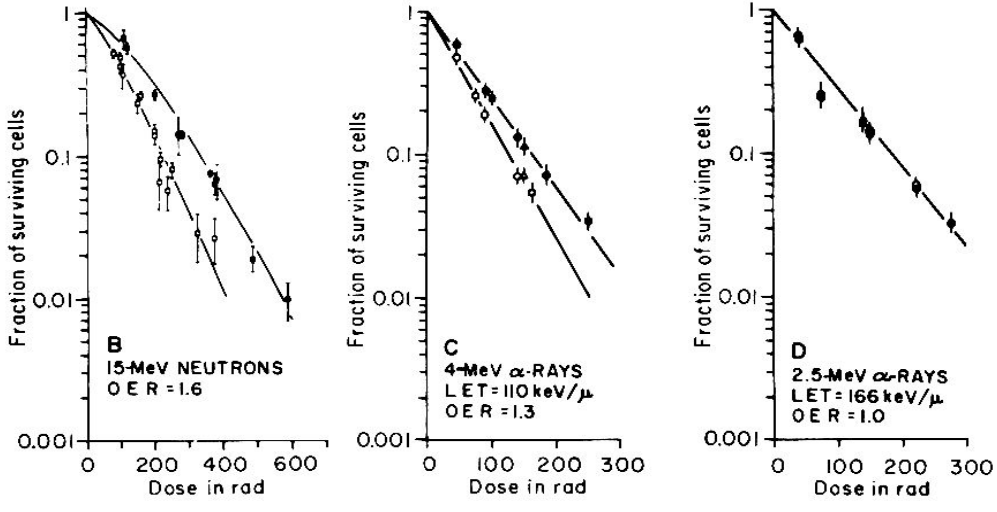
RBE Increases with LET to a Peak, then Decreases



(from Bushberg *et al*., 2012)

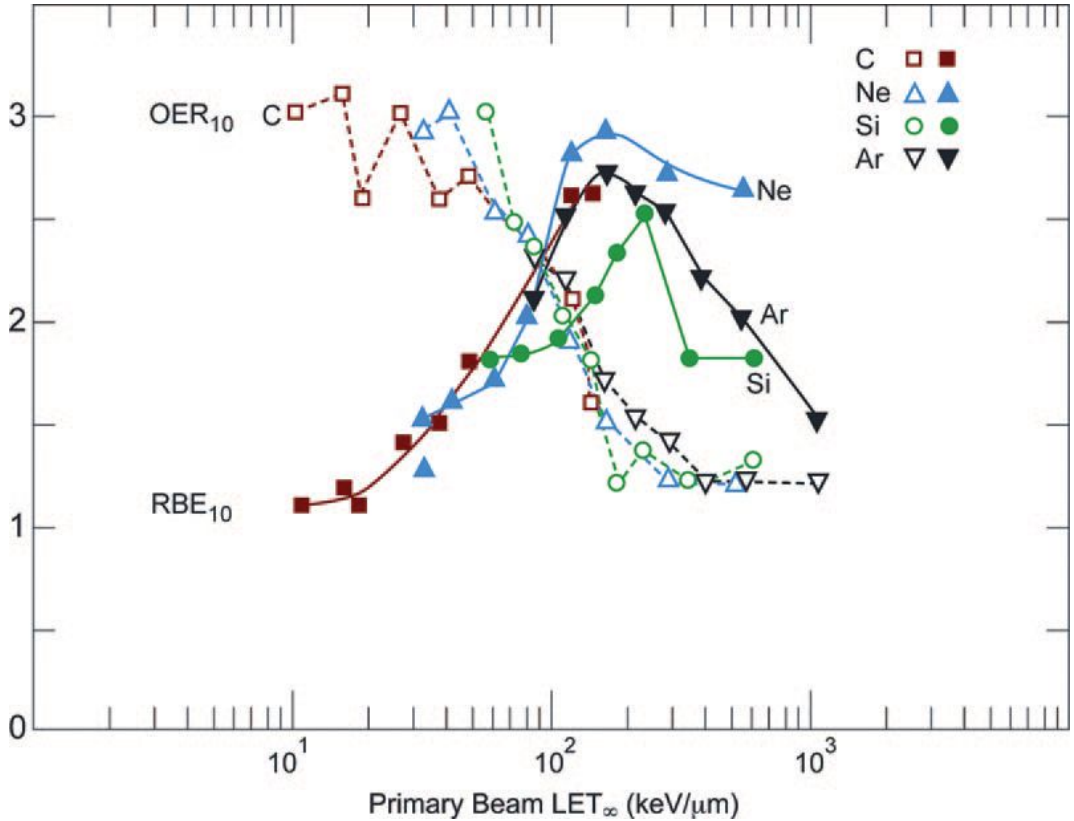
OER depends on LET





(from Hall 2000)

Summary:
RBE and OER Depend on LET



(from Blakely and Chang, 2009, based on pioneering work of Blakely *et al*. at Berkeley National Lab)

Take Home Messages - RBE & LET

- Relative biological effectiveness (clonogenic survival, chromosome aberrations, etc.) increases with LET.
  - Magnitude of RBE depends on dose and dose rate.
  - RBE of diagnostic X-rays may be somewhat higher than for ^{60}Co γ-rays.
- Increased RBE thought to be due to increased complexity of DNA damage at higher LET.

Radiation Biology for Radiology Residents

- Molecular and cellular effects of radiation
- Modification of radiation response

- Systems effects of radiation
- Radiation mutagenesis and carcinogenesis
- Risk and risk models

Next year

THANK YOU