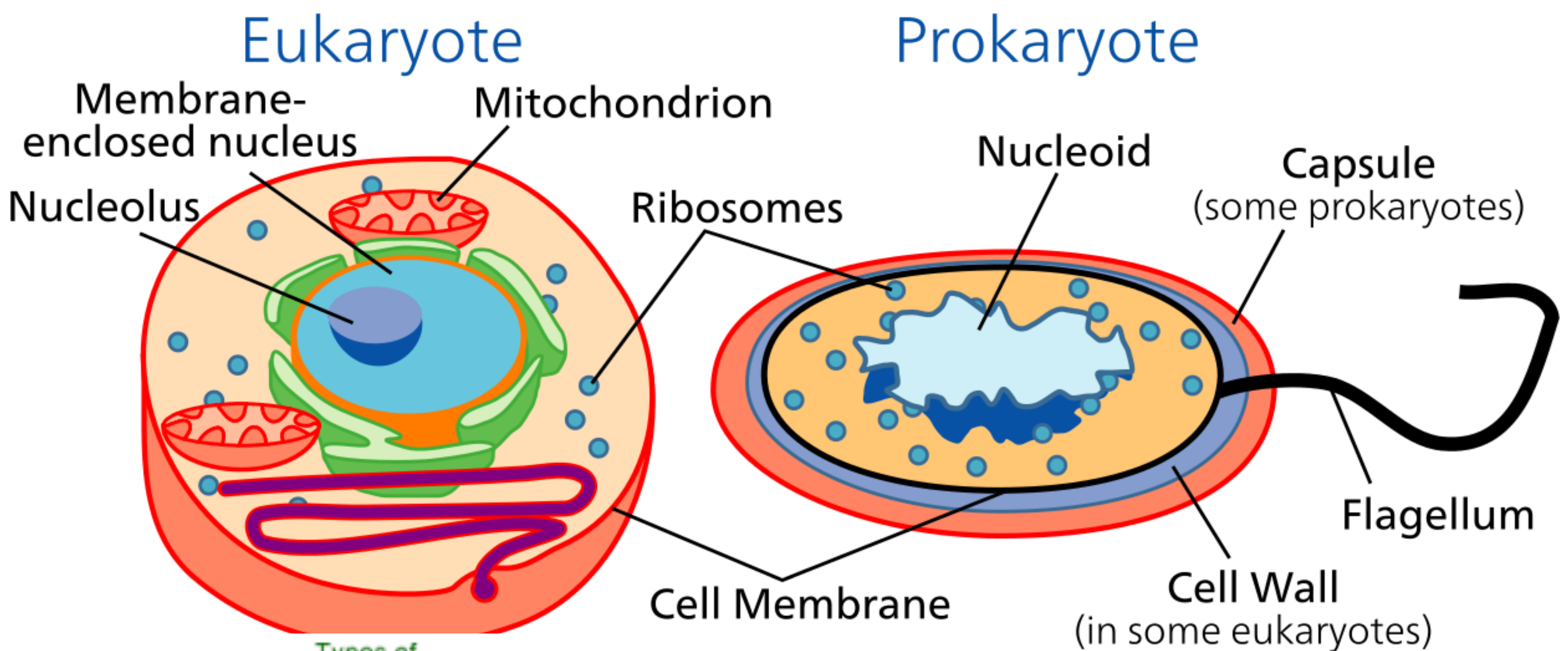
Review of Radiobiology for particles
&
Symbiology Tutorial

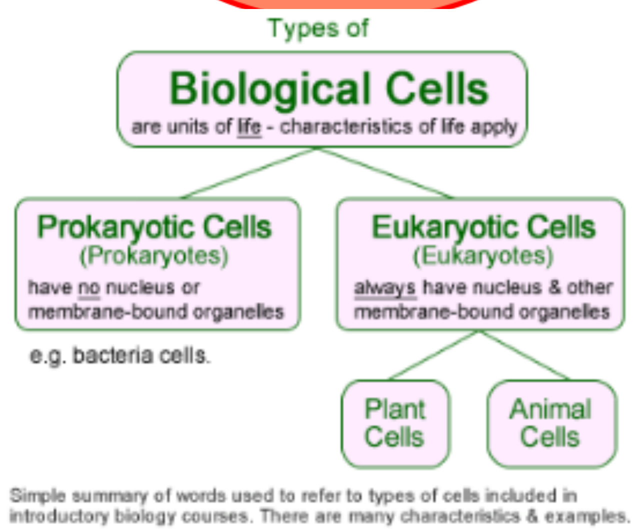
Prof Joao Seco
BioMedical Physics in Radiation Oncology
DKFZ, Heidelberg

Radiation Biology

- Holy grail of oncology
- Identify characteristics that distinguish tumor cells from normal cells
- Design a <u>Monotherapy</u> that selectively ablates tumor cells

Some Biology…



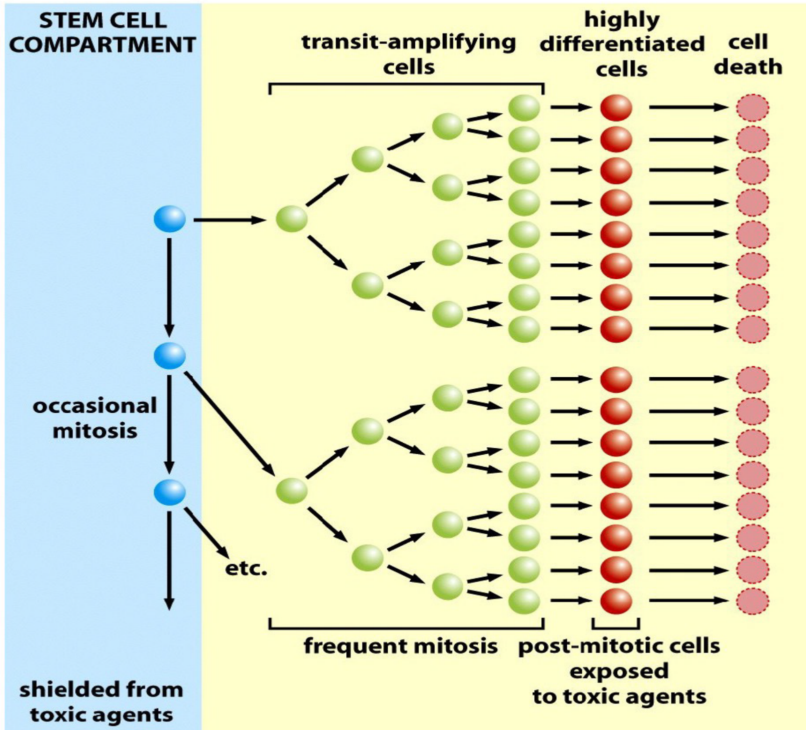


Some Biology…

Tissue organization and protection of the stem cell genome

stem cells can renew themselves through mitotic cell division and can differentiate into a diverse range of specialized cell types

the two broad categories of mammalian stem cells are embryonic stem cells & adult stem cells



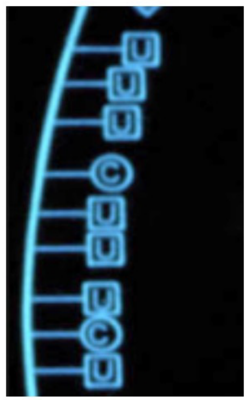
The Biology of Cancer (© Garland Science 2007)

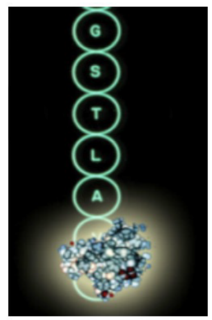
Some Biology…

The flow of genetic information

transcription → translation

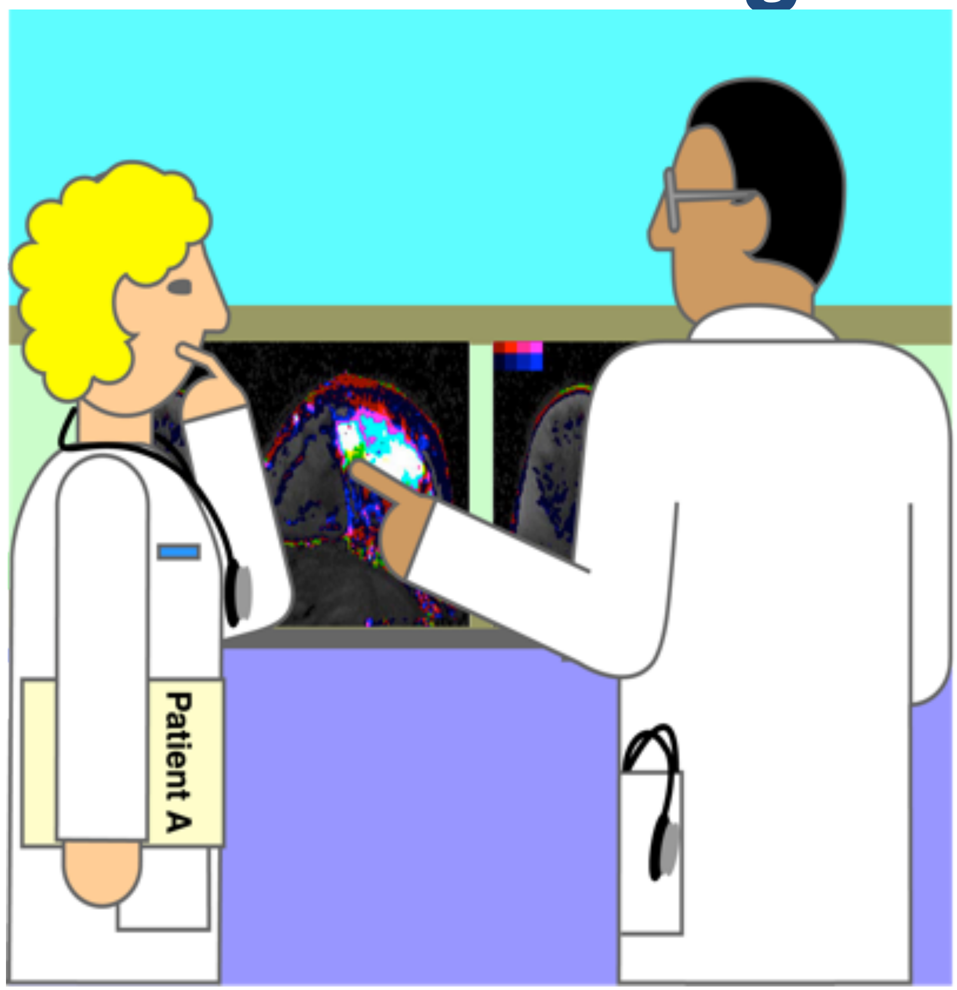
DNA → RNA → Proteins





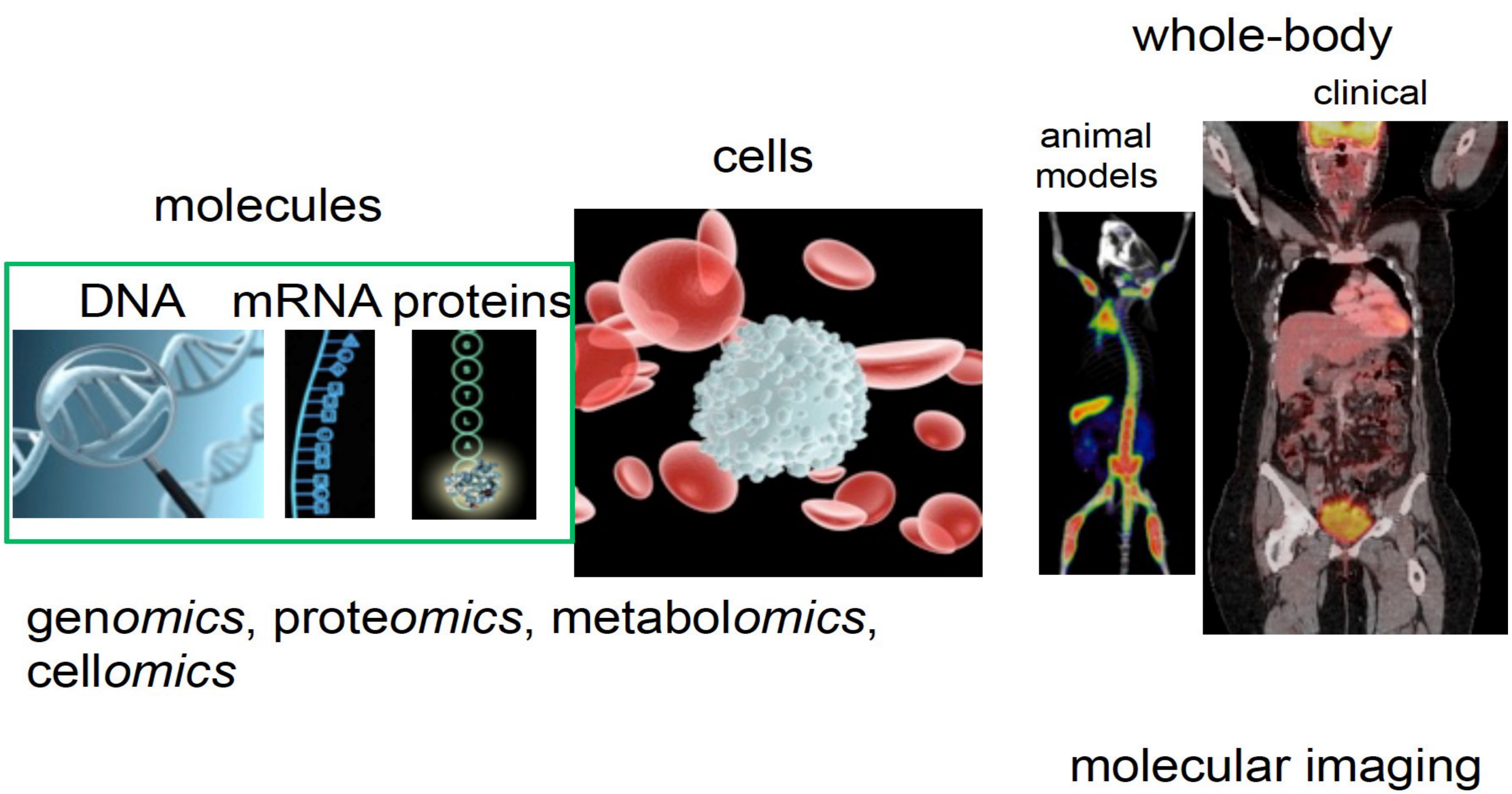
Some Biology…

How is cancer diagnosed?



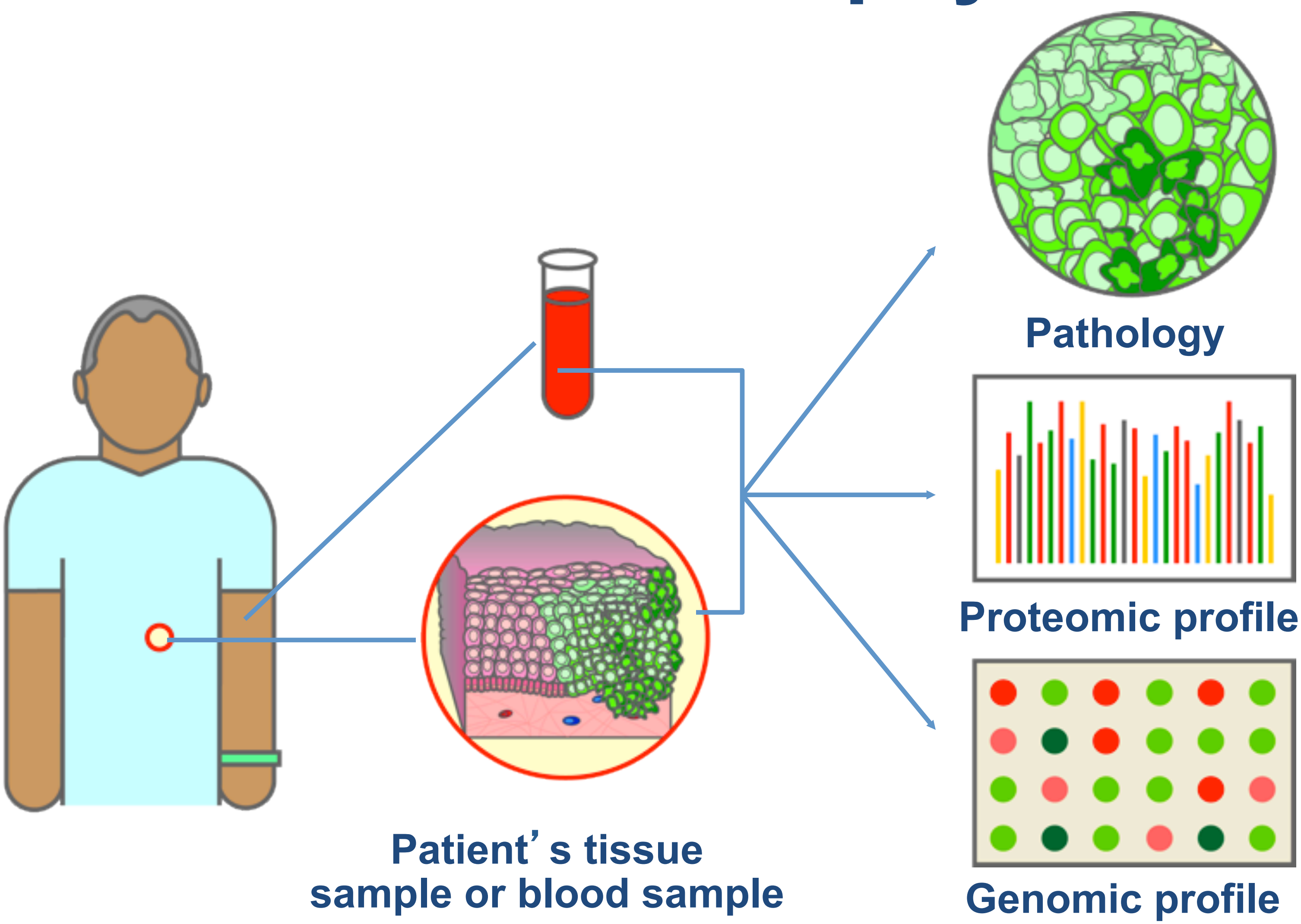
Patient Diagnostic Evaluation

Measuring biological processes at different scales

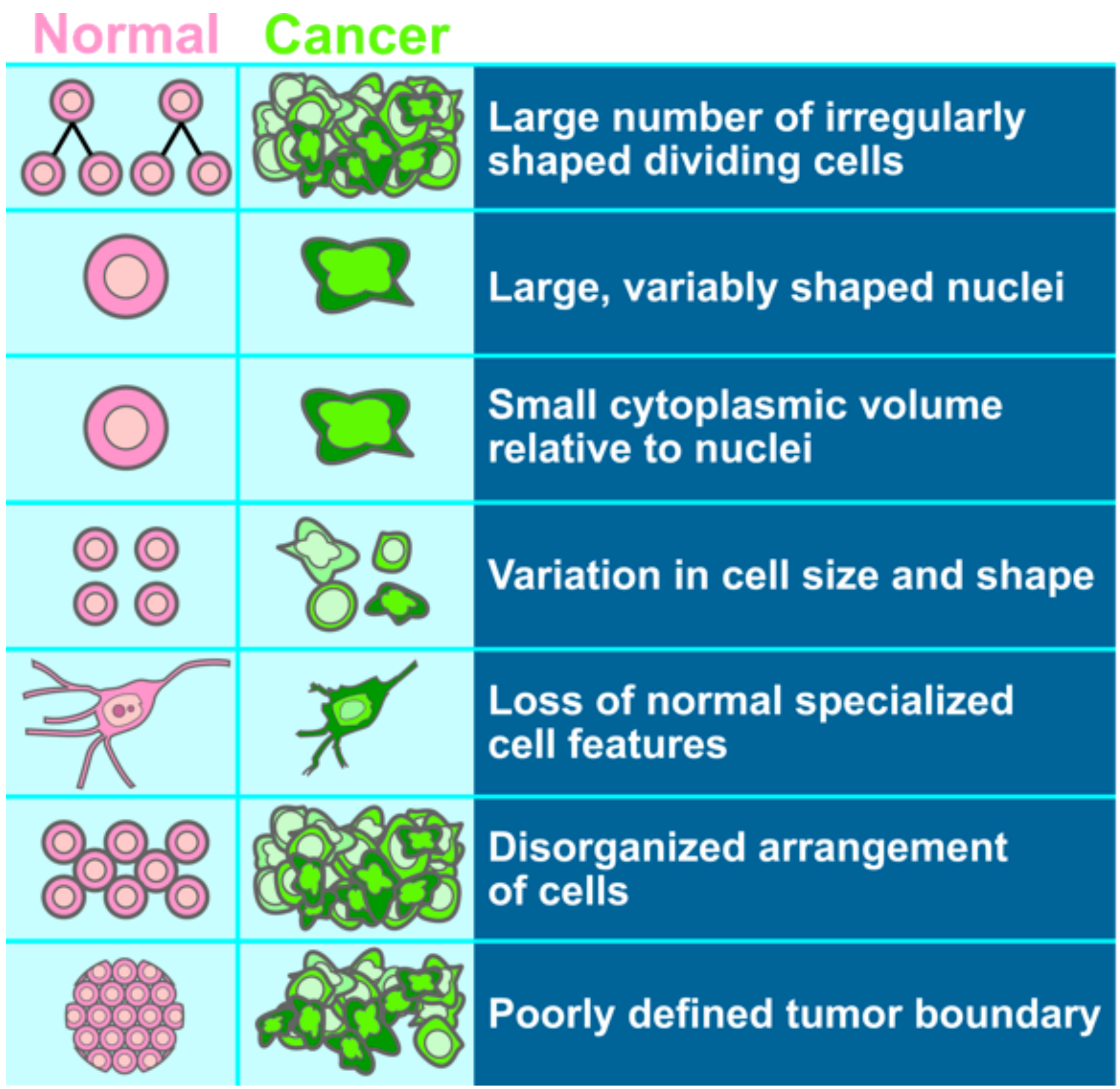


Some Biology …

What is a biopsy?

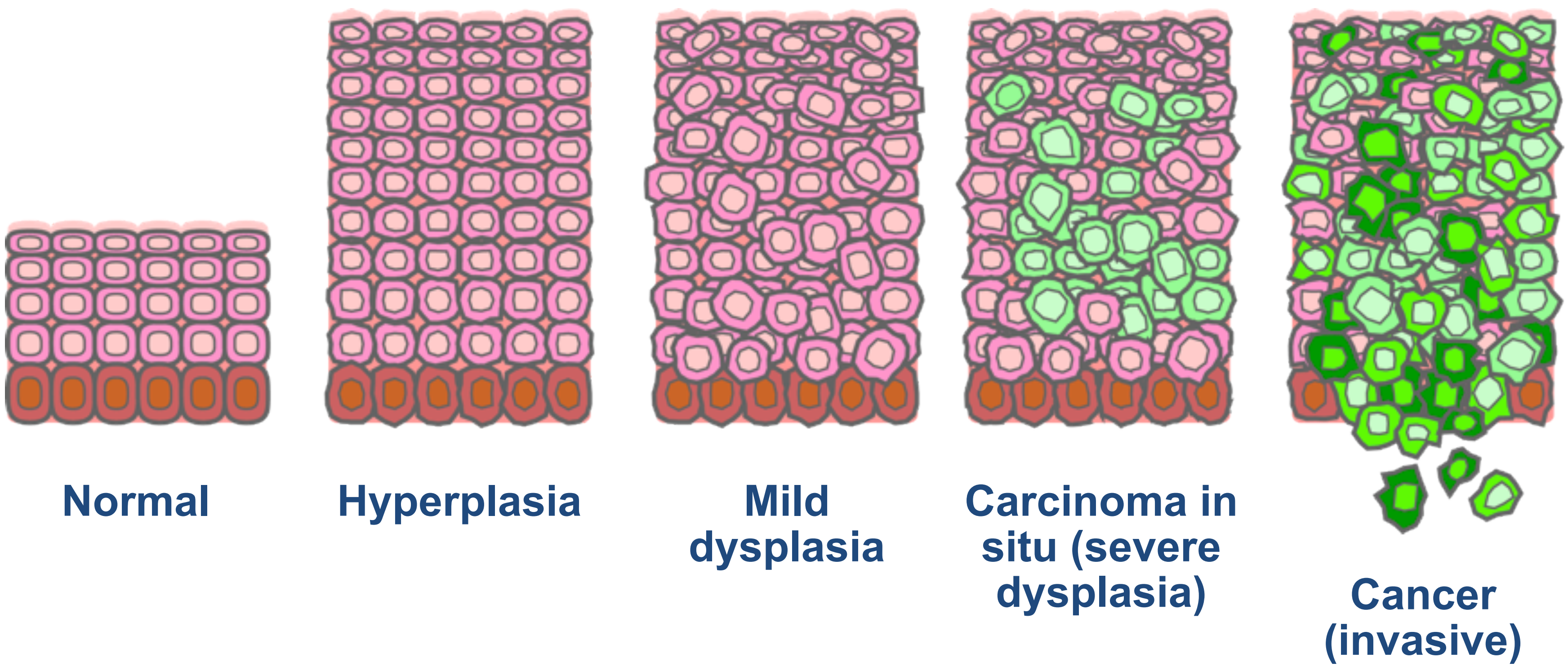


What does a pathologist look for examining biopsy tissue?

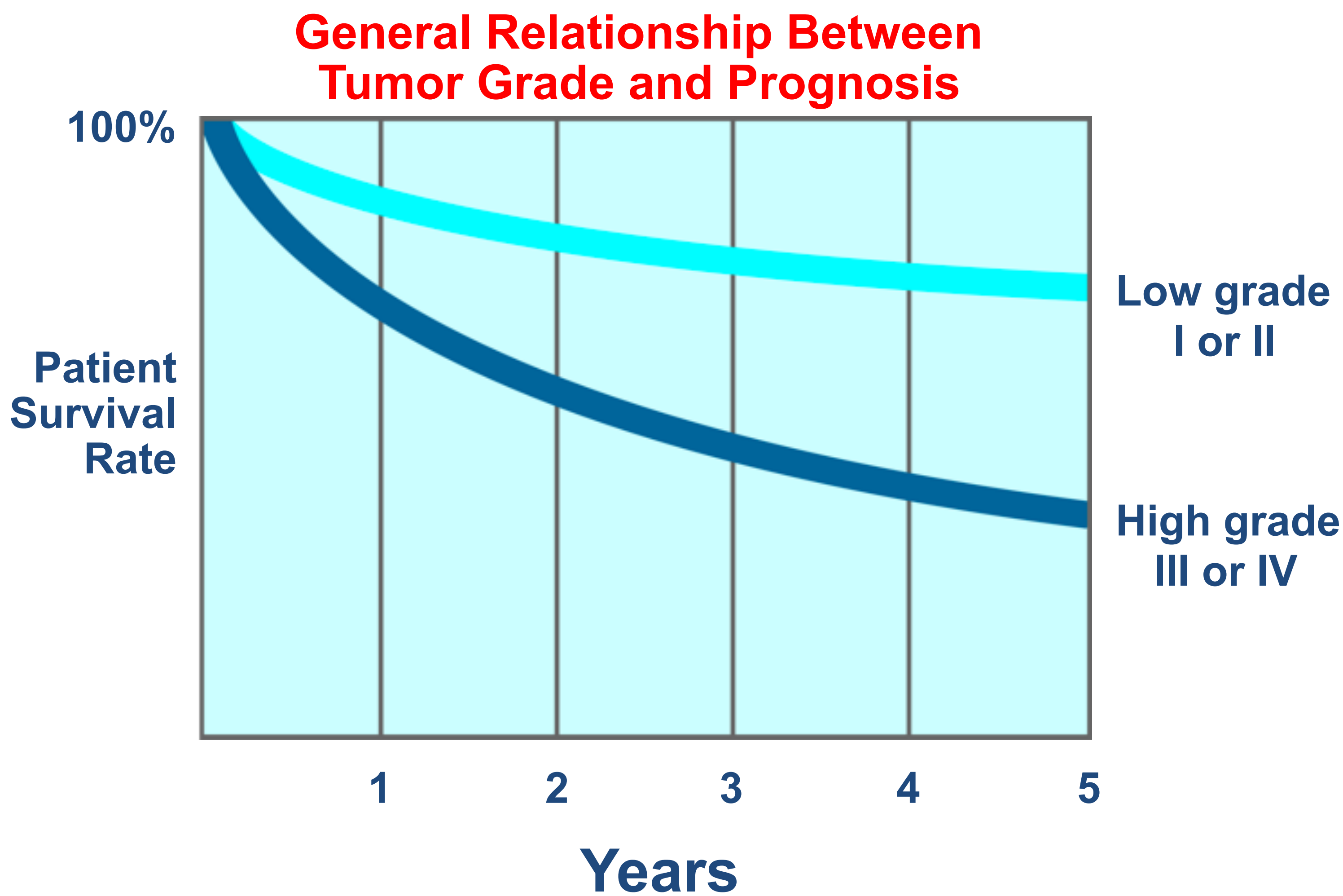


Some Biology…

What does a pathologist look for examining biopsy tissue?



What is the relationship between tumor grade and patient survival?



Hallmark of Cancer
Warburg Effect

Adequate oxygen

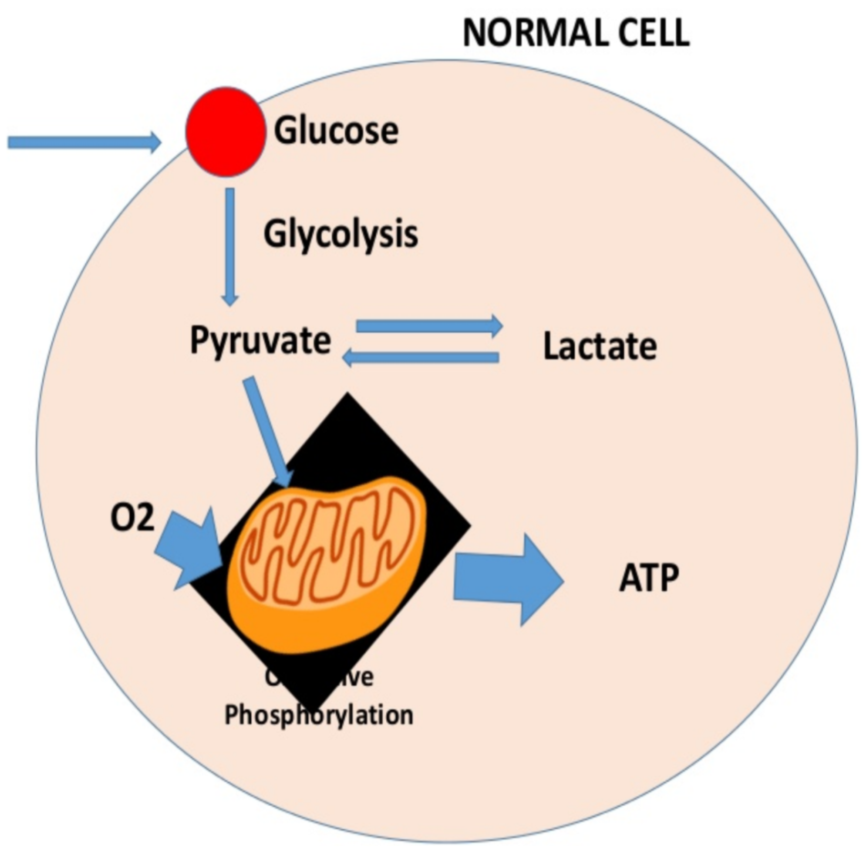
ATP is generated by Oxidative Phosphoryation

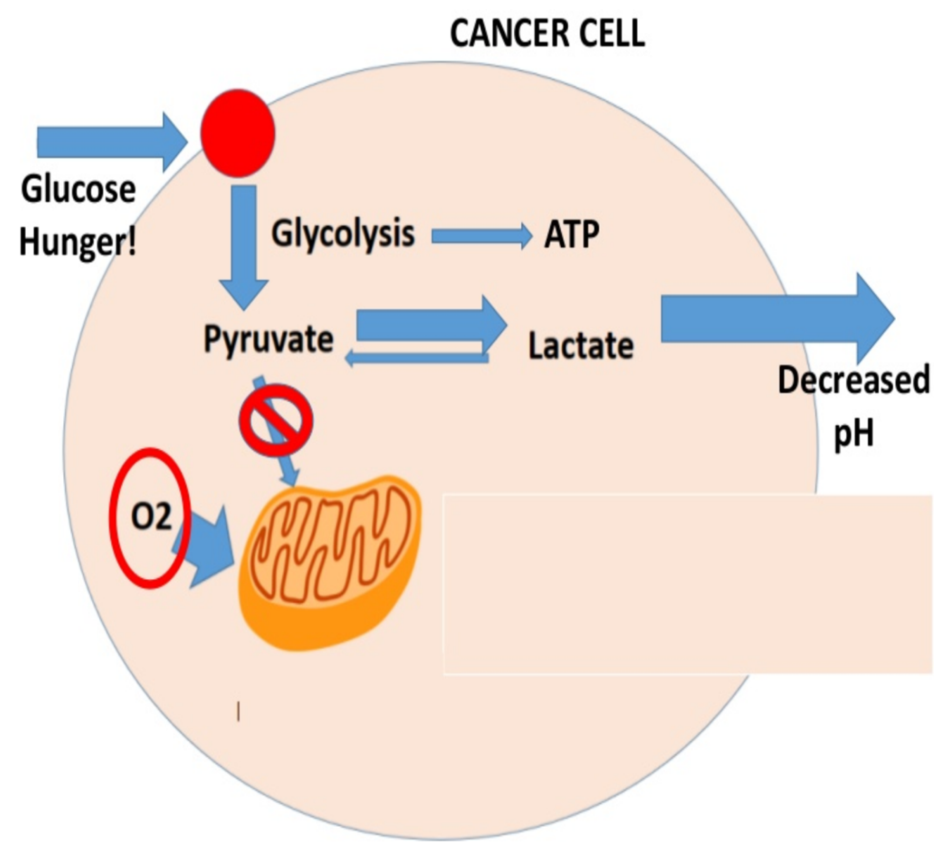
As Oxygen Decreases

Shift from Oxidative phosphorylation to **Glycolysis**

Anaerobic glycolysis

PASTEUR EFFECT





Early 20th Century

Otto Heinrich Warburg
German Physiologist

Observed that cancer cells had increased rates of glycolysis

Despite the availability of adequate oxygen levels

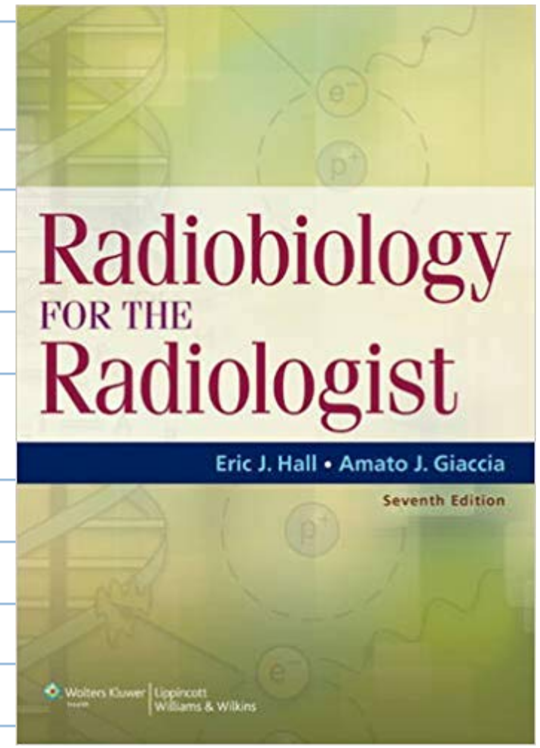
Aerobic glycolysis

WARBURG EFFECT

Why do cancer cells activate glycolysis despite the presence of oxygen?

Overview of Course

1. Physics and Chemistry of Radiation Absorption
2. Molecular Mechanisms of DNA and Chromosome Damage and Repair
3. Cell Survival Curves
4. Radiosensitivity and Cell Age in the Mitotic Cycle
5. Fractionated Radiation and the Dose-Rate Effect
6. Oxygen Effect and Reoxygenation
7. Linear Energy Transfer and Relative Biologic Effectiveness
8. Acute Radiation Syndrome
9. Radioprotectors
10. Radiation Carcinogenesis
11. Heritable Effects of Radiation
12. Effects of Radiation on the Embryo and Fetus

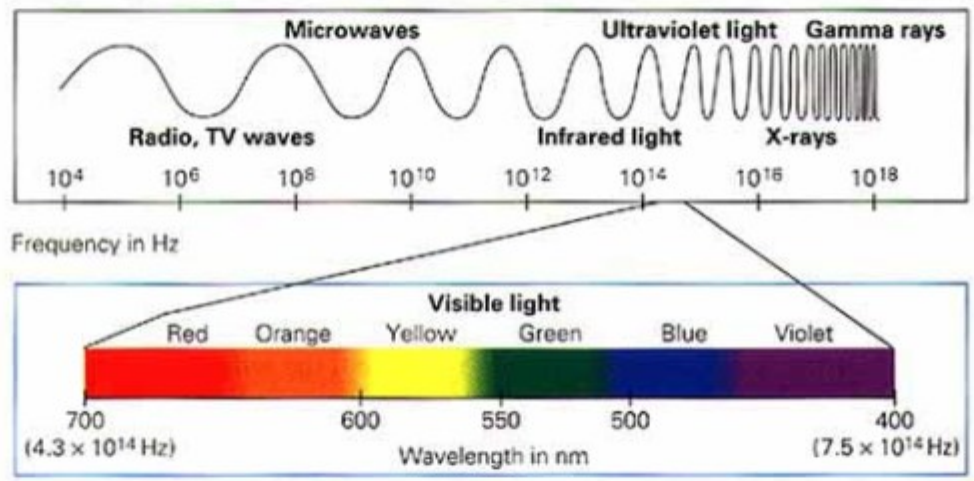


1. Physics and Chemistry Radiation Absorption

Radiation may be classified as *directly* or *indirectly* ionizing. All of the charged particles previously discussed are **directly ionizing**; that is, provided the individual particles have sufficient kinetic energy, they can disrupt the atomic structure of the absorber through which they pass directly and produce chemical and biologic changes. Electromagnetic radiations (x- and γ-rays) are **indirectly ionizing**. They do not produce chemical and

Directly Ionizing: Electrons, protons, alpha, etc

Indirectly Ionizing: photons



Excitation

$$H_2O \xrightarrow{rad} H_2O^*$$

- The excited water molecule can dissipate excess energy by ***bond breakage*** to produce hydroxyl and hydrogen radicals.

$$H_2O^* \rightarrow HO\cdot + H\cdot$$

Ionizing

$$H_2O \xrightarrow{rad} H_2O\cdot^+ + e^-$$

The electron is captured by water through dipolar interactions, becoming solvated, and referred to as an **aqueous electron** or a **solvated electron:**

$e^- + H_2O \rightarrow e^-_{aq}$ surrounded by a "cage" of water;

$e^- + H^+ \rightarrow H\cdot$ or it can react with H^+ to form a radical.

- The radical ion of water can dissociate to produce a hydroxyl radical and a hydrogen ion.

$$H_2O\cdot^+ \rightarrow H^+ + HO\cdot$$

THe specific heat of the human body compared to protein and wood:

Substance	Specific Heat - c_p - (J/(kg °C))
Human Body (average)	3470
Protein	1700
Wood	1700

- *1 J/(kg °C) = 2.389x10^{-4} kcal/(kg °C) = 2.389x10^{-4} Btu/(lb$_m$ °F)*

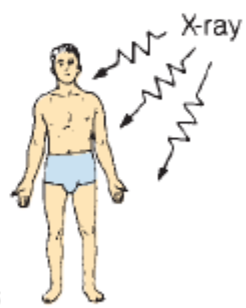
Up to 60% of the human adult body is water. Specific heat of water is *4187 J/kg oC (1 Btu/lb$_m$ °F).*

Temperature Change Due to Radiation

Total-Body Irradiation

Mass = 70 kg
$LD_{50/60}$ = 4 Gy
Energy absorbed =

$$70 \times 4 = 280 \text{ joules}$$
$$= \frac{280}{4.18} = 67 \text{ calories}$$

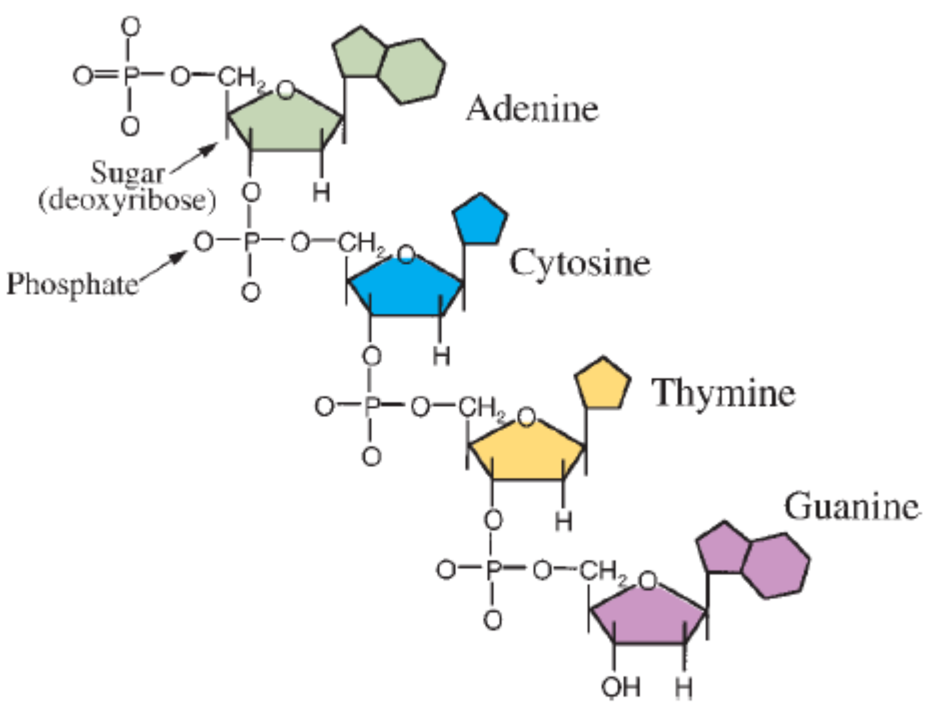


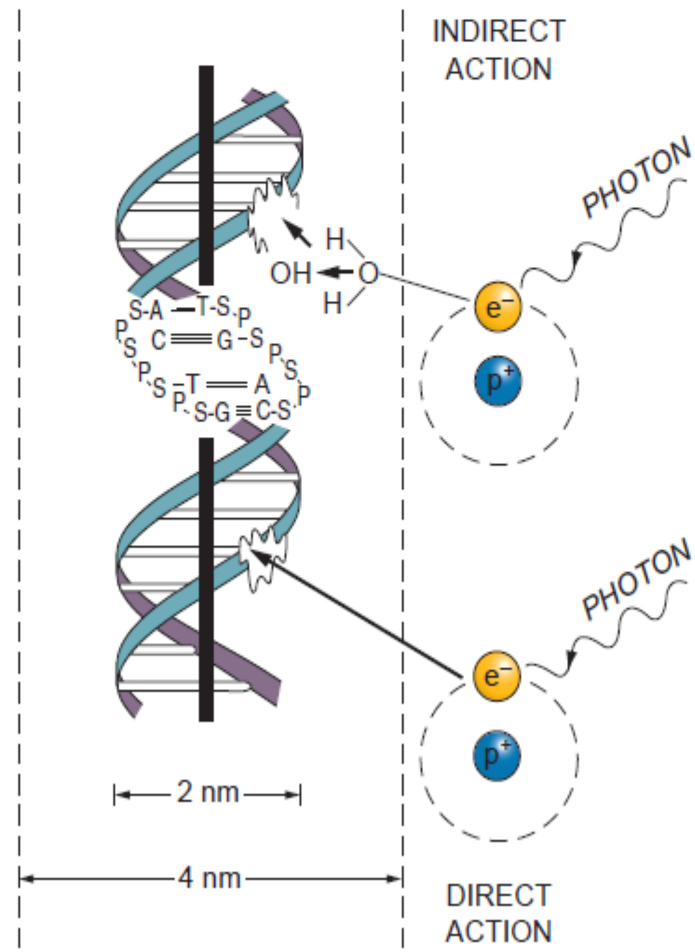
$$Cp = 3470 J/Kg\ °C = 280\ J/70\ Kg * T °C$$

$$T\ (°C) = 1.15\ m°C = 0.00115\ °C$$

DIRECT AND INDIRECT ACTION

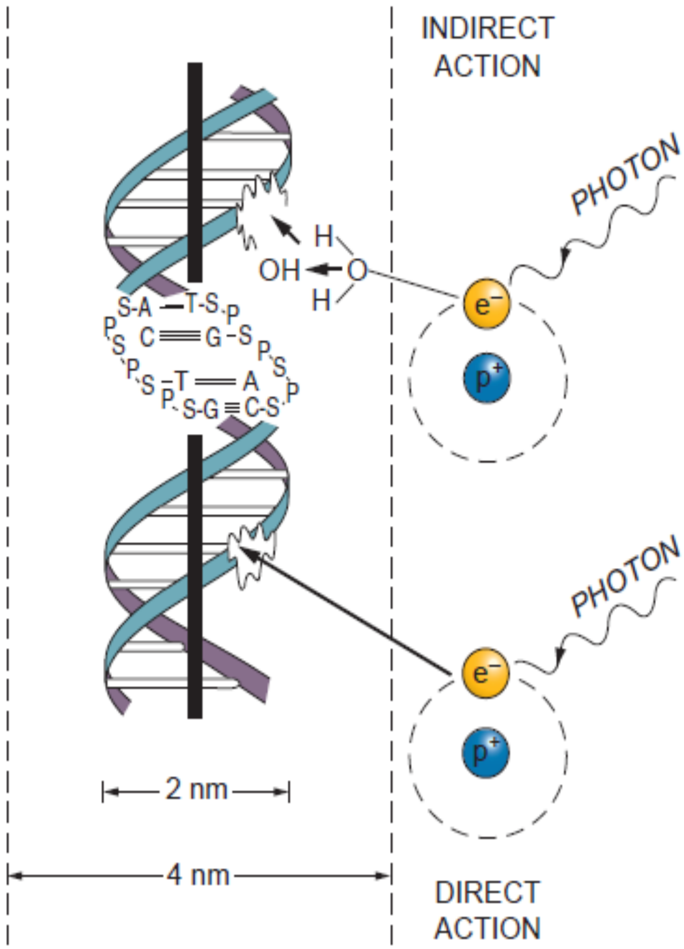
The biologic effects of radiation result principally from damage to deoxyribonucleic acid (DNA), which is the critical target, as described

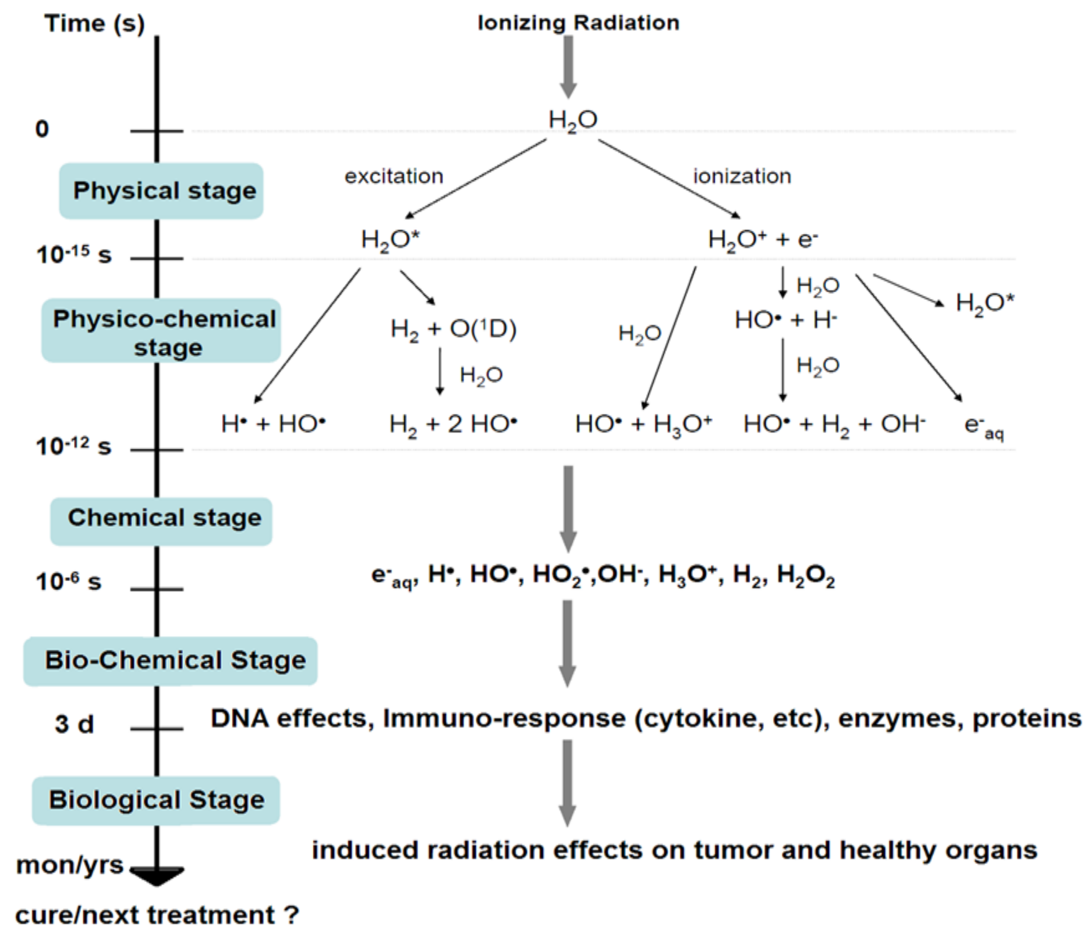




▪ DIRECT AND INDIRECT ACTION

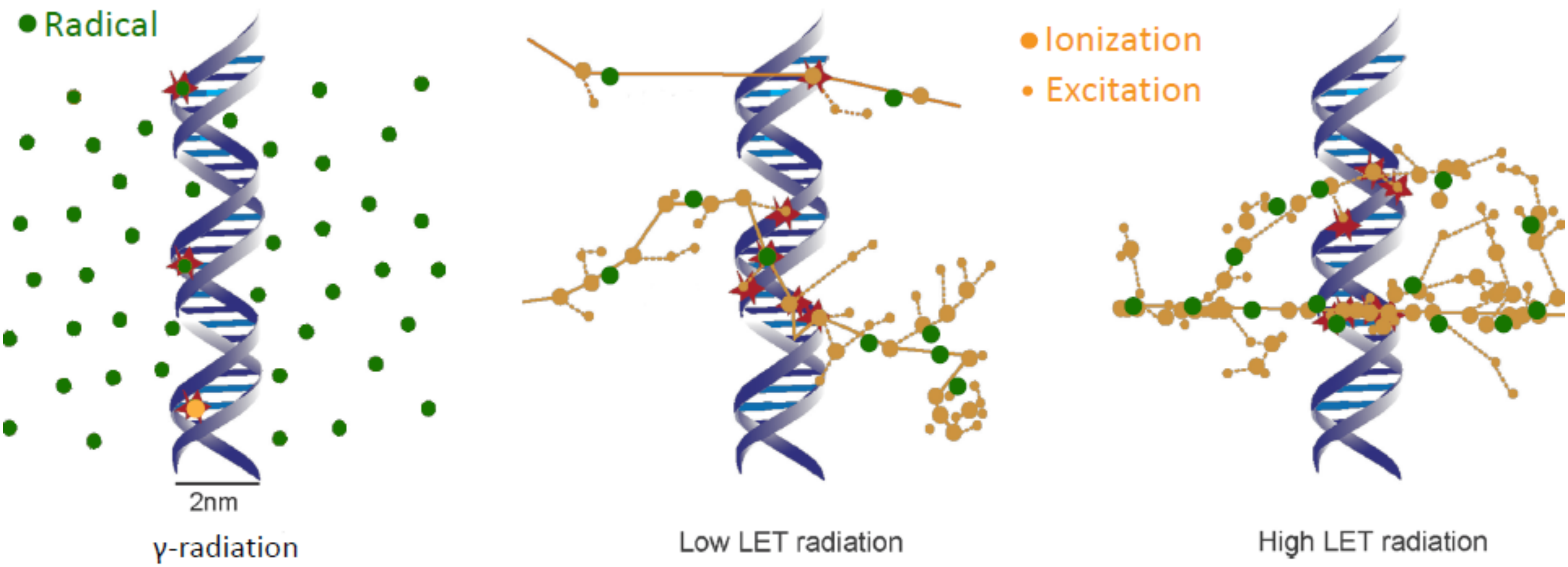
The biologic effects of radiation result principally from damage to deoxyribonucleic acid (DNA), which is the critical target, as described





▪ DIRECT AND INDIRECT ACTION

The biologic effects of radiation result principally from damage to deoxyribonucleic acid (DNA), which is the critical target, as described



Low and homogeneous ionization density / radical production
→ Random distribution of indirect damage
→ Easier to repair by cell!

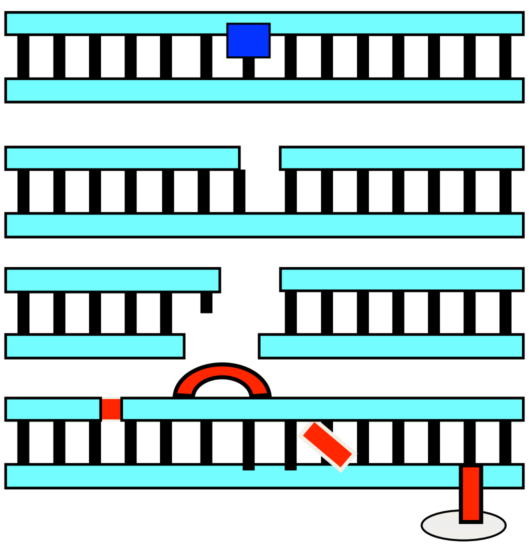
LET ↗

High and localized ionization density / (radical production)
→ Clustered/Complex DNA Damage
→ Very difficult to repair by cell!

2. Mechanism of DNA Damage and Repair

IR-induced DNA Damage is heterogeneous

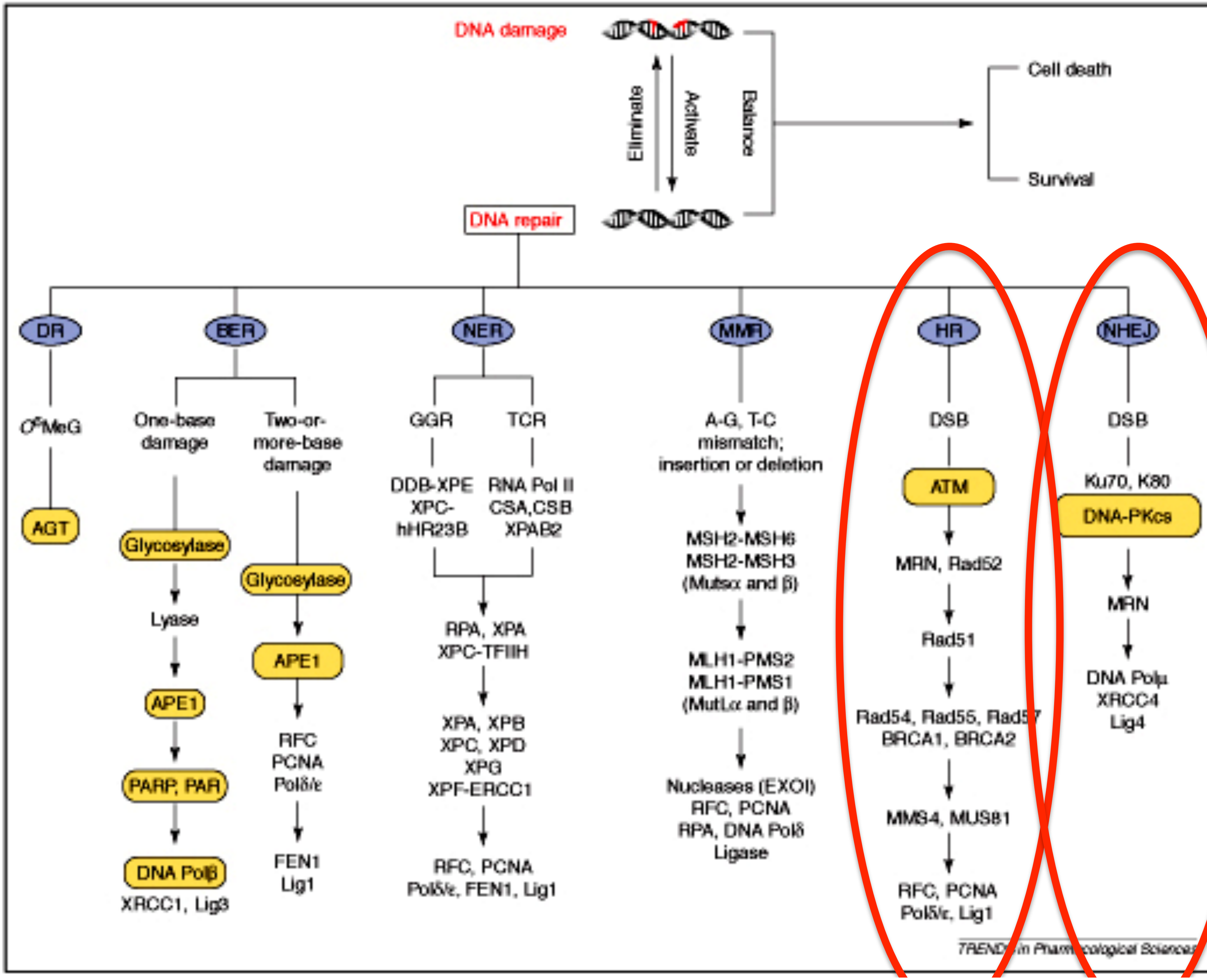
- **LowLET (X-rays,e-,protons) and HighLET are referred to as *ionizing radiation*.**
- **Passage of IR through biological material deposits energy, producing free radicals, particularly OH radicals, and stable molecules that produce DNA damage.**
- **Reaction of radicals and molecules with DNA leads to chemical damage to the target.**



DAMAGE TYPE	No./Gy/cell
base damage	> 1000
Single-Strand Break (SSB)	500-1000
Double-Strand Break (DSB)	~ 30
sugar damage, DNA-DNA + DNA-protein cross links	various

There are Six Major DNA Repair Pathways in Human Cells

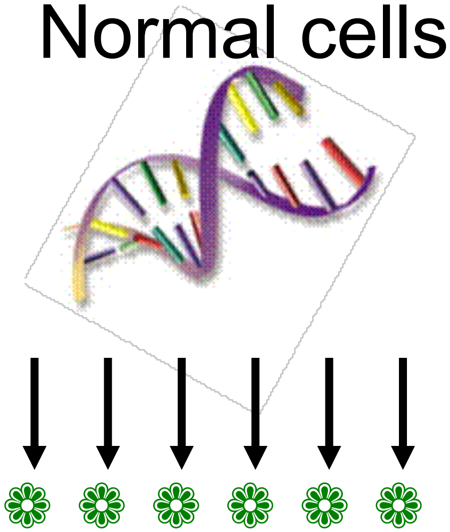
1) Base Excision Repair (BER)
2) Nucleotide Excision Repair (NER)
3) Mismatch Repair (MMR)
4) Homologous Recombination, FA/BRCA pathway (HR)
5) Non-Homologous End-Joining (NHEJ)
6) Translesion DNA Synthesis (TLS)



DNA damage
Eliminate
Activate
Balance
Cell death
Survival
DNA repair
DR
BER
NER
MMR
HR
NHEJ
O6MeG
AGT
One-base damage
Two-or-more-base damage
Glycosylase
Lyase
APE1
PARP, PAR
DNA Polβ
XRCC1, Lig3
Glycosylase
APE1
RFC
PCNA
Polδ/ε
FEN1
Lig1
GGR
TCR
DDB-XPE
XPC-hHR23B
RNA Pol II
CSA,CSB
XPAB2
RPA, XPA
XPC-TFIIH
XPA, XPB
XPC, XPD
XPG
XPF-ERCC1
RFC, PCNA
Polδ/ε, FEN1, Lig1
A-G, T-C mismatch; insertion or deletion
MSH2-MSH6
MSH2-MSH3
(Mutsα and β)
MLH1-PMS2
MLH1-PMS1
(MutLα and β)
Nucleases (EXOI)
RFC, PCNA
RPA, DNA Polδ
Ligase
DSB
ATM
MRN, Rad52
Rad51
Rad54, Rad55, Rad57
BRCA1, BRCA2
MMS4, MUS81
RFC, PCNA
Polδ/ε, Lig1
DSB
Ku70, K80
DNA-PKcs
MRN
DNA Polμ
XRCC4
Lig4
TRENDS in Pharmacological Sciences

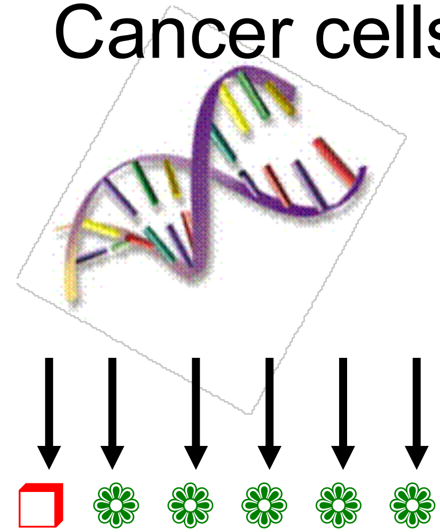
Cancer Cells are often defective in one DNA Repair Pathway

Normal cells



Six normal DNA repair pathways

Cancer cells



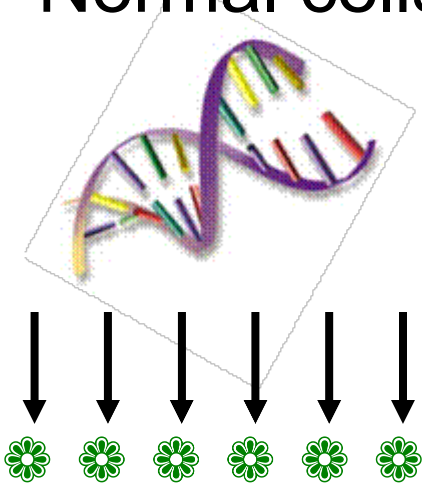
BRCA1 mutation

Predicts PARPi sensitivity of breast cancer

The specific pathway lost may determine the best course of chemotherapy and radiation (personalized medicine)

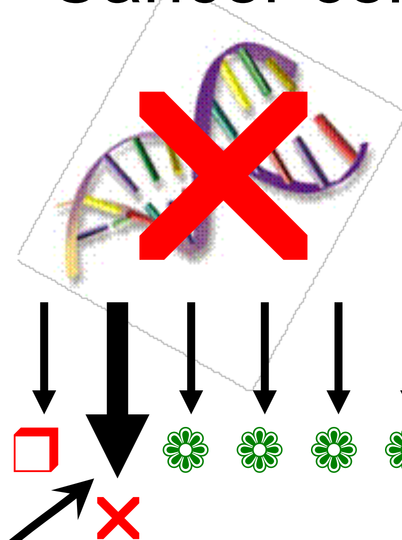
An inhibitor of a second DNA Repair Pathway can kill a cancer directly (Monotherapy)

Normal cells



Six normal DNA repair pathways

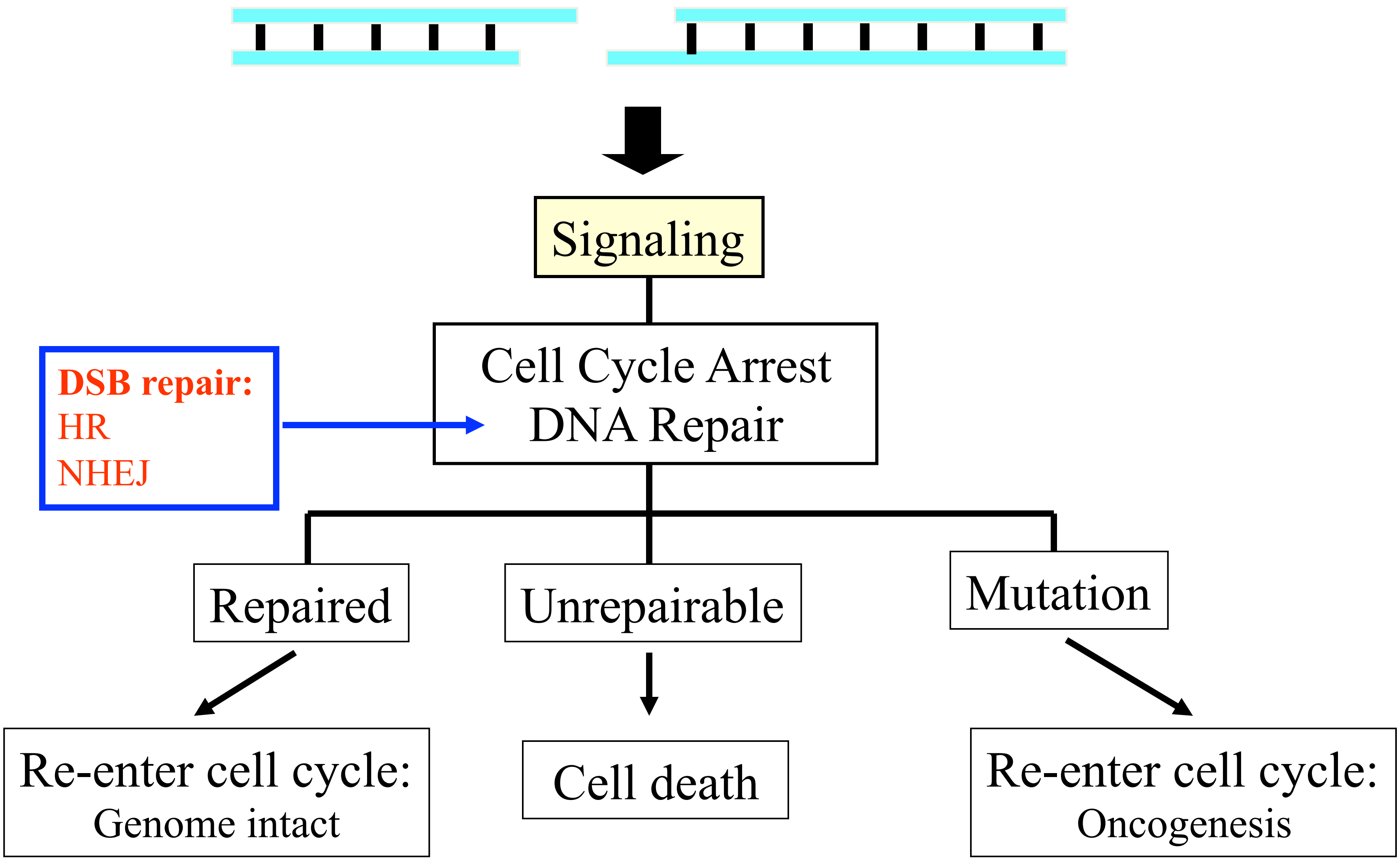
Cancer cells



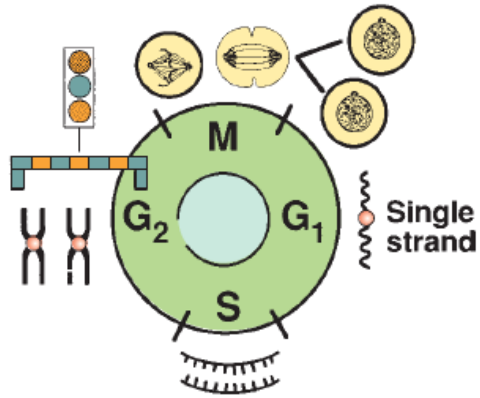
One defective pathway leads to hyper-dependence on a second pathway

An inhibitor for the second pathway will kill the cancer cell

DSB Repair

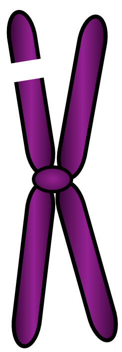

Signaling
Cell Cycle Arrest
DNA Repair
DSB repair:
HR
NHEJ
Repaired
Unrepairable
Mutation
Re-enter cell cycle:
Genome intact
Cell death
Re-enter cell cycle:
Oncogenesis

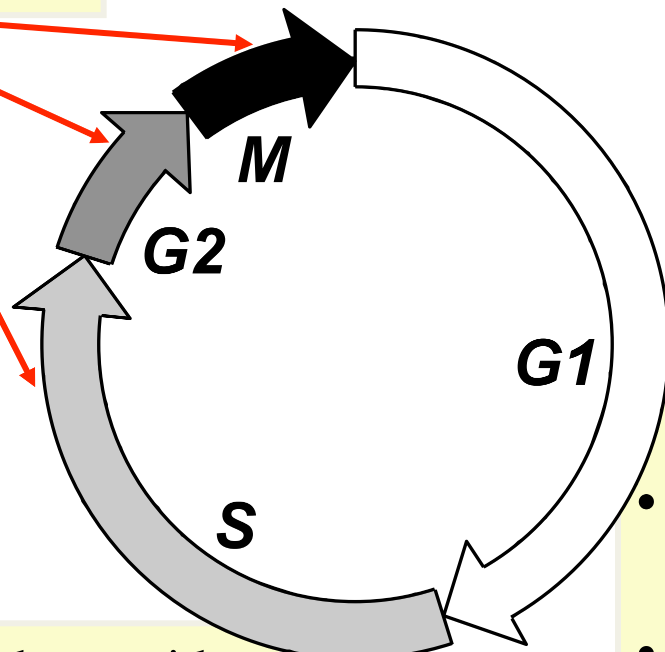
Cell Cycle Dependence of DSB Repair :

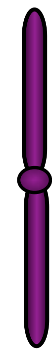


Homologous Recombination (HR)

Non-homologous End joining (NHEJ)







Repair without sister chromatid

- Low fidelity, prone to errors.
  –mutations + small deletions.
- Operates mainly during G1.
- Tolerated because DSBs likely to occur in non-coding regions.

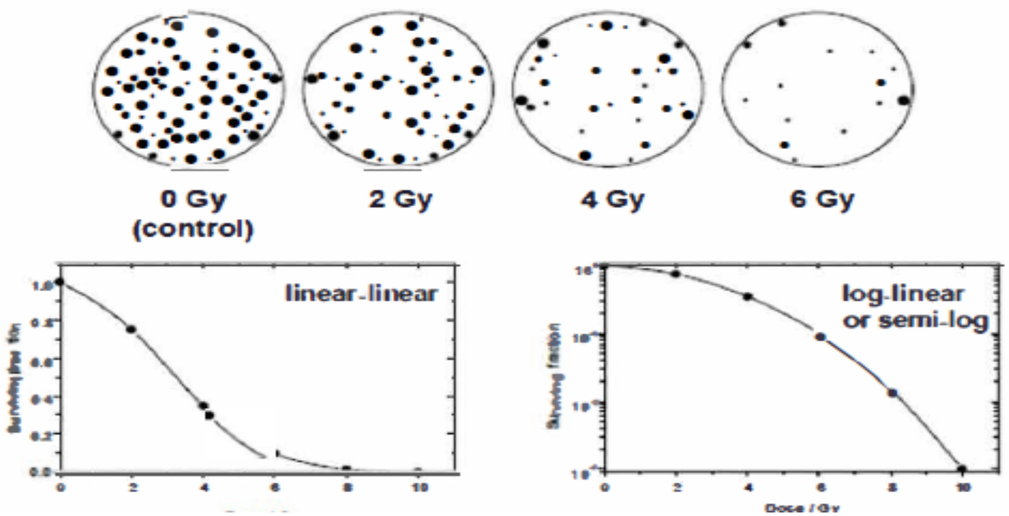
- Repair using sister chromatid.
- High fidelity.
- Restricted to S-G2-M

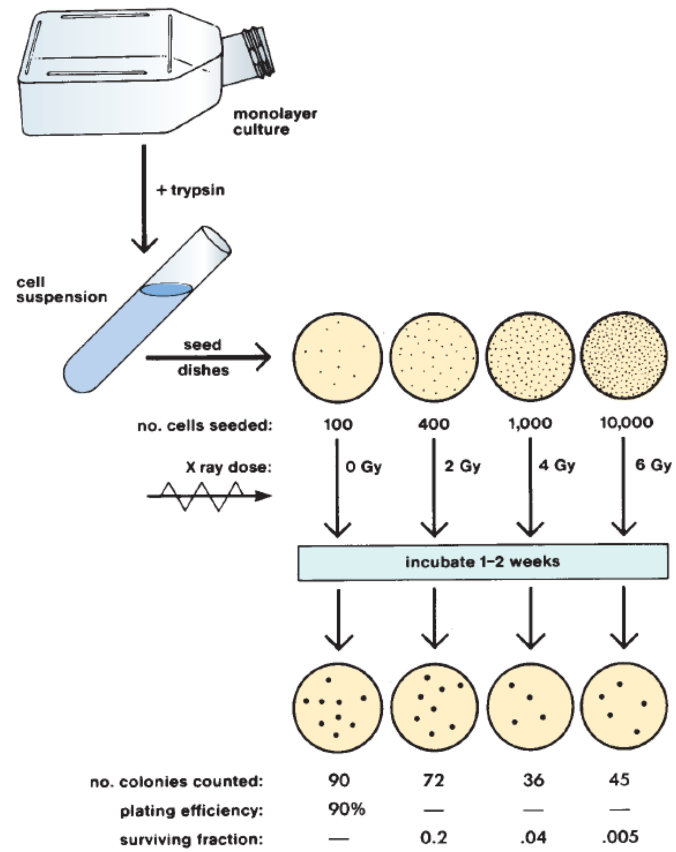
SHORT BREAK

3. Cell Survival Curves

In vitro experimental assay of radiation damage

Measuring cell survival *in vitro*





- Puck and Marcus (1955) developed a new method for the quantitative culture of mammalian cells. (HeLa cells, feeder cell technique)
- Elkind and Sutton (1960) proposed a model for repair of sublethal damage. In split-dose experiments, they measured recovery of survival as a function of the time interval between two doses

The first mammalian cell survival curve

INTRINSIC RADIOSENSITIVITY 117

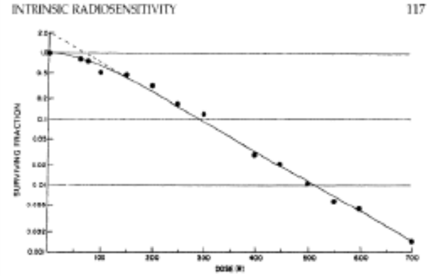


Figure 8.1. Radiation dose-response of human cancer cells *in vitro*. (Reproduced from Puck and Marcus, 1956, by copyright permission of The Rockefeller University Press.)

THREE POPULAR ESTABLISHED CELL-LINES

HeLa Cells (human cancer cells)

CHO Cells (Chinese hamster ovary cells)

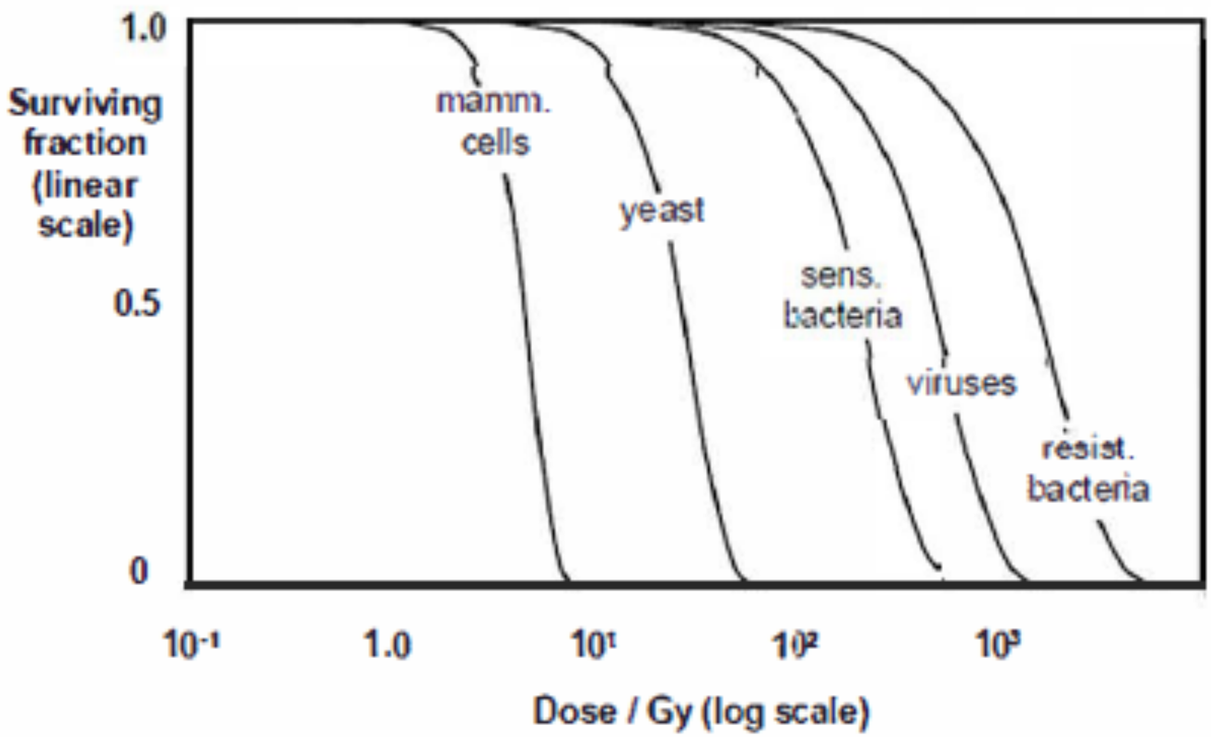
V79 Cells (Chinese hamster lung fibroblast cells)

Culturing Mammalian Cells

tissue → trypsin → single cell suspension → seeding →(medium+incubation) →crisis →established

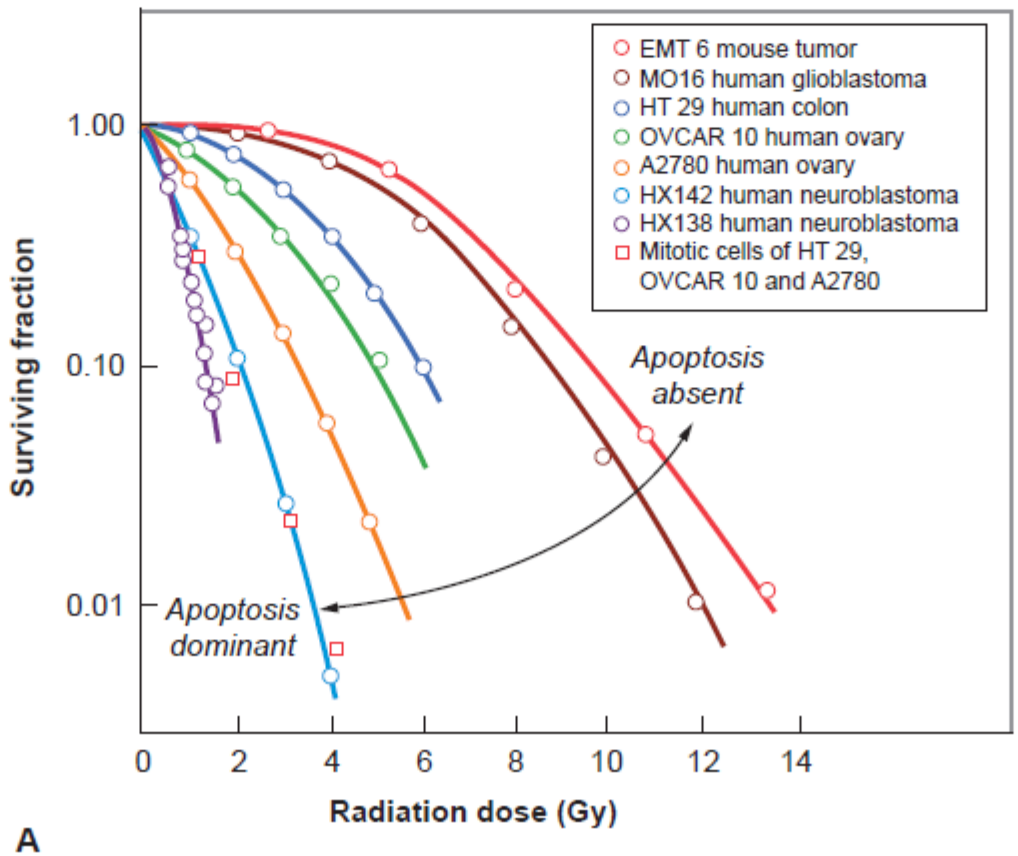
3. Cell Survival Curves

Survival and radiosensitivity in various systems



3. Cell Survival Curves

FIGURE 3.8 **A:** Compilation of survival curves for asynchronous cultures of several cell lines of human and rodent origin. Note the wide range of radiosensitivity (most notably the size of the shoulder) between mouse EMT6 cells, the most resistant, and two neuroblastoma cell lines of human origin (the most sensitive). The cell survival curve for mitotic cells is very steep, and there is little difference in radiosensitivity for cell lines that are very different in asynchronous culture. (Data compiled by Dr. J.D. Chapman, Fox Chase Cancer Center, Philadelphia.) **B:** DNA purified from various cell lines (survival curves shown in Fig. 3.8A) 18 hours after irradiation with 10 Gy and electrophoresed for 90 minutes at 6 V/cm. Note the broad variation in the amount of "laddering"—which is characteristic of an apoptotic



3. Cell Survival Curves

Linear-Quadratic Model

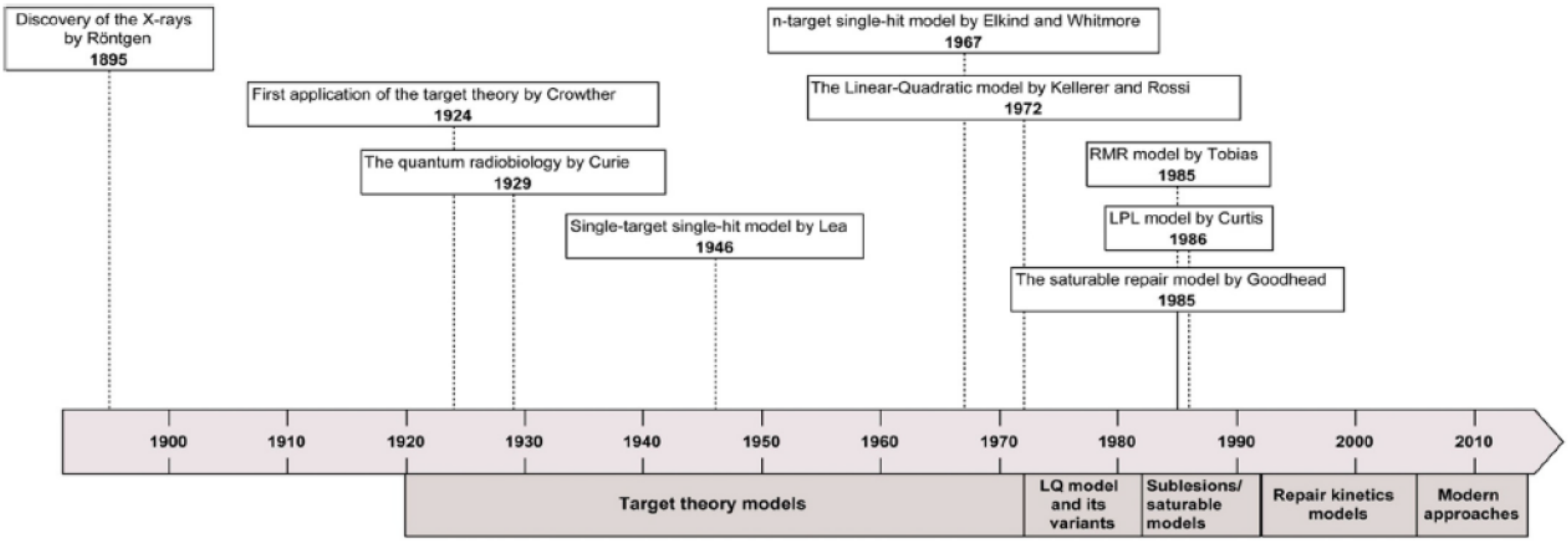


Fig. 1. Historical synopsis related to the cell survival models and their variants.

3. Cell Survival Curves

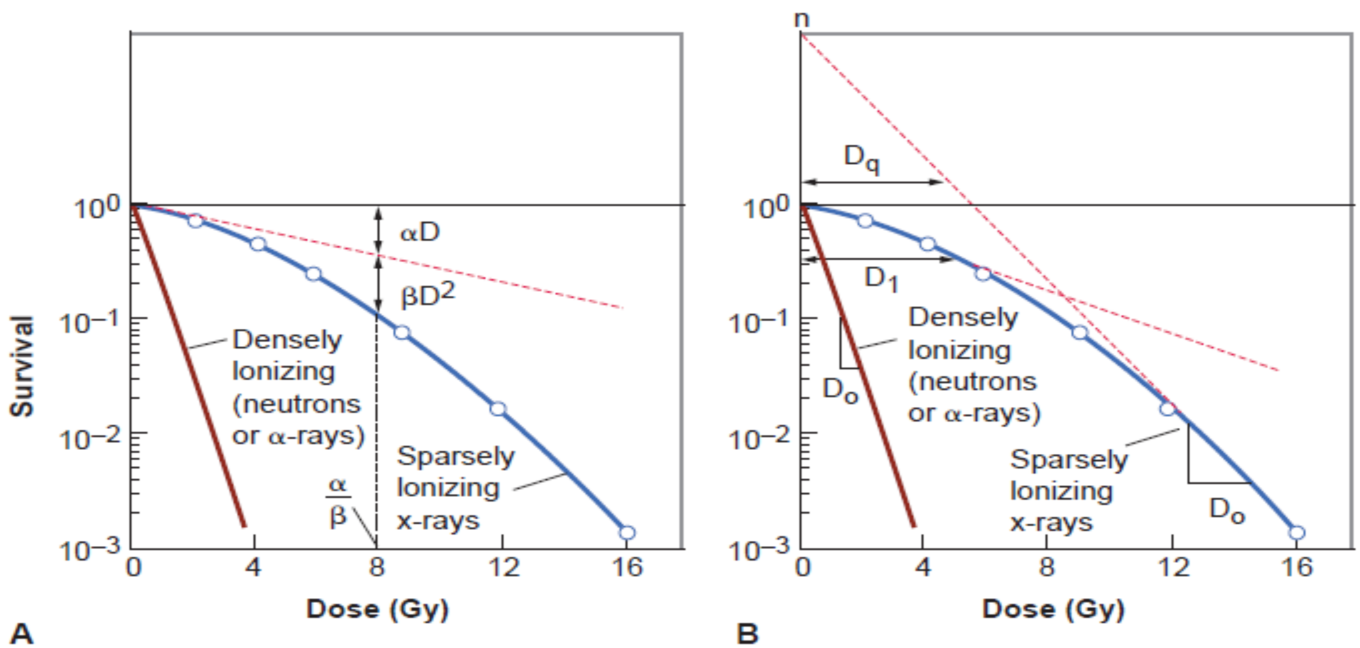
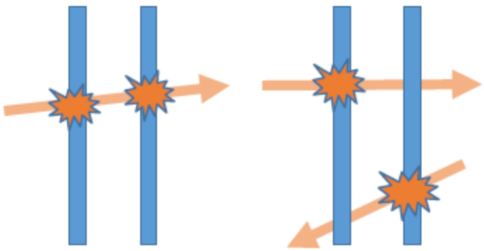


FIGURE 3.3 Shape of survival curve for mammalian cells exposed to radiation. The fraction of cells surviving is plotted on a logarithmic scale against dose on a linear scale. For α-particles or low-energy neutrons (said to be densely ionizing), the dose-response curve is a straight line from the origin (i.e., survival is an exponential function of dose). The survival curve can be described by just one parameter, the slope. For x- or γ-rays (said to be sparsely ionizing), the dose-response curve has an initial linear slope, followed by a shoulder; at higher doses, the curve tends to become straight again. **A:** The linear quadratic model. The experimental data are fitted to a linear-quadratic function. There are two components of cell killing: One is proportional to dose (αD); the other is proportional to the square of the dose (βD^2). The dose at which the linear and quadratic components are equal is the ratio α/β. The linear-quadratic curve bends continuously but is a good fit to experimental data for the first few decades of survival. **B:** The multitarget model. The curve is described by the initial slope (D_1), the final slope (D_0), and a parameter that represents the width of the shoulder, either n or D_q.

Linear-Quadratic-Model (LQM)

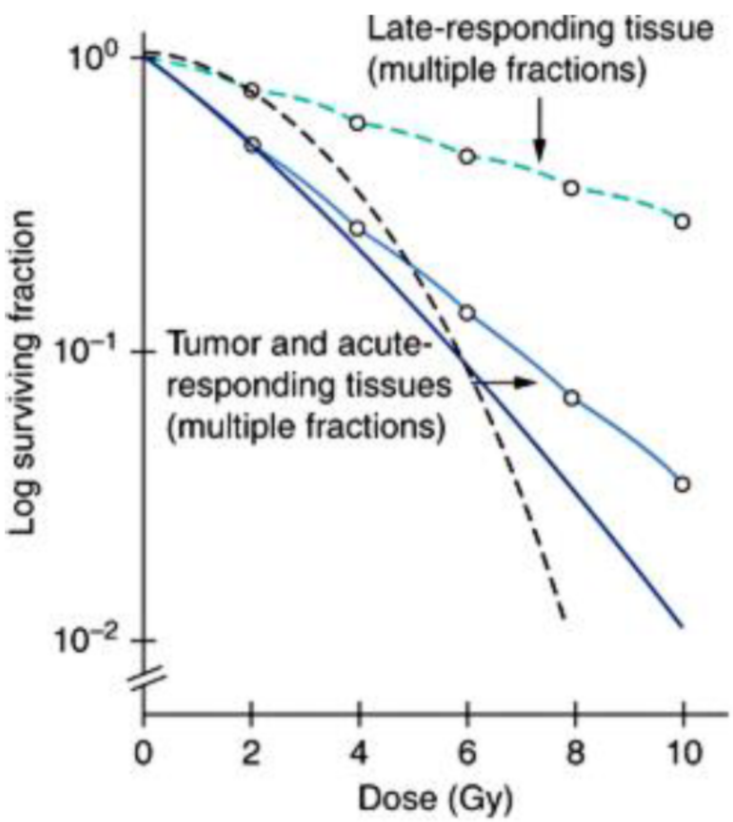
- Assumptions:
  - DSB = Lethal Event
  - DSBs can occur after single hit or two independent hits
  - Yield of single hit DSBs (Y_S) scales linearly with Dose
  - Yield of double hit DSBs (Y_D) scales quadraticly with Dose
  - Total Yield Y_{tot} is given by: $Y_s + Y_D = \alpha D + \beta D^2$
  - Distribution of DSB over cells is given by Poisson-Statistics: P(n Hits) = $\frac{Y^n e^{-Y}}{n!}$



Probability of 0 hits (= Survival Fraction) is given by:

$$\text{SF(D)} = \text{P(0 Hits)} = \exp(-Y_{tot}) = \boxed{\exp(-\alpha D - \beta D^2)}$$

2.) Irradiation Pattern in Time



Most malignant cells show reduced repair capacity (i.e. higher α/β values) compared to healthy cells

Strategy of <u>Fractionation</u>

<u>Prerequisits for „classical“ LQM Fract. </u>:

- Range of Dose ≈1.5-8 Gy per Fx
- Complete Repair (>8-10h break)
- No repopulation between Fx

Corresponding LQM-Extensions available

4. Radiosensitivity and Cell Cycle Dependence

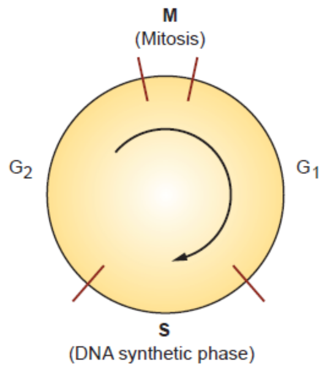
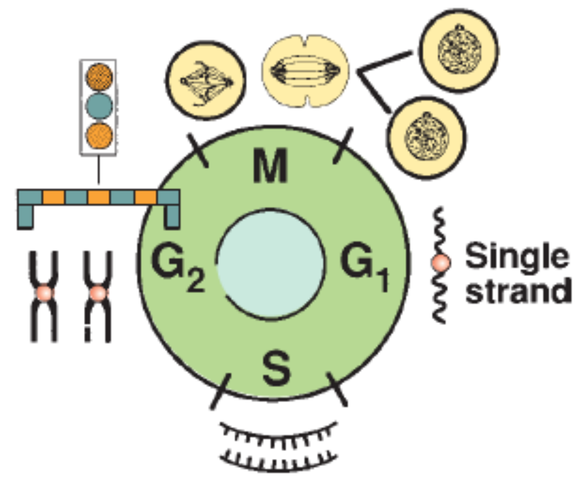
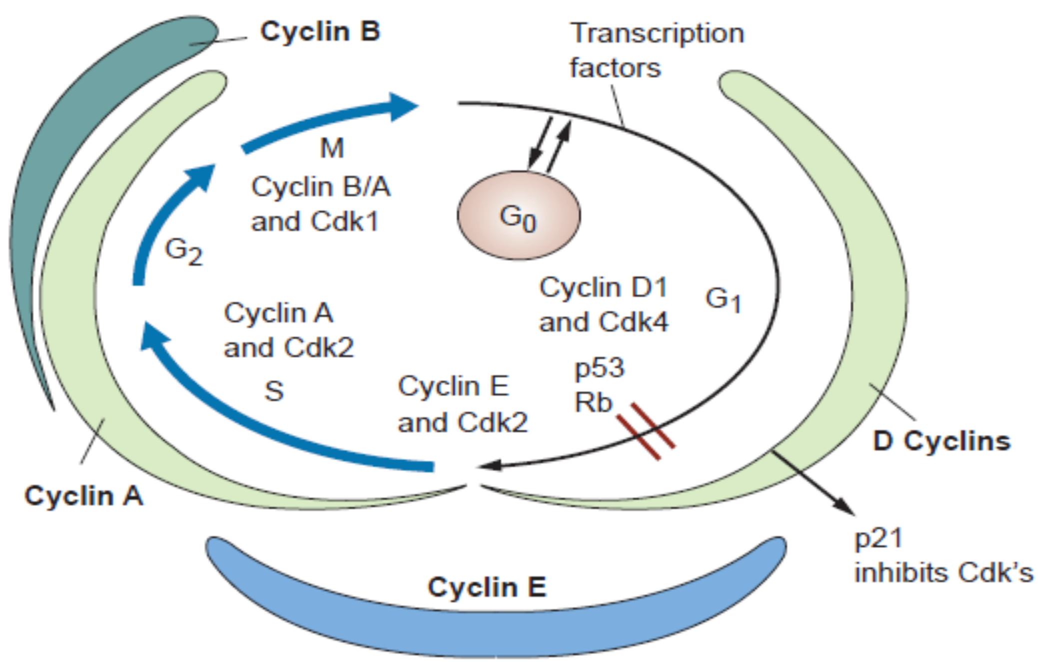
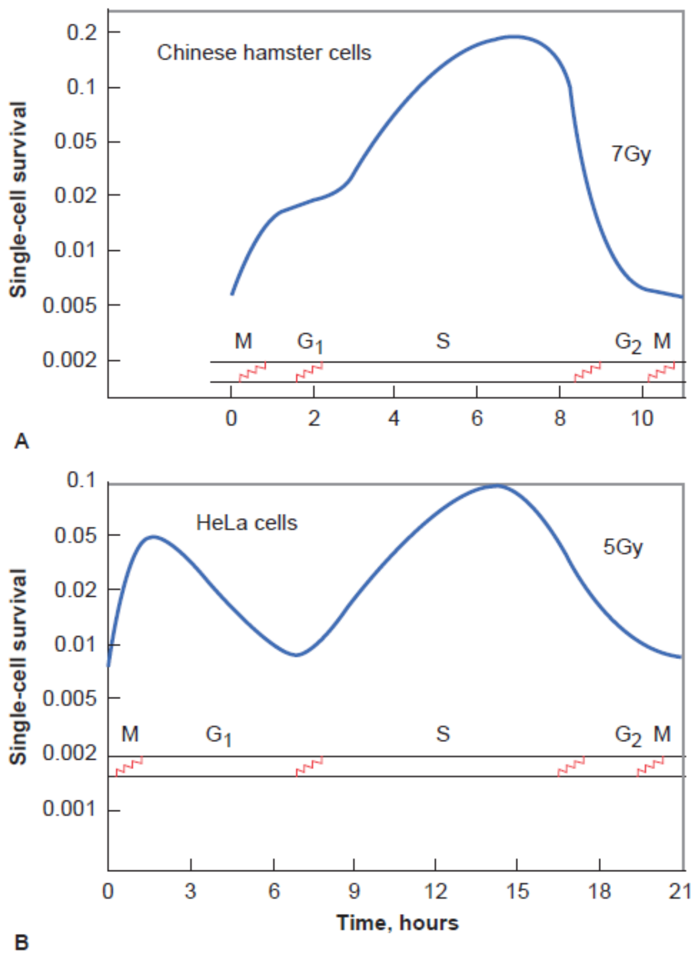


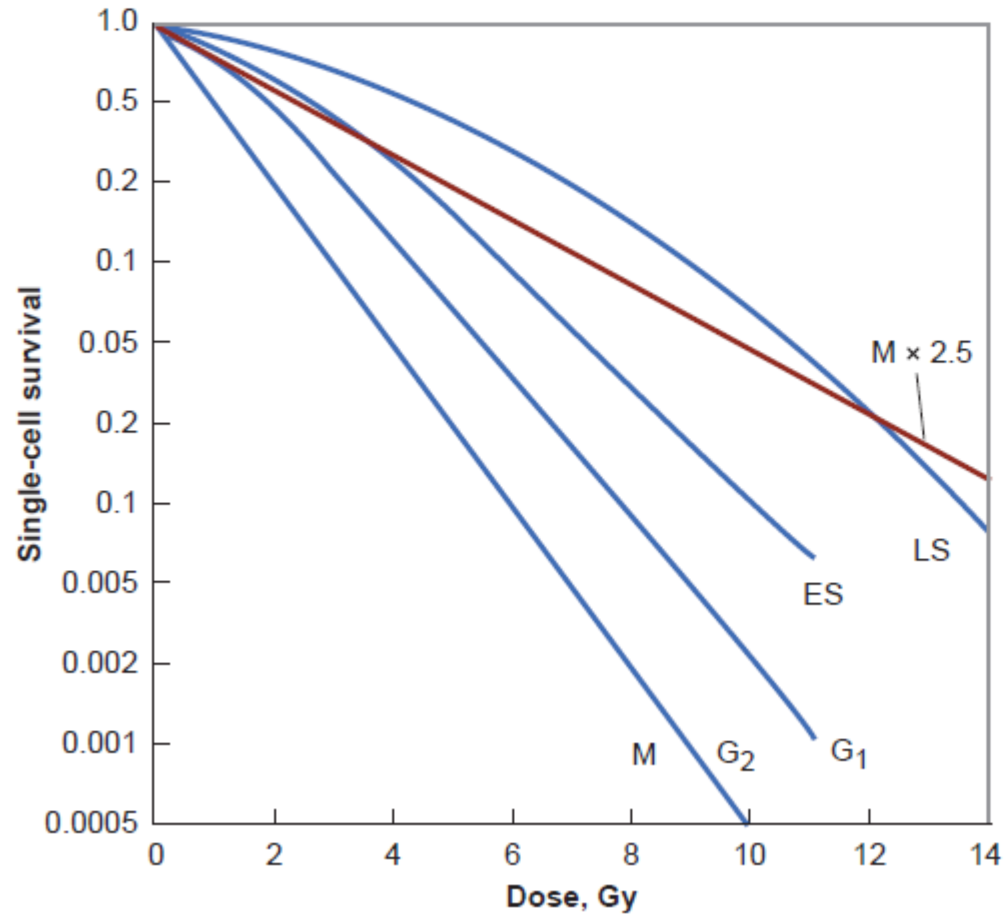
FIGURE 4.1 The stages of the mitotic cycle for actively growing mammalian cells. M, mitosis; S, DNA synthetic phase; G_1 and G_2, "gaps," or periods of apparent inactivity between the major discernible events in the cycle.





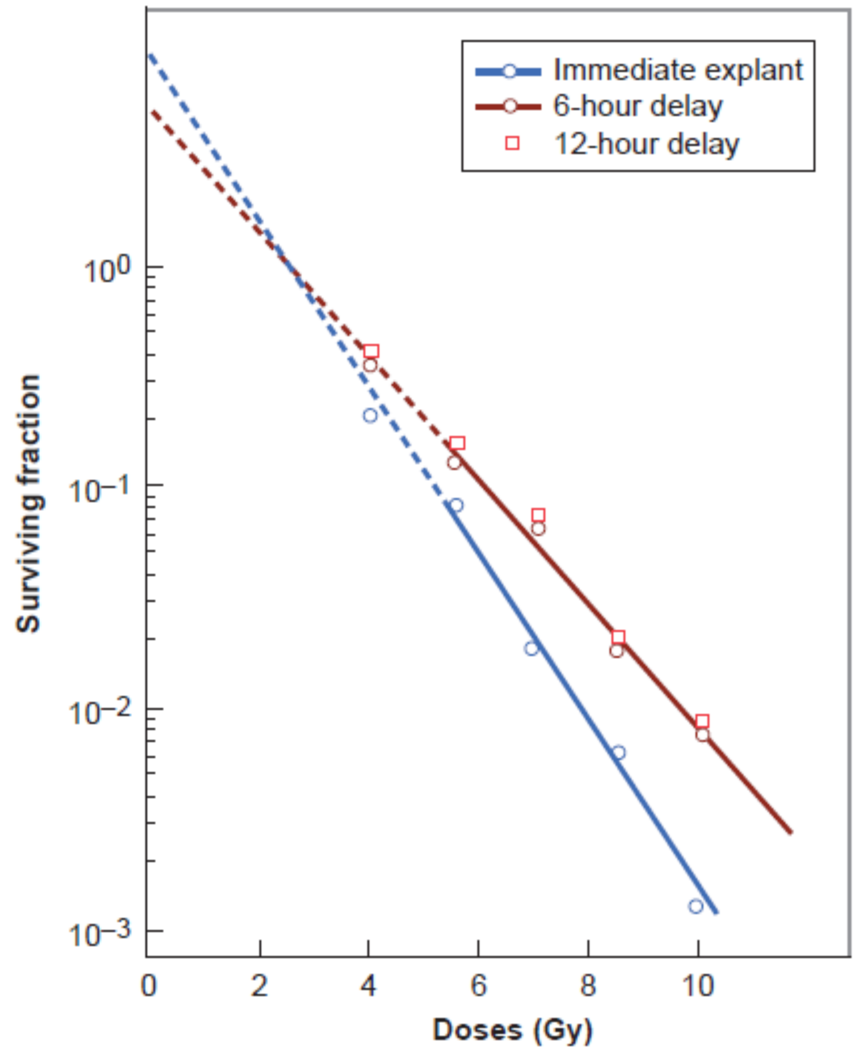
4. Radiosensitivity and Cell Cycle Dependence





5. Fractionated Radiation and Dose Rate Effects

FIGURE 5.1 X-ray survival curves for density-inhibited stationary-phase cells, subcultured (trypsinized and plated) either immediately or 6 or 12 hours after irradiation. Cell survival is enhanced if cells are left in the stationary phase after irradiation, allowing time for the repair of potentially lethal damage. (Adapted from Little JB, Hahn GM, Frindel E, et al. Repair of potentially lethal radiation damage in vitro and in vivo. *Radiology.* 1973;106:689–694, with permission.)



5. Fractionated Radiation and Dose Rate Effects

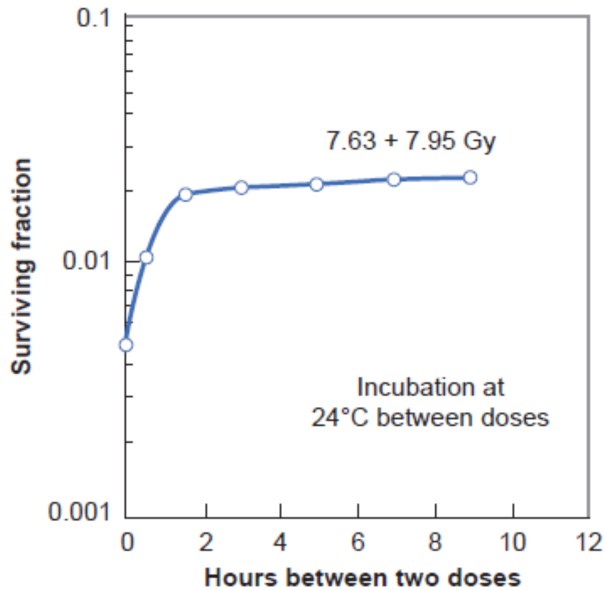


FIGURE 5.3 Survival of Chinese hamster cells exposed to two fractions of x-rays and incubated at room temperature for various time intervals between the two exposures. (Adapted from Elkind MM, Sutton-Gilbert H, Moses WB, Alescio T, Swain RB. Radiation response of mammalian cells in culture: V. Temperature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

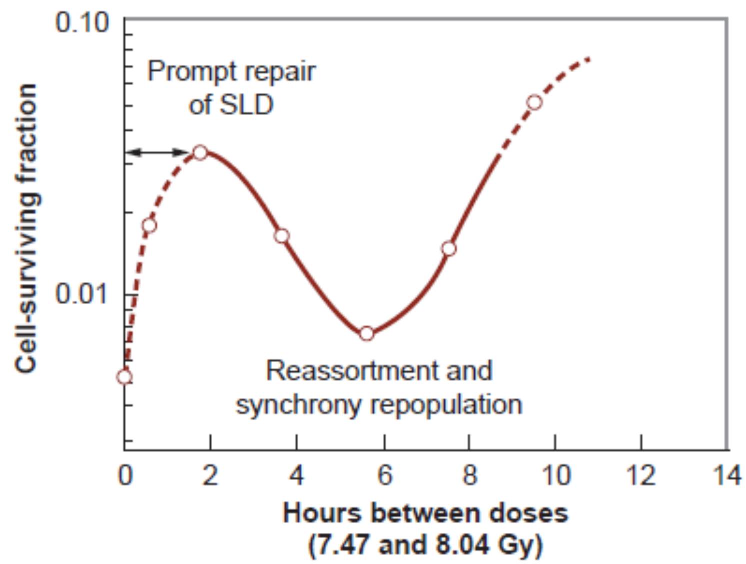
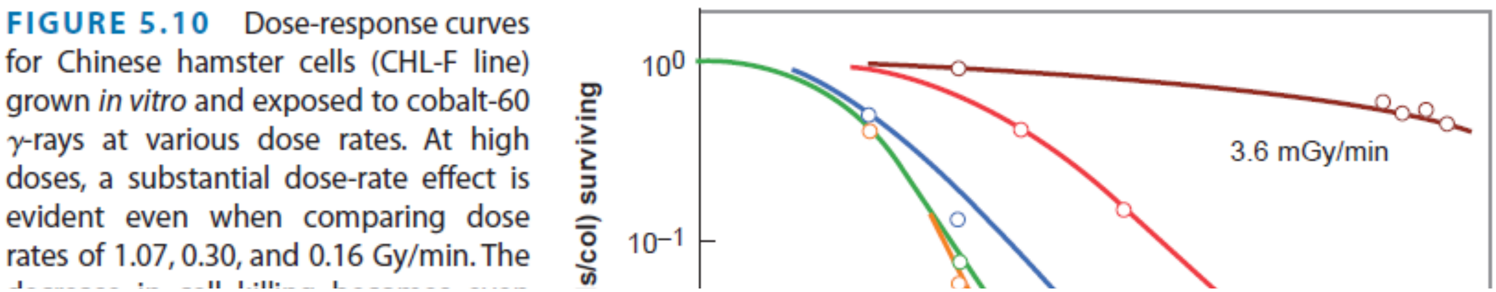
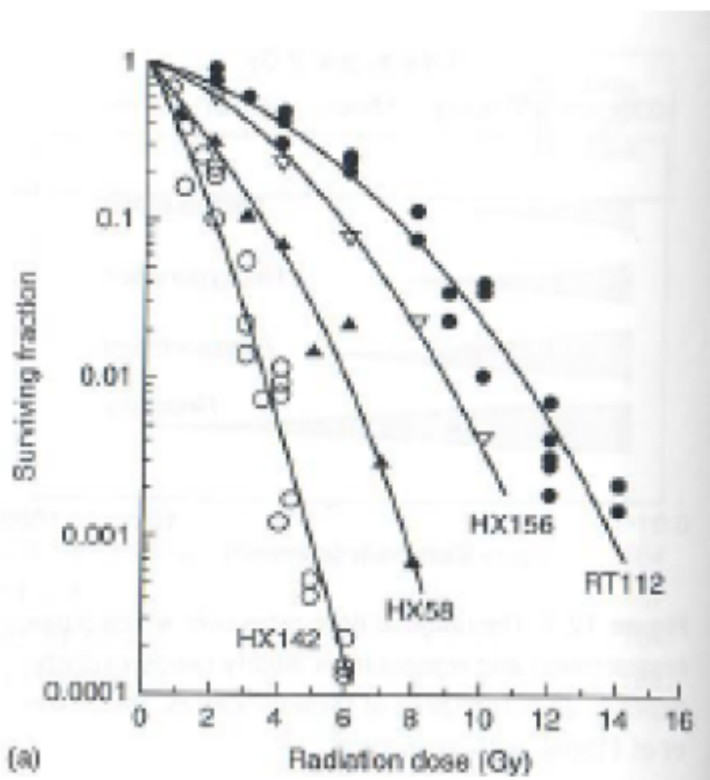


FIGURE 5.4 Survival of Chinese hamster cells exposed to two fractions of x-rays and incubated at 37° C for various time intervals between the two doses. The survivors of the first dose are predominantly in a resistant phase of the cycle (late S). If the interval between doses is about 6 hours, these resistant cells have moved to the G_2M phase, which is sensitive. (Adapted from Elkind MM, Sutton-Gilbert H, Moses WB, et al. 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.* 1965;25:359–376, with permission.)

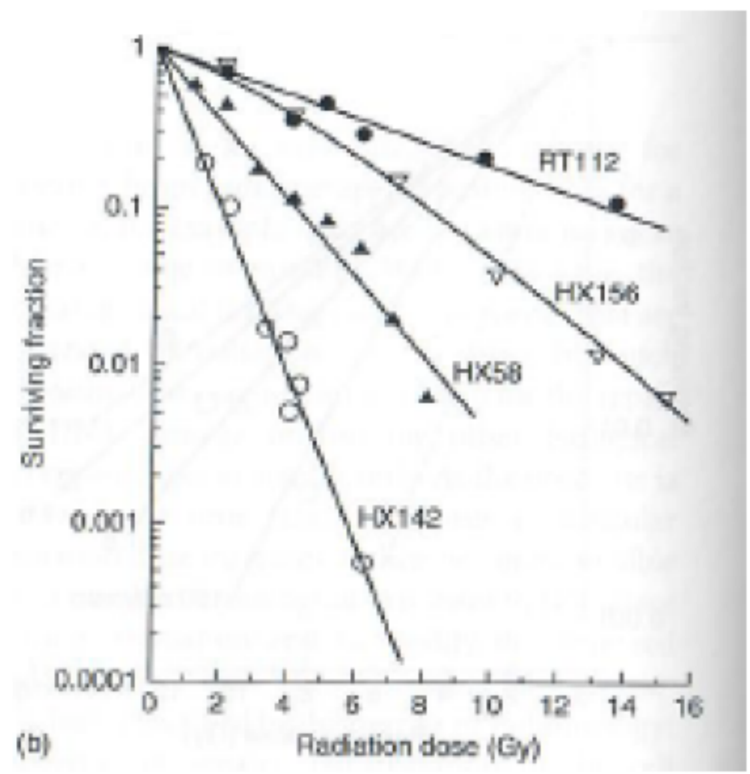
5. Fractionated Radiation and Dose Rate Effects



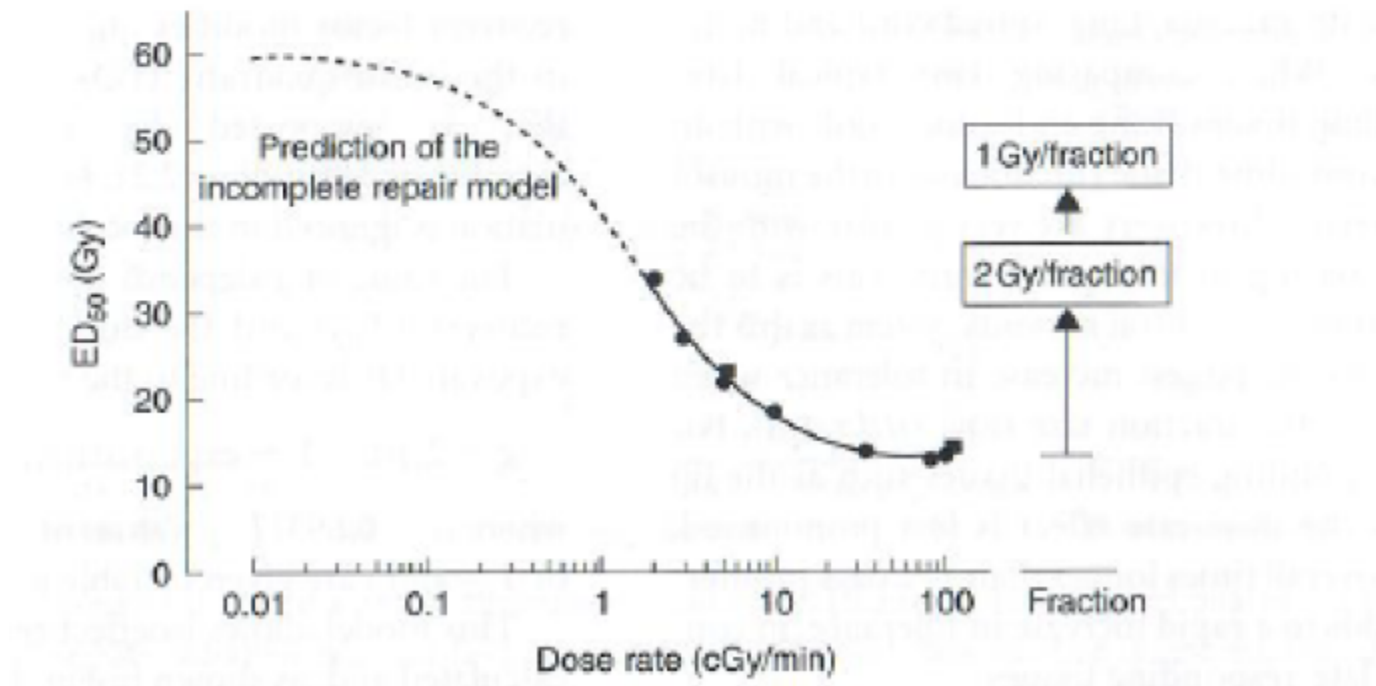
150 cGy/min



1.6 cGy/min



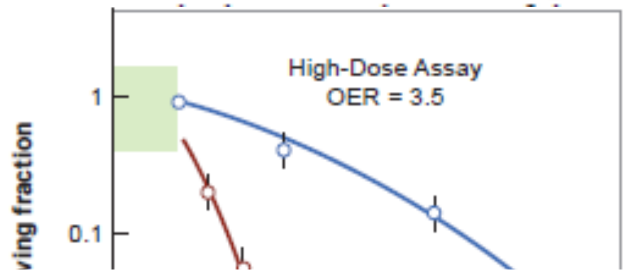
5. Fractionated Radiation and Dose Rate Effects

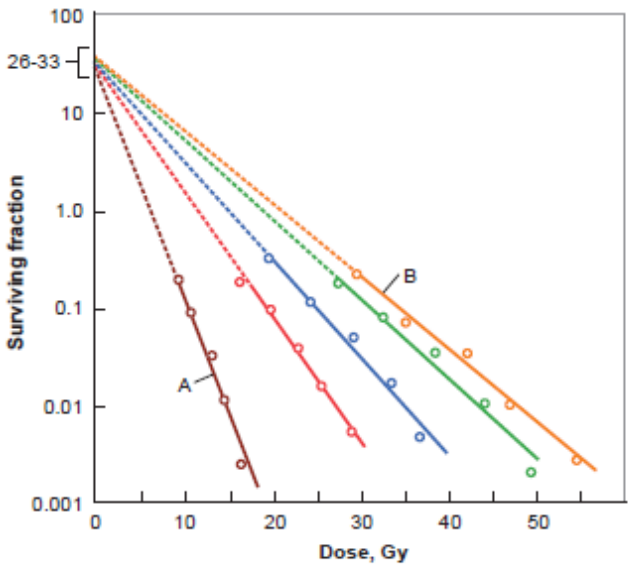


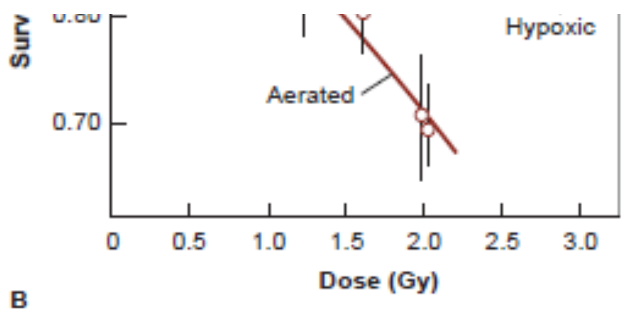
Dose-rate effect for pneumonitis in mice, where ED50 (Effect Dose-50%)

6. Oxygen Effect and Reoxygenation

FIGURE 6.1 Cells are much more sensitive to x-rays in the presence of molecular oxygen than in its absence





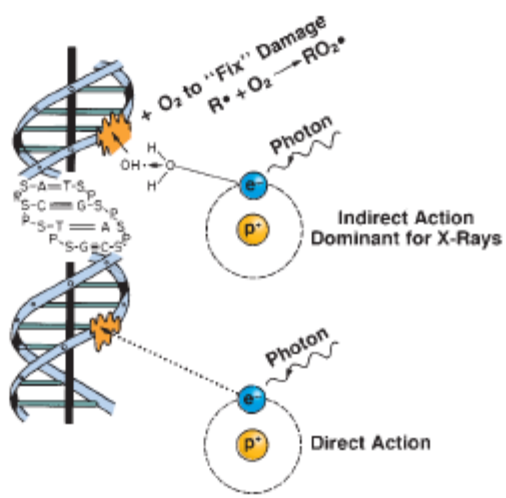


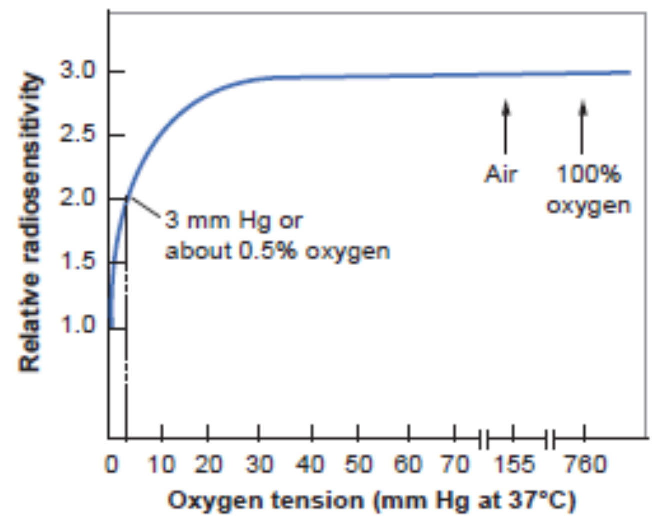
Oxygen is the best known and most general radiation sensitizer.

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

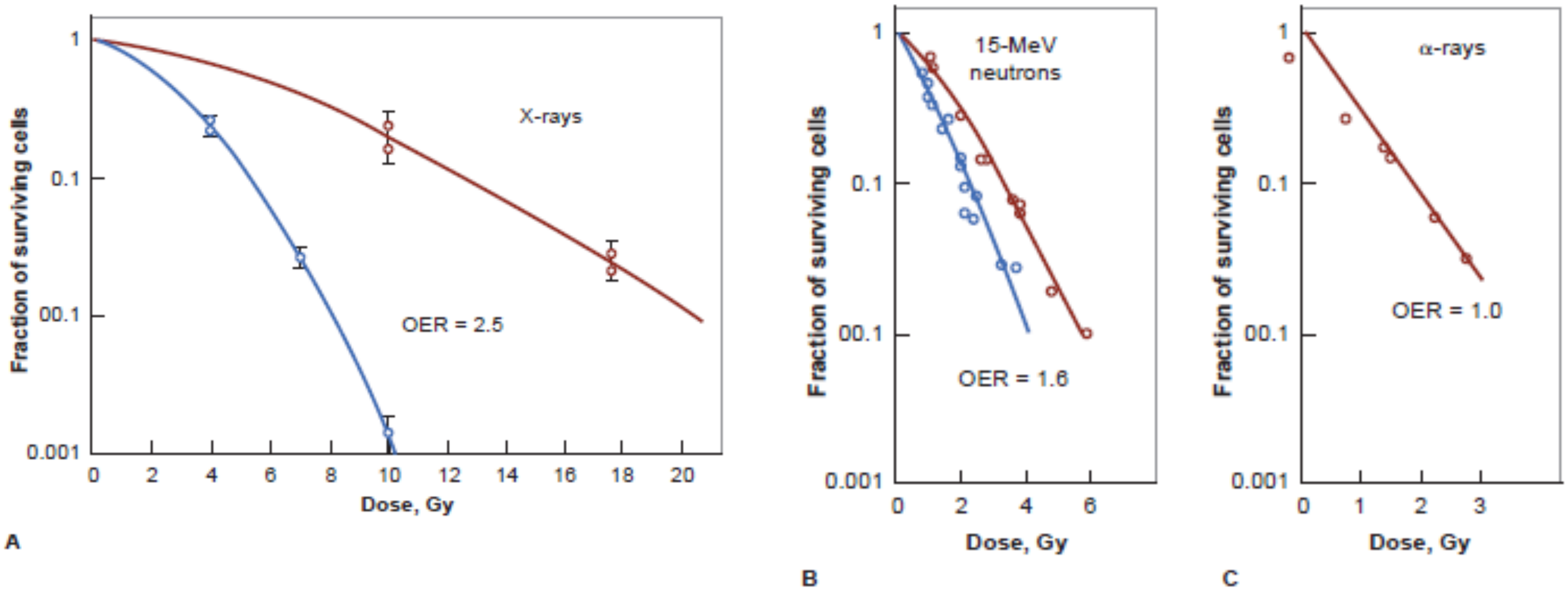
$$OER = \frac{Dose(hypoxia)}{Dose(oxygenated)}$$

<u>Oxygen Fixation Hypothesis (OFH)</u>





6. Oxygen Effect and LET Dependency



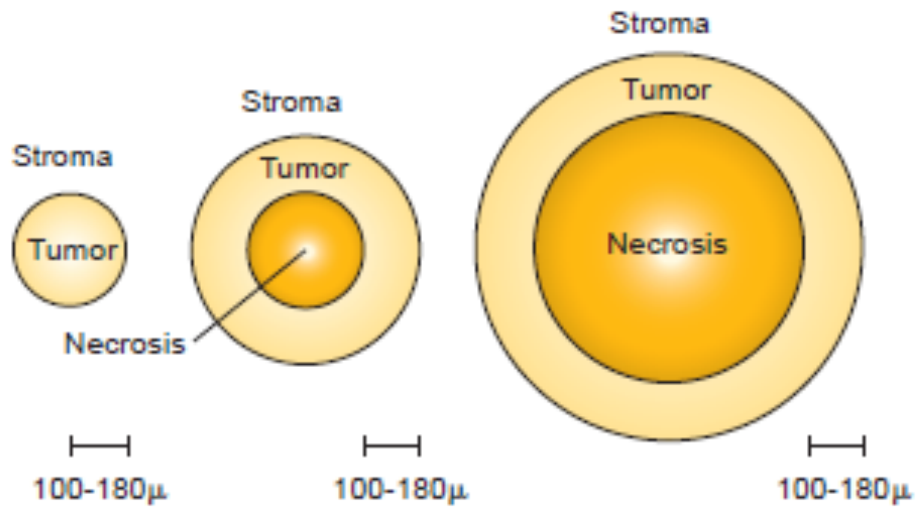
Response to Ionizing Radiation Depends on Radiation Quality

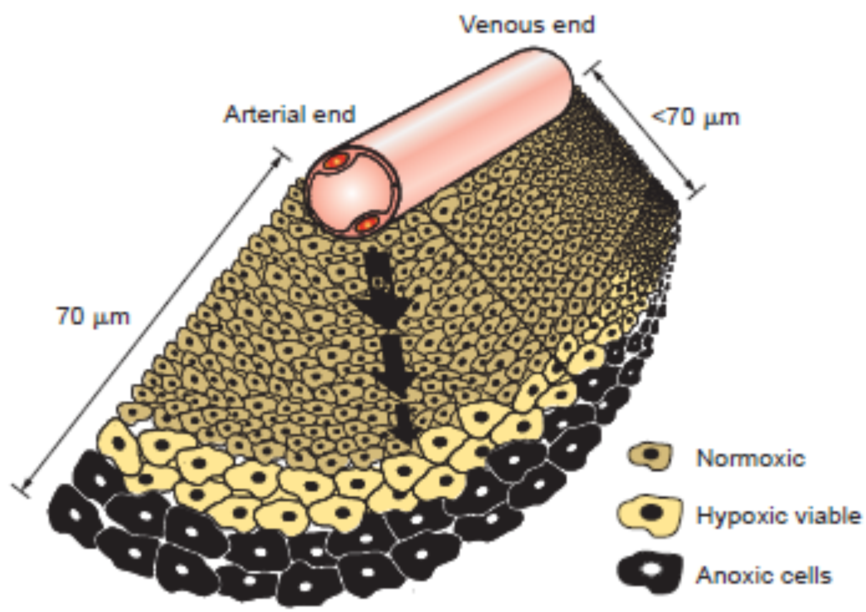
- LET, linear energy transfer = average energy imparted to a medium by a charged particle per unit track length (keV/µm)
  - Low LET: sparsely ionizing (x-rays, γ-rays)
  - High LET: densely ionizing (α-particles, heavy charged ions)

Typical LET Values

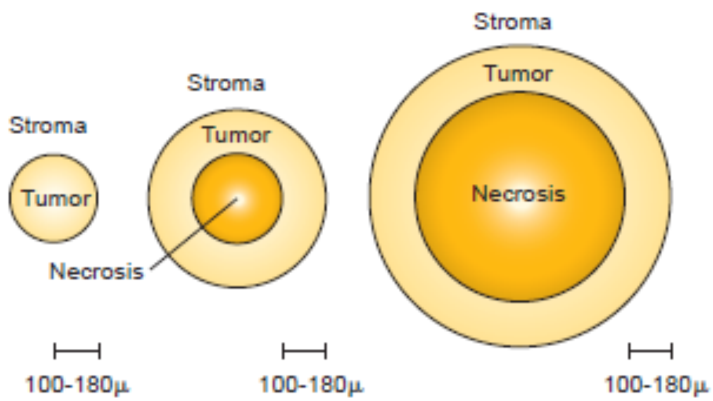
Radiation	LET (keV/µm)
Cobalt-60 γ-rays	0.2
250 kVp X-rays	2.0
10 MeV protons	4.7
150 MeV protons	0.5
14 MeV neutrons	12 (track average)
	100 (energy average)
290 MeV Carbon ions	12
2.5 MeV α-particles	166
2 GeV Iron ions	1,000

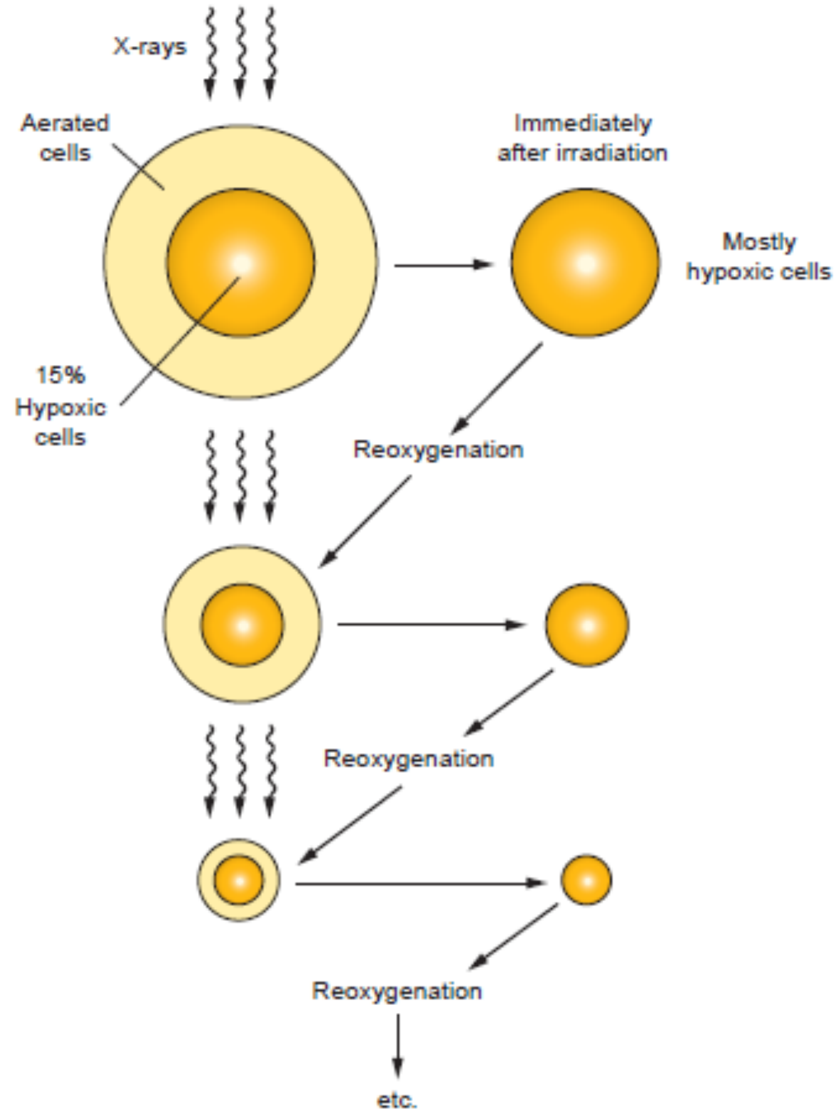
6. Oxygen Effect, Tumor Size abd Vessel Distance





6. Process of Reoxygenation

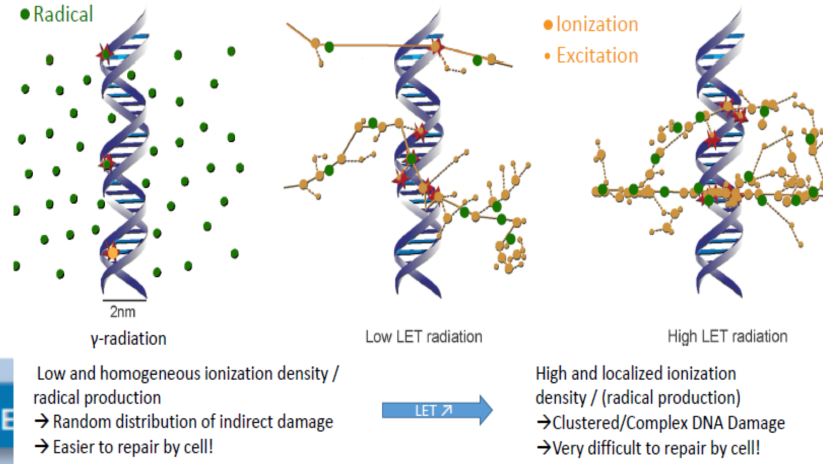




7. Linear Energy Transfer (LET) and RBE

LET: is the average energy locally imparted to the medium per unit length of the track.

LET = dE/dL

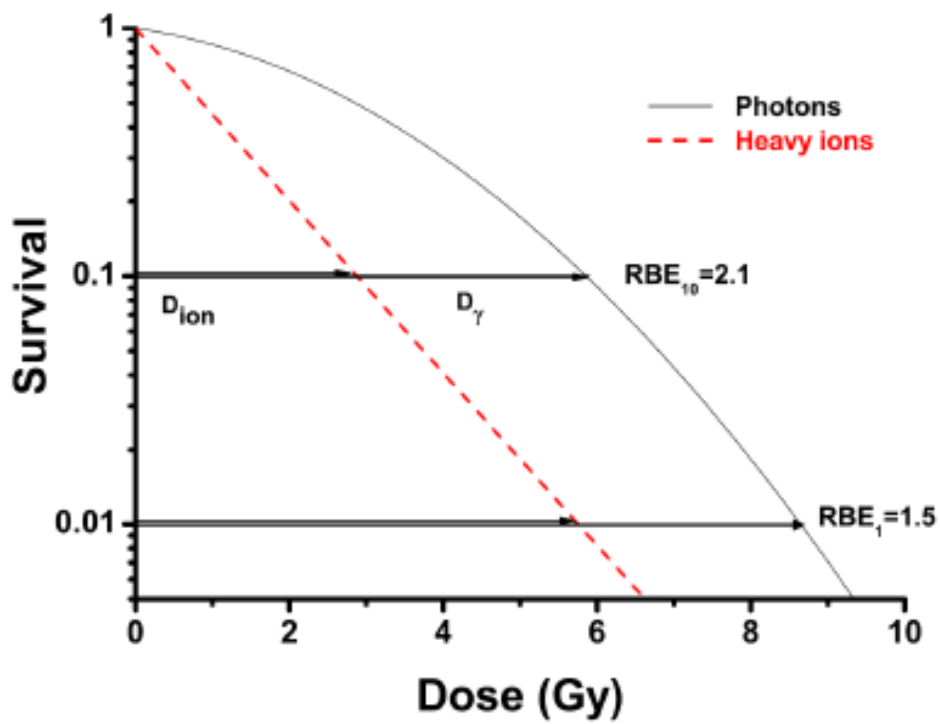


TABLE

Radiation		Linear Energy Transfer, keV/μm
Cobalt-60 γ-rays	—	0.2
250-kV x-rays	—	2.0
10-MeV protons	—	4.7
150-MeV proton	—	0.5
	Track average	—
14-MeV neutrons	12	—
2.5-MeV α-particles	—	166
2-GeV Fe ions (space radiation)	—	1,000

7. Linear Energy Transfer (LET) and RBE

Radiation Type/Quality –Relative Biological Effectiveness (RBE)

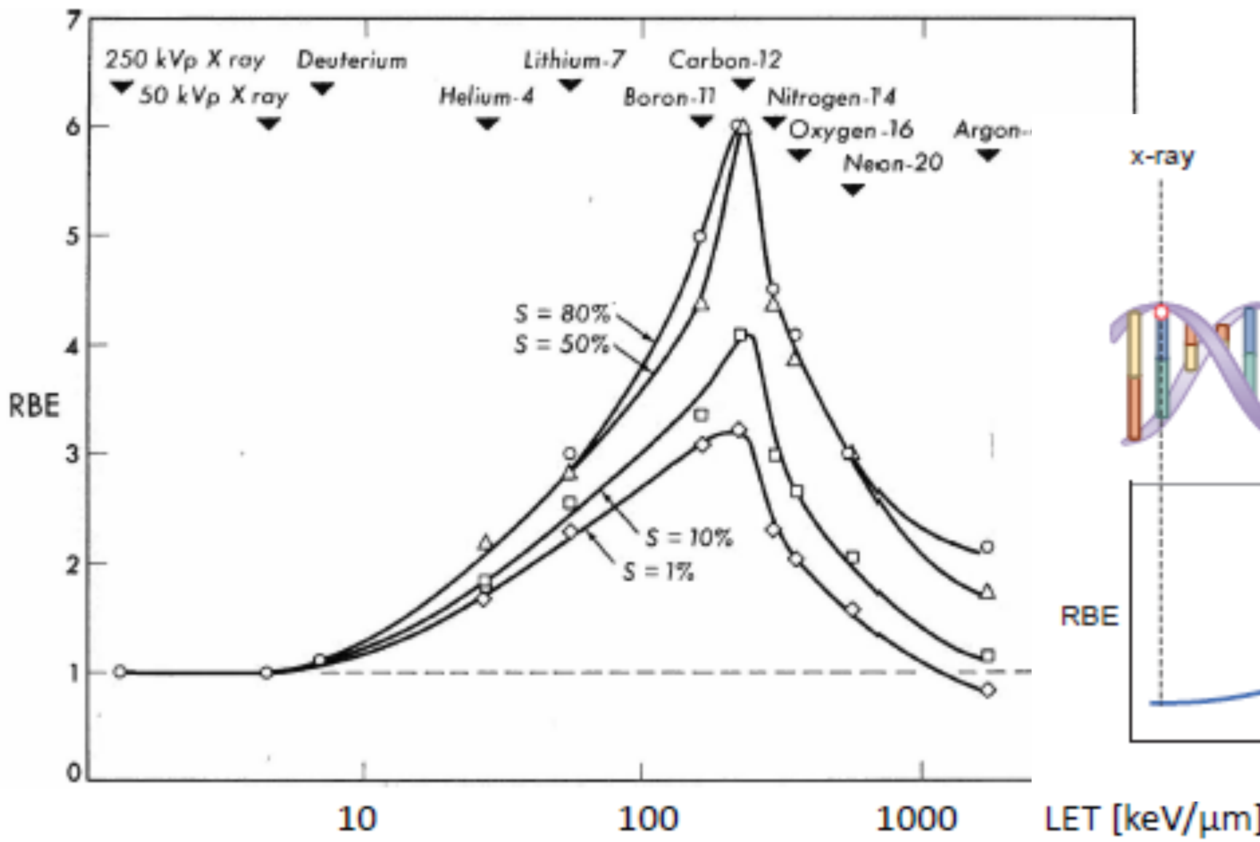


$$RBE = \frac{D_{ref}}{D_{particle}}\bigg|_{iso-effect}$$

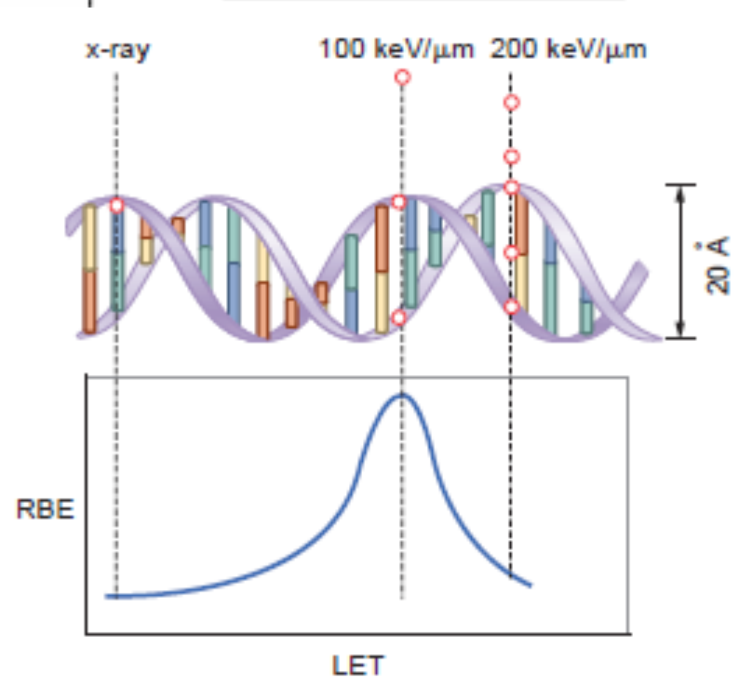
- RBE depends on:
  - Dose
  - Particle Type
  - Cell Line
  - Biological Endpoint
  - LET (Reminder: $LET_\Delta = \frac{dE}{dl}_\Delta$)

7. Linear Energy Transfer (LET) and RBE

Quantitative LET-dependency of RBE



Overkill Effect

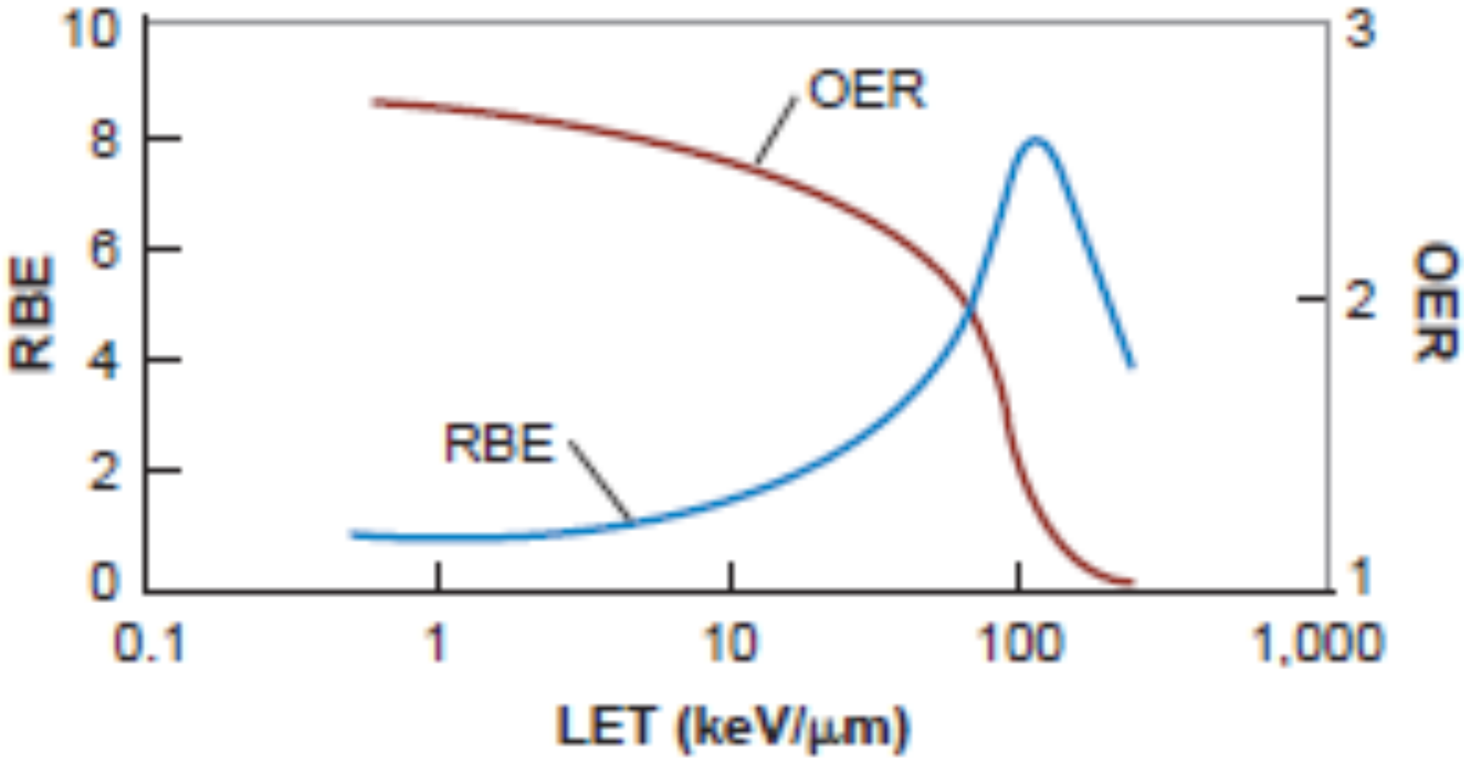


RBE drops after peak due to „Overkill-Effect"

Reminder: $RBE = \left.\frac{D_{ref}}{D_{particle}}\right|_{iso-effect}$

7. Linear Energy Transfer (LET), RBE and OER

OER Dependency on LET



8. Acute Radiation Syndrome

How Is Radiation Measured?

There are several properties of radiation that must be considered when measuring or quantifying radiation. These include the magnitude of radioactivity of the source, the energy of the radiation itself, the amount of radiation in the environment, and the amount of radiation energy that is absorbed. Collectively, these properties determine the nature of the radiation itself. It is very important to understand that equal doses of different kinds of radiation are not equally as damaging. To account for the difference, radiation dose is expressed as "dose equivalent." The following chart summarizes each parameter:

Parameter	Radioactivity	Absorbed Dose	Dose Equivalent*	Exposure (for x-rays and gamma rays only)	Energy
Definition	Rate of radiation emission (transformation or disintegration) from a radioactive substance	Energy imparted by radiation per unit mass onto an absorbing material	Expression of dose in terms of its biological effect	Quantity that expresses the ability of radiation to ionize air and thereby create electric charges that can be collected and measured	The capacity to do work
Common Units Measurement Label	Curie (Ci) 1 Ci = 37 GigaBq (this is a large amount)	rad 1 rad = 100 ergs/g	rem	Roentgen (R)	Joule (J)
International System of Units (SI) Measurement Label	Becquerel (Bq) 1 Bq = 1 event of radiation emission per second (this is a very small amount)	Gray (Gy) 1 Gy = 100 rad	Sievert (Sv) 1Sv = 100 rem (this is a large dose) 1 Gy air dose equivalent = 0.7 Sv 1 R ≈ 10 mSv of tissue dose	Coulomb/kilogram (C/kg) 1 R = 2.58×10^{-4} C/kg air	electronvolts (eV)

*DE = Absorbed Dose × Quality Factor (Q), where Q depends on the type of radiation
Q = 1 for gamma, x-ray, or beta radiation; Q = 20 for alpha radiation

8. Acute Radiation Syndrome

Relationship between effective, equivalent and absorbed doses

Dose Quantities

Absorbed dose

⇩

Energy "deposited" in a kilogram of a substance by radiation

Equivalent dose

⇩

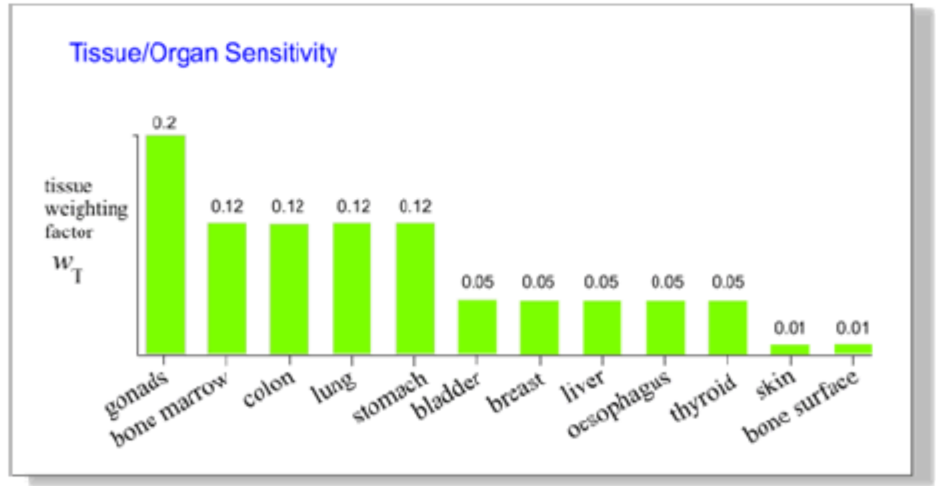
Absorbed dose weighted for the degree of the effect of different radiations (radiation weighting factor w_R)

Effective dose

⇩

Equivalent dose weighted for susceptibility to effect of different tissues (tissue weighting factor w_T)

Tissue weighting factors



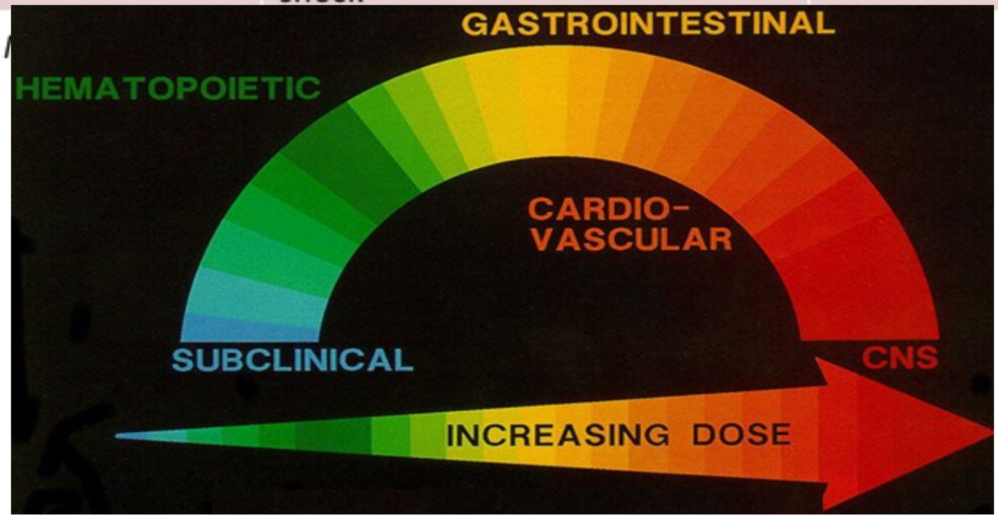
Radiation doses, dose limits and potential

Dose	Limit or Health Effect
More than 5,000 mSv	Dose that may lead to death when received all at once
1,000 mSv	Dose that may cause symptoms of radiation sickness (symptoms include tiredness and nausea) if received within 24 hours
100 mSv	Lowest acute dose known to cause cancer
30–100 mSv	Radiation dose from a full-body computed axial tomography (CAT) scan
50 mSv	Annual radiation dose limit for nuclear energy workers
1.8 mSv	Average annual Canadian natural background dose
1 mSv	Annual public radiation dose limit in Canada
0.1–0.12 mSv	Dose from lung X-ray
0.01 mSv	Dose from dental X-ray
0.01 mSv	Average annual dose due to air travel

Phases of Radiation Injury

Dose (Gy)	Prodromal Phase	Manifest Phase	Prognosis without Supportive Care
0.5–1.0	Mild	Modest decline in blood counts	Survival
1.0–2.0	Mild–moderate	Some bone marrow damage	Survival >90%
2.0–3.5	Moderate	Moderate–severe bone marrow damage	Probable survival
3.5–5.5	Severe	Severe bone marrow damage; modest GI damage	Death within 3.5–6 wk (50% of victims)
5.5–7.5	Severe	Pancytopenia and moderate GI damage	Death probable within 2–3 wk
7.5–10.0	Severe	Severe GI and bone marrow damage	Death probable within 2 wk
10	Severe	Severe GI damage, radiation-induced lung injury, altered mental status; at higher doses (>20.0 Gy), cardiovascular collapse, fever, shock	Death within 2 wk

Ann Intern



Acute Radiation Syndrome

LD50/60 = 4 Gy

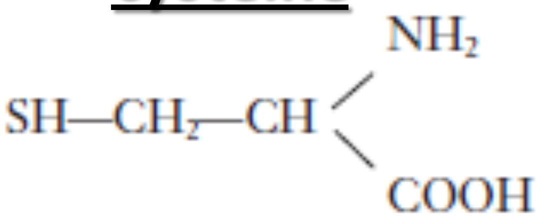
Symptoms and treatment strategy		Mild (1-2Gy)	Moderate (2-4Gy)	Severe (4-6Gy)	Very severe (6-8Gy)	Lethal (a) (>8Gy)
Vomiting	Onset Incidence	After 2 hrs 10-50%	After 1-2 hrs 70-90%	Within 1hr 100%	Within 30 min 100%	Within 10 min 100%
Diarrhea	Onset Incidence	None - -	None - -	Mild 3-8hrs <10%	Heavy 1-3hrs >10%	Heavy within minutes-1hr almost 100%
Headache	Onset Incidence	Slight - -	Mild - -	Moderate 4-24hrs 50%	Severe 3-4hrs 80%	Severe 1-2hrs 80-90%
Consciousness	Onset Incidence	Alert - -	Alert - -	Alert - -	Possibility of impairment - -	Unconsciousness by order of seconds or minutes Seconds-minutes 100% (>50Gy)
Body Temperature	Onset Incidence	Normal - -	Increased 1-3 hrs 10-80%	Fever 1-2 hrs 80-100%	High fever < 1 hrs 100%	High fever < 1 hrs 100%
Treatment Strategy		Outpatient observation	Observation at general hospital, treatment at specialized hospital if required	Treatment at specialized hospital	Treatment at specialized hospital	Palliative treatment (a) (advanced medical care including stem cell transplantation)

9. Radioprotectors

DRF=Dose Reduction Factor

$$DRF = \frac{\text{Dose of radiation in the presence of the drug}}{\text{Dose of radiation in the absence of the drug}}$$

cysteine



cysteamine

$SH—CH_2—CH_2—NH_2$

The mechanisms most implicated in SH-mediated cytoprotection include:

1. Free-radical *scavenging* that protects against oxygen-based free radical generation by ionizing radiations or chemotherapy agents such as alkylating agents
2. Hydrogen atom donation to facilitate direct chemical *repair* at sites of DNA damage

10. Radiation Carcinogenesis

FIGURE 10.1 Marie Curie (seated) at work with her daughter, Irene. Both are thought to have died of leukemia as a consequence of the radiation exposure they received during their experiments with radioactivity. (Courtesy of the Austrian Radium Institute and the International Atomic Energy Bulletin.)

TABLE 10.4 Standard Mortality Ratios for All Causes of Death in British Radiologists, 1897–1997

Years	Standard Mortality Ratio
1897–1920	1.75
1921–1935	1.24
1936–1954	1.12
1955–1979	0.71
All post-920	1.04

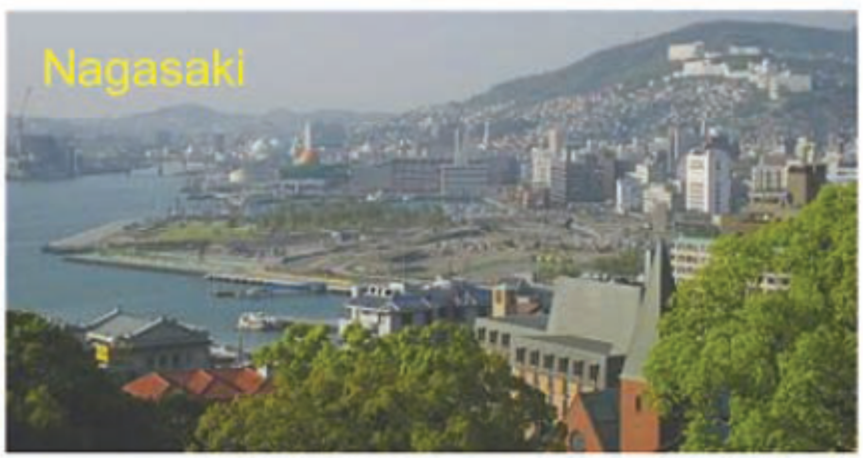
Source: Doll R, Wakeford R. Risk of childhood cancer from fetal irradiation. *Br J Radiol.* 1997;70:130–139.

Radiation Effects

Deterministic effect: severity increases with dose; practical threshold; probability of occurrence increases with dose (e.g., cataract).

Stochastic effect: severity independent of dose; no threshold; probability of occurrence increases with dose (e.g., cancer).

10. Radiation Carcinogenesis



RERF A-Bomb Cohorts

Cohort	Size
Life Span Study	**120,000** Allows an estimate of cancer incidence and mortality
In-Utero Cohort	**3,600** Allows estimates of mental retardation, microcephaly, etc.
Children of exposed individuals	**77,000** Allows estimate of heritable effects

10. Radiation Carcinogenesis

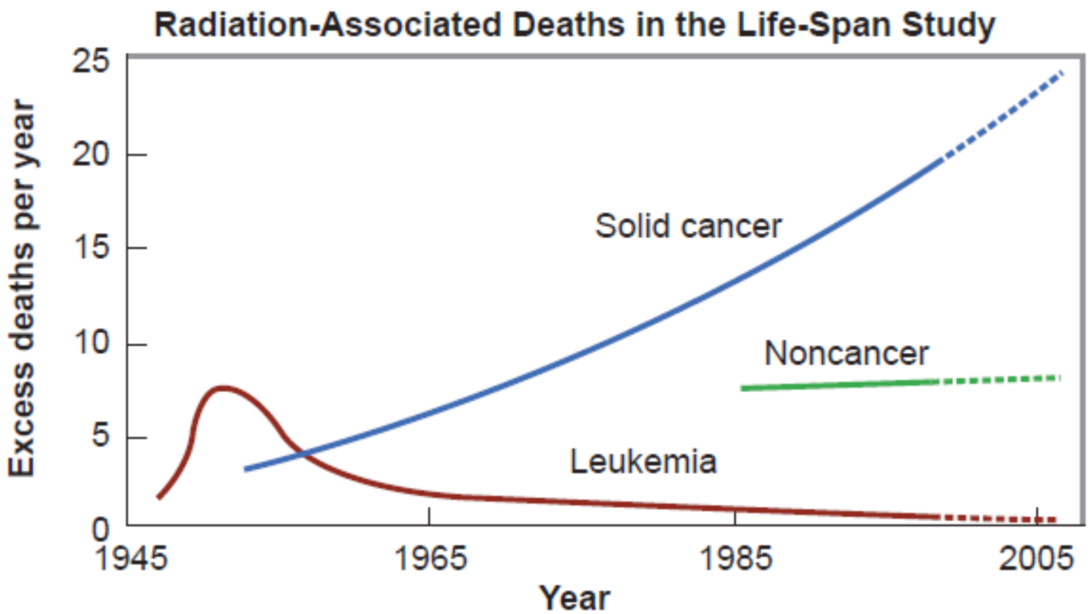


FIGURE 10.7 Illustrating the pattern of radiation-associated deaths in the life span study in the A-bomb survivors. Leukemia appeared first, reaching a peak by 5 to 7 years after irradiation, before falling off later. Solid cancers did not appear in excess for several years, but have continued to increase ever since. By about 1990, it was evident that there is also an excess of noncancer deaths, especially stroke and heart disease. (Courtesy of Dr. Mabuchi.)

10. Radiation Carcinogenesis

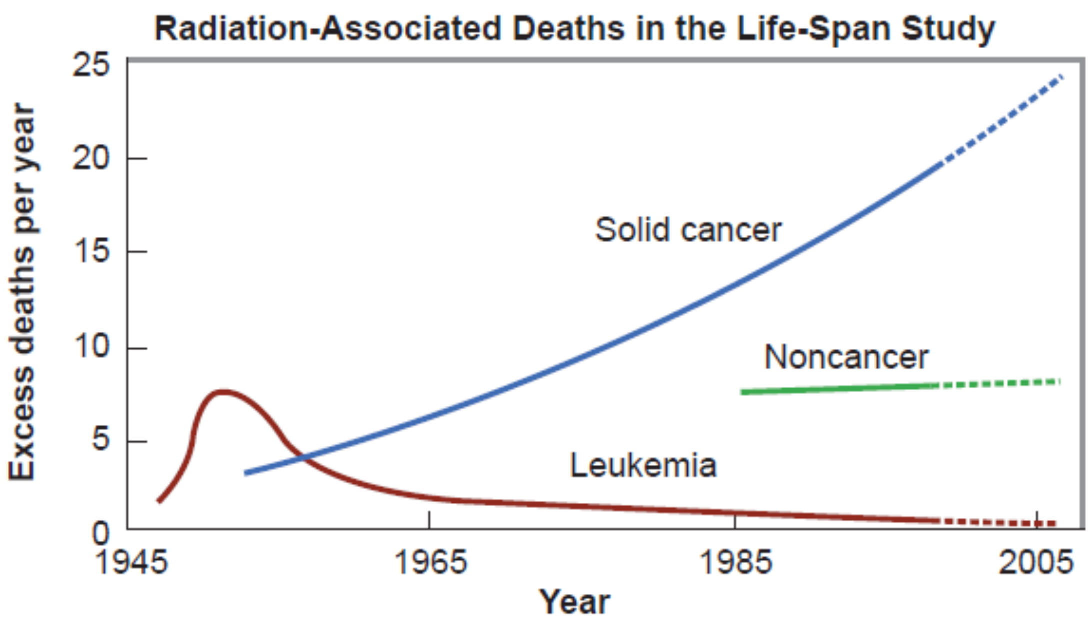
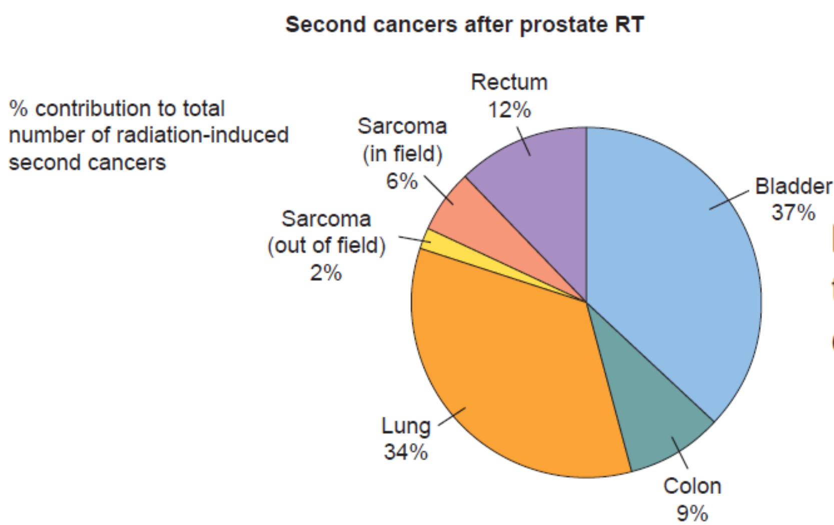


FIGURE 10.7 Illustrating the pattern of radiation-associated deaths in the life span study in the A-bomb survivors. Leukemia appeared first, reaching a peak by 5 to 7 years after irradiation, before falling off later. Solid cancers did not appear in excess for several years, but have continued to increase ever since. By about 1990, it was evident that there is also an excess of noncancer deaths, especially stroke and heart disease. (Courtesy of Dr. Mabuchi.)



Distribution of radiation-induced second cancer at 5+ years postradiotherapy. (Illustration prepared by Dr. David Brenner based on the data from Brenner DJ, Curtis RE, Hall EJ, et al. Second cancers after radiotherapy for prostate cancer. *Cancer.* 2000;88:398–406.)