COLUMBIA UNIVERSITY
COLLEGE OF PHYSICIANS & SURGEONS

DEPARTMENT OF RADIATION ONCOLOGY
CENTER FOR RADIOLOGICAL RESEARCH

RADIATION BIOLOGY
LECTURE OUTLINE

Definition

Types of radiation-induced biological effects:
- Direct effect
- Indirect effect

Effects of radiation on macromolecules

Effects of radiation on cells
- Dose response survival curve
- Cell cycle effect

Modulators of radiation effects
- Relative Biological Effectiveness (RBE)
- Linear Energy Transfer (LET)
- Dose rate, dose fractionation
- Oxygen effect and OER

Radiosensitive and radioresistant tissues in human

Acute effects of whole body irradiation
- Hematopoietic
- Gastrointestinal
- Cerebrovascular

Late effect of radiation exposure
- Mutagenesis
- Carcinogenesis

Risk estimation from medical and environmental exposure to radiation

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RADIATION BIOLOGY is the study of the effects of ionizing Radiation on living organisms.

RADIATION EFFECTS

- DIRECT
  - atoms of the traget become ionized to initiate damages
  - dominant process with high LET radiations such as α-particles
  - cannot be modified by biological or chemical modifiers

- INDIRECT
  - ionized medium releases free radicals to damage critical targets

    $$H_2O \rightleftharpoons H_2O^+ + e^-$$

    $$H_2O^+ + H_2O \rightleftharpoons H_3O^+ + OH\bullet$$

    $$H_2O \rightleftharpoons H\bullet + OH\bullet$$

  - dominant process with low LET radiation such as X-rays
  - can be modulated by chemical sensitizers or protectors

SEQUENCE OF EVENTS IN INDIRECT ACTION

T1/2 in sec	Incident X-ray photons
	↓
10^{-15}	Fast electrons
	↓
	Ion radicals
10^{-5}	↓
	Free radicals
	↓
	macromolecular changes from breakage of chemical bonds
	↓
	Biological effects
days	- cell killing
generations	- mutation
years	- carcinogenesis

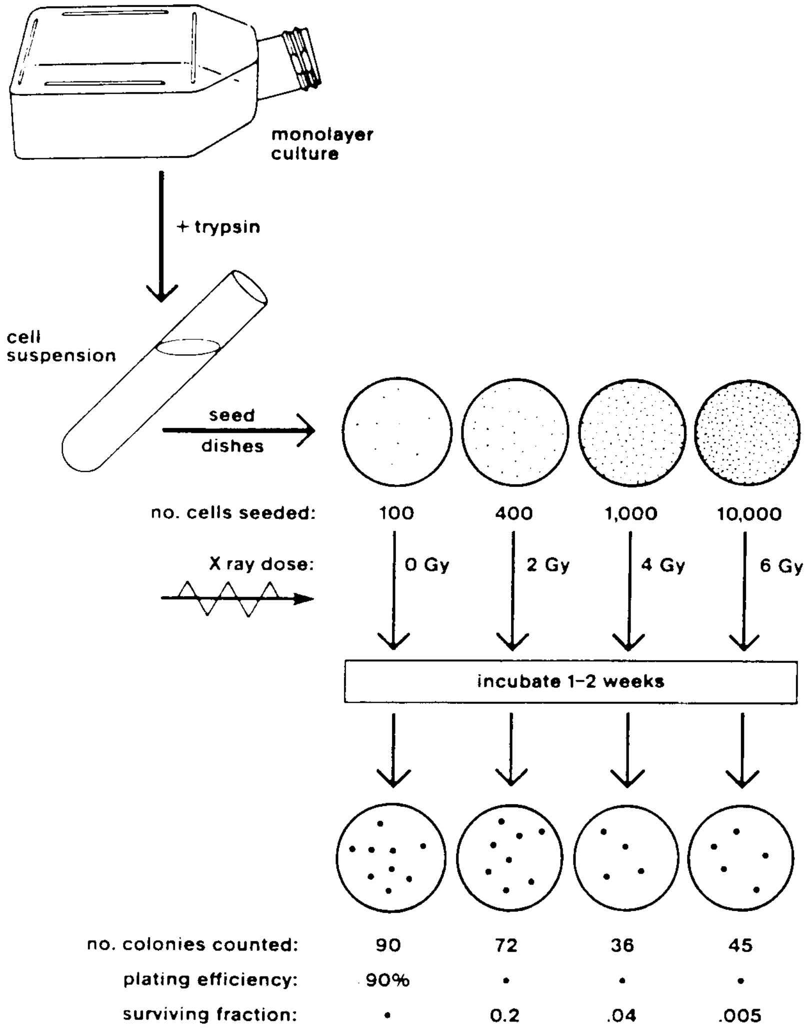


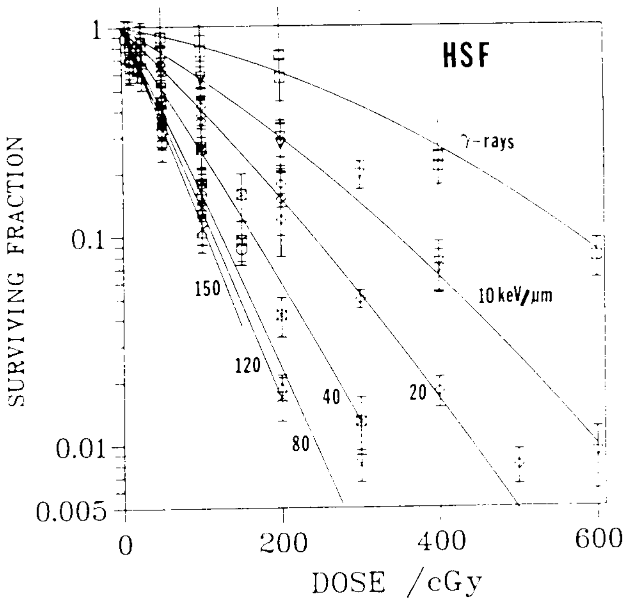
Diagram showing cell culture technique to determine cell survival

RADIATION-INDUCED DOSE RESPONSE SURVIVAL CURVES

$$\text{Plating efficiency} = \frac{\text{Number of colonies formed}}{\text{Number of cells seeded}}$$

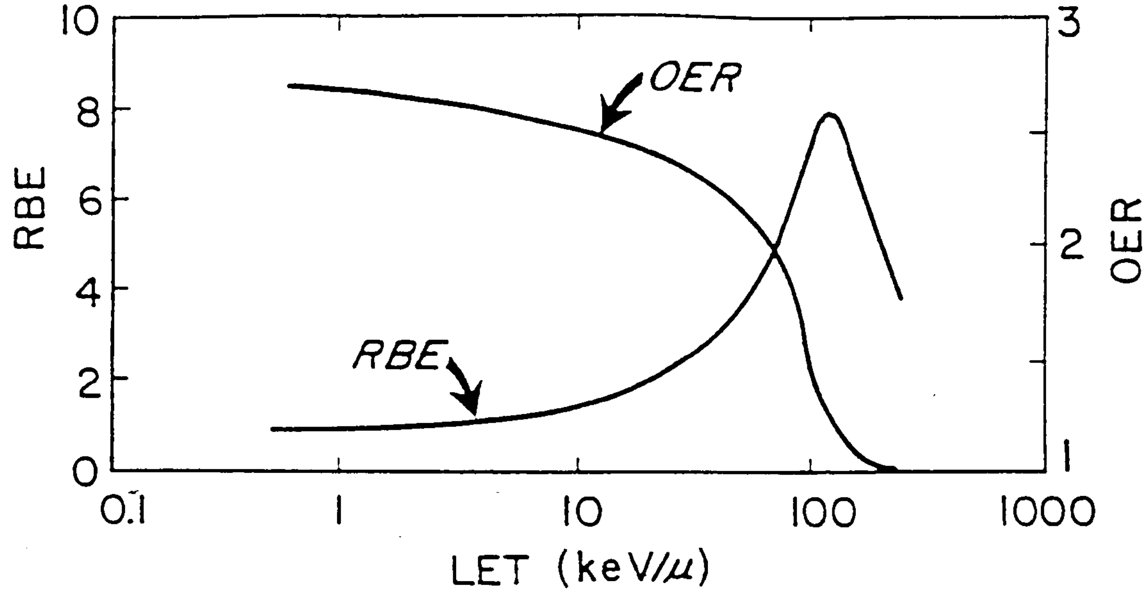
$$\text{Surviving fraction} = \frac{\text{P.E. of treated population}}{\text{P.E. of control population}}$$

Example:

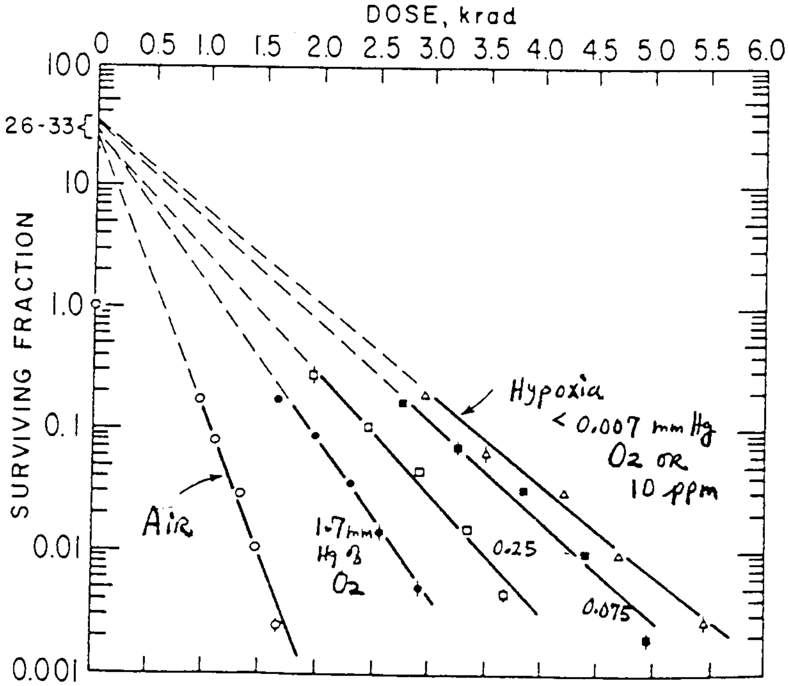


Relative Biological Effectiveness: a term used to describe the biological effectiveness of a particular radiation type relative to low LET radiation such as X-rays or γ-rays. It is defined as the ratio of doses for X- or γ-rays and that of the tested radiation type to produce **equal** biological effect. In the figure above, at a survival level of, say 10%, it takes a 600 cGy dose of γ-rays but, only 100 cGy dose of 150 keV/μm alpha particles to achieve the same killing of human fibroblasts, the RBE is thus 600 cGy/ 100 cGy or ~ 6 at the 10% killing level. As you will see later, the RBE values changes with effect level examined and with LET.

Linear Energy Transfer : a term used to describe the quality of ionizing radiation. It is defined as the energy deposited by that particular radiation type per unit track length as it traverses the irradiated field. The unit is thus keV (energy) per micron (track length). For X-rays, the LET is ~ 2 keV/μm.

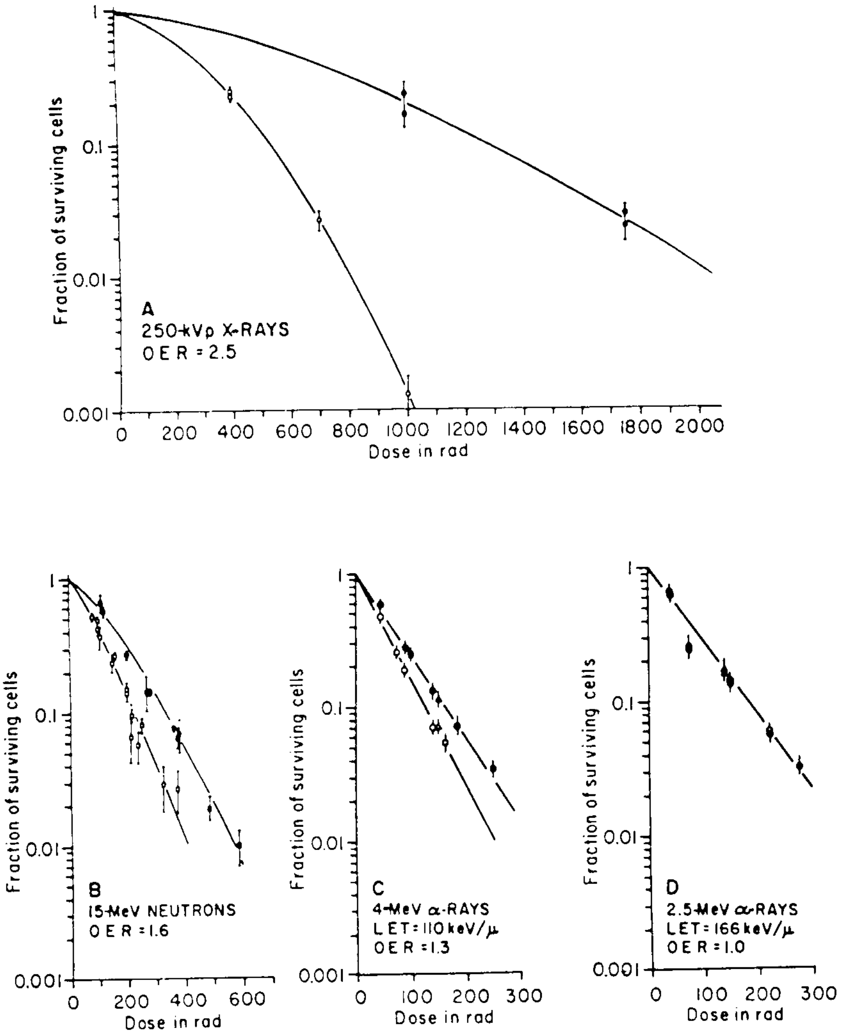


Oxygen Enhancement Ratio: ratio of doses without and with oxygen to produce the same biological effect. For X-rays, the OER at high doses has a value of between 2.5 and 3. For densely ionizing radiation such as α - particles, the OER is 1.



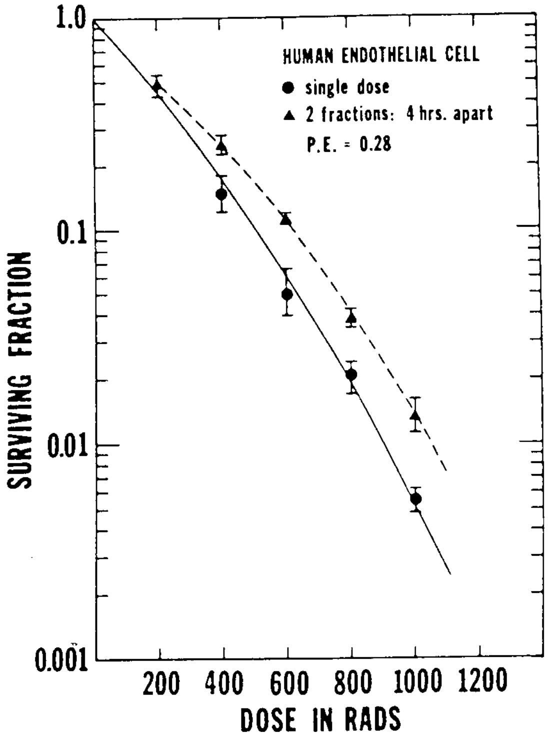
Effects of oxygen tension on survival of CHO cells irradiated with graded doses of X-rays [From Elkind et al. 1965]

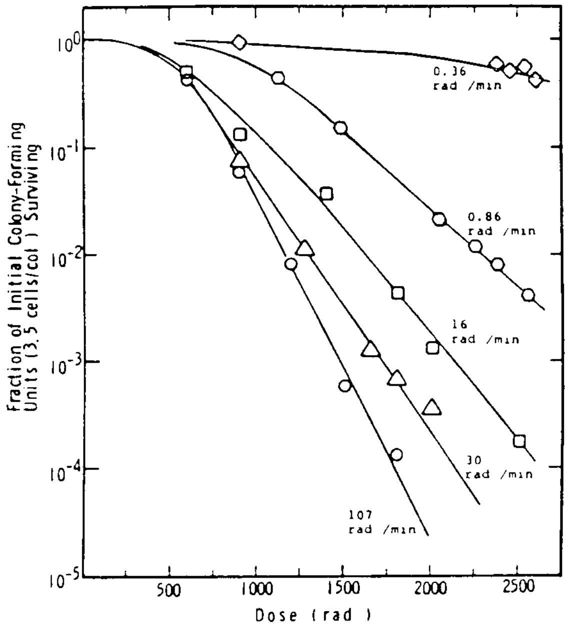
The effectiveness of oxygen in modulating radiosensitivity decreases with increasing LET of the radiation



The biological effectiveness of ionizing radiation decreases with:

1). Dose fractionation
2). Reduce dose rate





Summary of pertinent conclusions

- X- and γ-rays are called sparsely ionizing radiation because the tracks consist of well separated events.

- Alpha particles and neutrons are densely ionizing because the tracks are made up of dense column of ionization.

- LET for γ-rays is around 0.3 keV/μm, 2 keV/μm for X-rays, 80 to 150 keV/μm for radon alpha particles and several thousand keV/μm for galactic heavy ions.

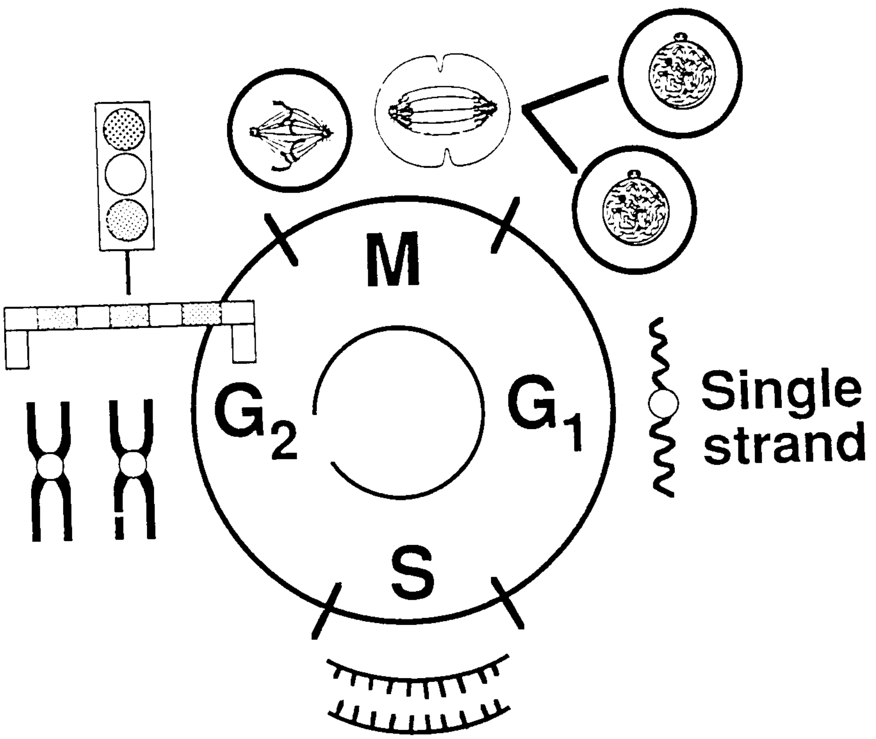
- RBE increases with LET to a maximum at about 100 keV/μm, thereafter decreases with further increase in LET because of overkill.

- In contrast, OER (oxygen enhancement ratio) decreases with increasing LET such that the OER for alpha particles is ~1.

- The RBE values vary according to the tissues and endpoint studied.

- RBE depends on: Radiation quality
  Dose
  Number of fractions
  Endpoint examined
  Dose rate

Cell Cycle and Radiosensitivity



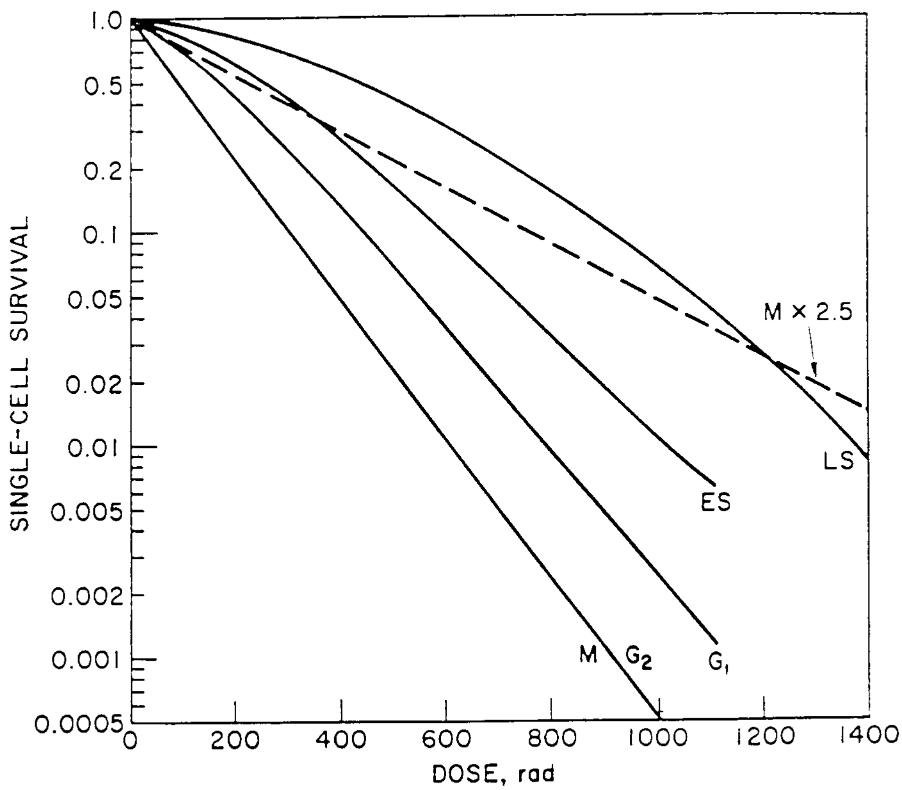


Figure 5–7. Cell-survival curves for Chinese hamster cells at various stages of the cell cycle. The survival curve for cells in mitosis is steep and has no shoulder. The curve for cells late in *S* is shallower and has a large initial shoulder. G_I and early *S* are intermediate in sensitivity. The broken line is a calculated curve expected to apply to mitotic cells under hypoxia. (From Sinclair WK: Radiat Res 33:620–643, 1968)

Categories of Mammalian Cell Radiosensitivity

Cell Type	Properties	Examples	Sensitivity
I. Vegetative intermitotic cells	Divide regularly, no differentiation	Erythroblasts, Intestinal crypt cells, Basal cells of oral mucous membrane	**High**
II. Differentiating intermitotic cells	Divide regularly, some differentiation between division	Spermatocytes, Oocytes, Inner enamel of developing teeth	
III. Connective Tissue	Divide irregularly	Endothelial cells, Fibroblasts	
IV. Reverting post-mitotic cells	Do not divide regularly, variably differentiated	Liver, Pancreas, Salivary glands	
V. Fixed post-mitotic cells	Do not divide, highly differentiated	Neurons, Striated muscle cells	**Low**

Table 17–2. The LD_{50} for Various Species from Mouse to Man and the Relation Between Body Weight and the Number of Cells that Needs to be Transplanted for a Bone Marrow "Rescue"

Species	Average Body Weight in kg	LD_{50} Total-Body Irradiation in Gy	Rescue Dose per kg $\times 10^{-8}$	Relative Hematopoietic Stem Cell Concentration
Mouse	0.025	7	2	10
Rat	0.2	6.75	3	6.7
Rhesus monkey	2.8	5.25	7.5	7.3
Dog	12	3.7	17.5	1.1
Humans	70	4	20	1

(Data from Vriesendorp HM, van Bekkum DW in Broerse JJ, MacVitrie T (eds): Response to Total Body Irradiation in Different Species. Amsterdam. Martinus Nijhoff. 1984)

Acute Radiation Syndrome

- Signs and symptoms experienced by individuals exposed to acute whole body irradiation
- Data collected largely through Japanese atomic bomb survivors at Hiroshima and Nagasaki
- Limited number of accidents at nuclear installations
- Clinical radiotherapy
- Well-characterized animal data base

PRODROMAL RADIATION SYNDROME

- Early symptoms that appear after exposure to whole body radiation:
  gastrointestinal: nausea, vomiting, diarrhea, anorexia
  neuromuscular: easy fatigability
- Effect is dose dependent
  - Varies in time of onset
  - Severity
  - Duration

EARLY LETHAL EFFECTS

Hematopoietic syndrome:

- cause of death at doses < 8 Gy
- peak incidence of death occurs at about 30 days post-irradiation, and continues for up to 60 days
- symptoms associated with hematopoietic syndrome are: chill, fatigue, hemorrhages, ulceration, infection and anemia. Death usually result unless receive bone marrow transplant

Gastrointestinal syndrome:

- occurs at dose >10 Gy of gamma-rays or its equivalence
- death usually occurs within 3 to 10 days
- symptoms due largely to depopulation of the epithelial lining of the GI tract by radiation
- no human has survived radiation dose >10 Gy
- clinical symptoms include nausea, vomiting, and prolong diarrhea, dehydration, loss of weight, complete exhaustion, and eventually death

Cerebrovascular syndrome:

- identified at doses > 100 Gy of gamma-rays
- death occurs within hours from cardiovascular and neuromuscular complications
- clinical manifestations include severe nausea, vomiting within minutes of exposure, disorientation, loss of muscular co-ordination, respiratory distress, seizures, coma and death

Radiation Carcinogenesis

- a stochastic late effect

- no threshold, an all or none effect

- severity is not dose related

- probability of carcinogenesis is dose dependent

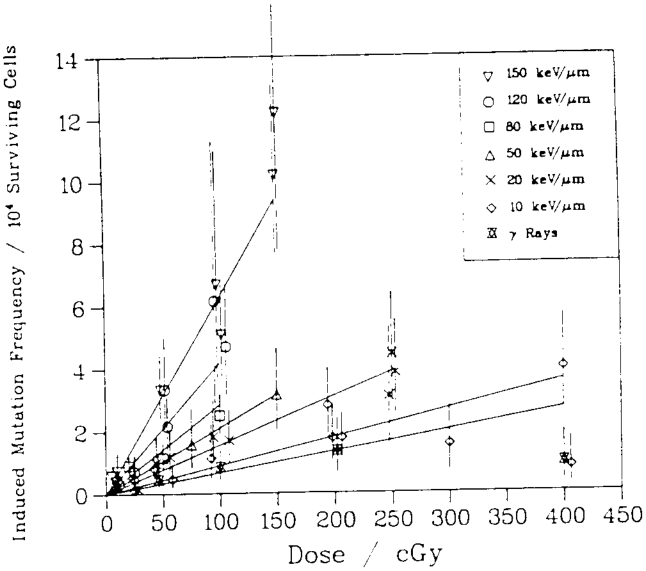
- leukemia has the shortest latency period of ~ 5 years. Sold tumors have a latency period of ~ 20 to 30 years.

- total cancer risk for whole body irradiation is one death per 10^4 individuals exposed to 1 rem

- for every leukemia induced, there are 3 to 4 sarcoma induced in the same irradiated population.

GENETIC EFFFECTS OF RADIATION- MUTAGENESIS

Figure: Dose response mutation induction in human fibroblasts by radiation of different qualities.



-Mutation incidence has no threshold and is a linear function of dose
-At equivalent doses, mutation frequency is a function of LET

Radiation-induced Mutagenesis

- Radiation <u>does not</u> produce *new*, *unique* mutations but increases the incidence of the same mutations that occur spontaneously
- Mutation incidence in human is *dose* and *dose- rate* dependent
- A dose of 1 rem (10m Sv) per generation increase background mutation rate by **1%**
- Information on the genetic effects of radiation comes almost entirely from animal and *in vitro* studies.
- Children of A-bomb survivors from Hiroshima and Nagasaki fail to show any significant genetic effects of radiation

Human Risk Estimation to Ionizing Radiation

- The average radiation dose to a member of the general population in the U.S., from either background or man-made sources is about **360 mrem/year**.

Radon	200 mrem/yr
Cosmic-ray	28 mrem/yr
Terrestrial source	28 mrem/yr
Internal source, ^{40}K	40 mrem/yr
Medical /dental sources	54 mrem/yr average
Consumer products	10 mrem/yr
Other, e.g. fallout	3 mrem/yr

- Radiation Dose Limit and Administrative Control Levels:

To minimize the potential risk of biological effects associated with radiation exposure, dose limits and administrative control levels (ACL) have been established. The dose limits established by the U.S. Department of Energy are based on guidelines from EPA, National Council on Radiation Protection and Measurement (NCRP) and the International Commission on Radiation Protection (ICRP). Limits are set by regulatory agencies and **are not** to be exceeded except for **approved** emergency actions. Administrative control levels are set below the regulatory limit to control worker' doses.

Whole body dose limit and ACL for radiological workers

DOE limit	5,000 mrem/yr
DOE ACL limit	2,000 mrem/yr
P& S limit	

Additional limits set by DOE

Extremities (forearms,/hands/ lower legs/ feet)	50,000 mrem/yr
Skin and other organs	50,000 mrem/yr
Lens of the eye	15,000 mrem/yr
Pregnant radiological workers	500 mrem/yr

Comparative mortality rates:

Cause	Death/year-million persons
Cardiovascular disease	4,800
Cancer of all sites	1,750
Automobile accidents	220
Home accidents	150
Homicides, U.S. average	100
Fire	30
Drowning	30
Poisoning	14
Radiation Effects (per rem)	9
Aircraft crashes	8
Lighting	1

Comparing the Risks: Radiation, Smoking, and Driving				
			Equivalent to	
Procedure	**Dose**	**Chance of Death**	*Number of Cigarettes Smoked*	*Number of Highway Miles Driven*
	Bone Marrow	*From Leukemia*		
^{131}I treatments for thyrotoxicosis	15 rems	3×10^{-4}	2200	5357
Chest radiograph	10 mrems	2×10^{-7}	1.5	3.6
Skull examination	78 mrems	1.6×10^{-6}	11.4	28
Barium enema	875 mrems	17.5×10^{-6}	128	313
	Thyroid	*From Thyroid Cancer*		
Chest radiograph (AP)	11.9 mrems	12×10^{-7}	8.7	21
Skull examination (AP & lateral)	197 mrems	20×10^{-6}	144	352