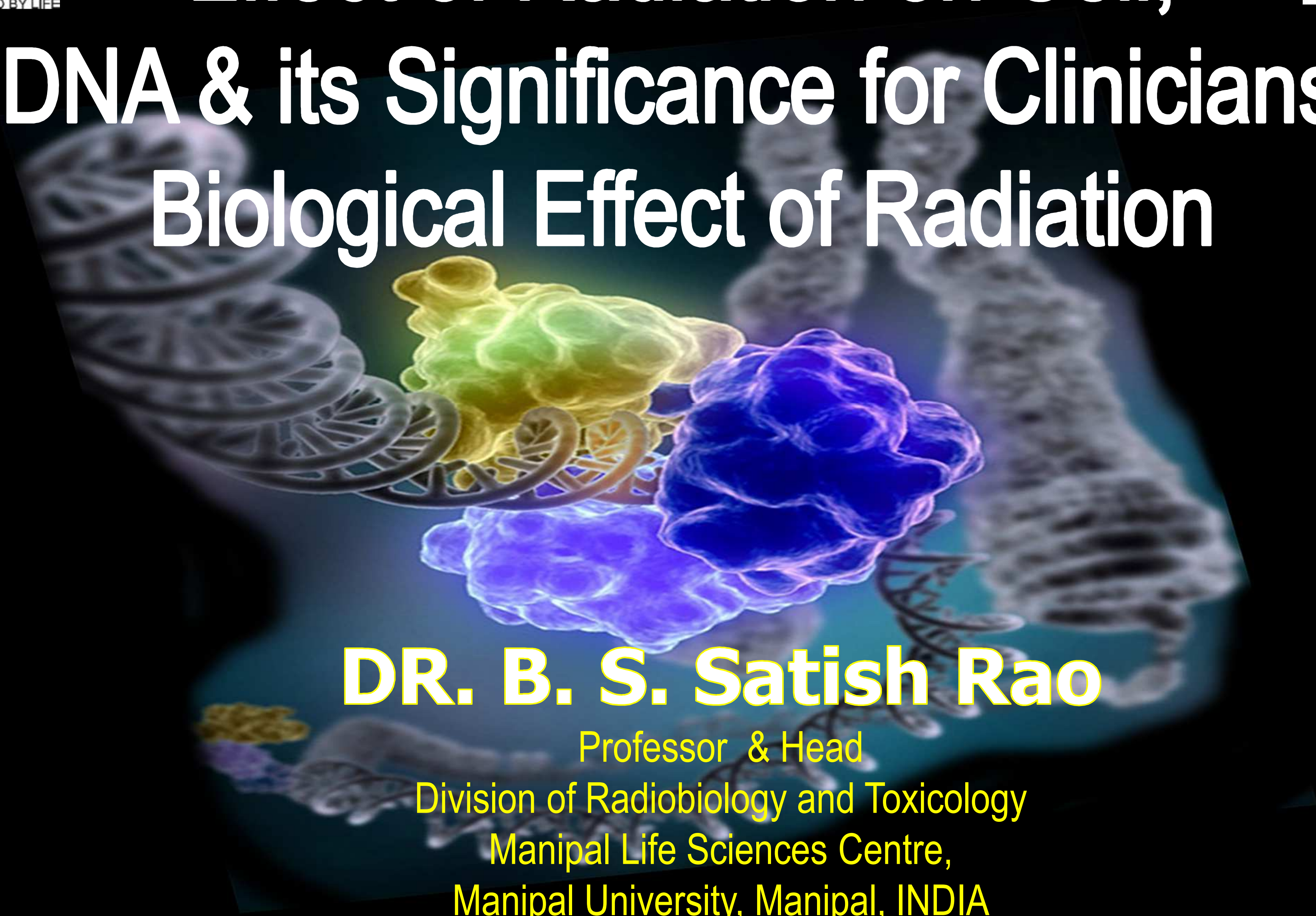
Effect of Radiation on Cell, DNA & its Significance for Clinicians: Biological Effect of Radiation



DR. B. S. Satish Rao

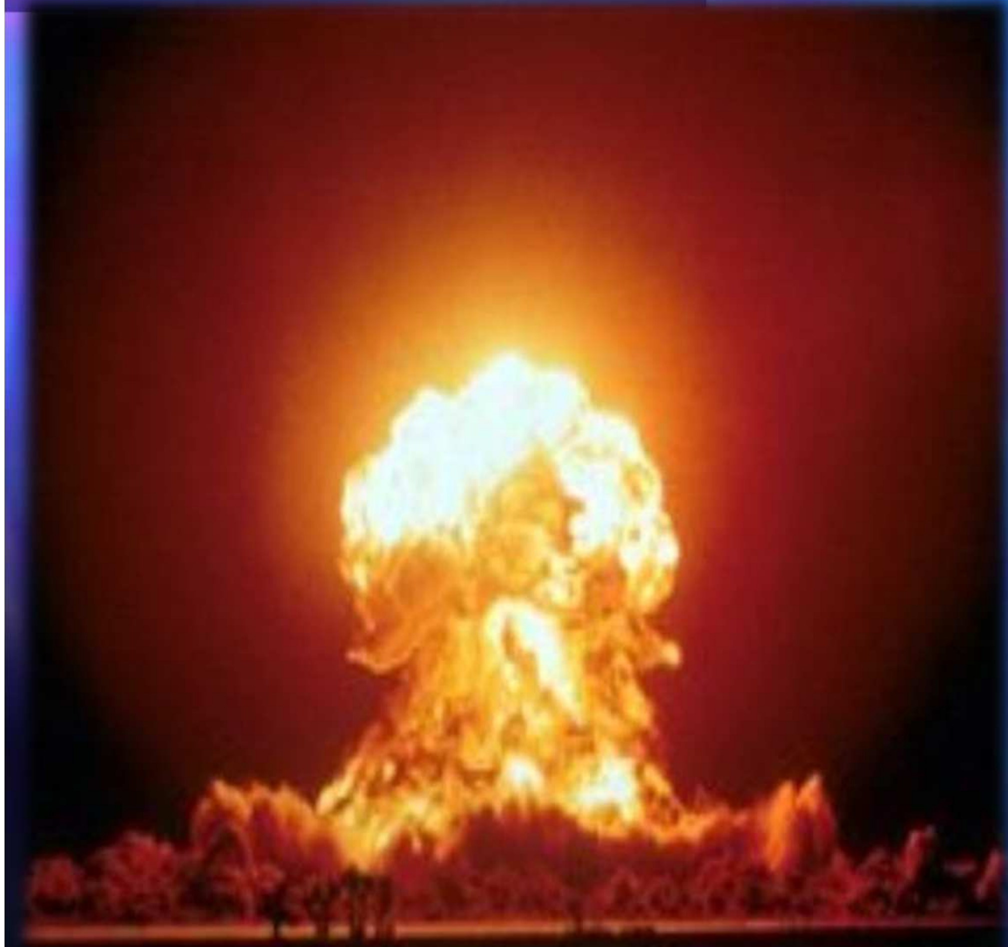
Professor & Head

Division of Radiobiology and Toxicology

Manipal Life Sciences Centre,

Manipal University, Manipal, INDIA

Discovery of A-bomb's effect in Japan (1945)

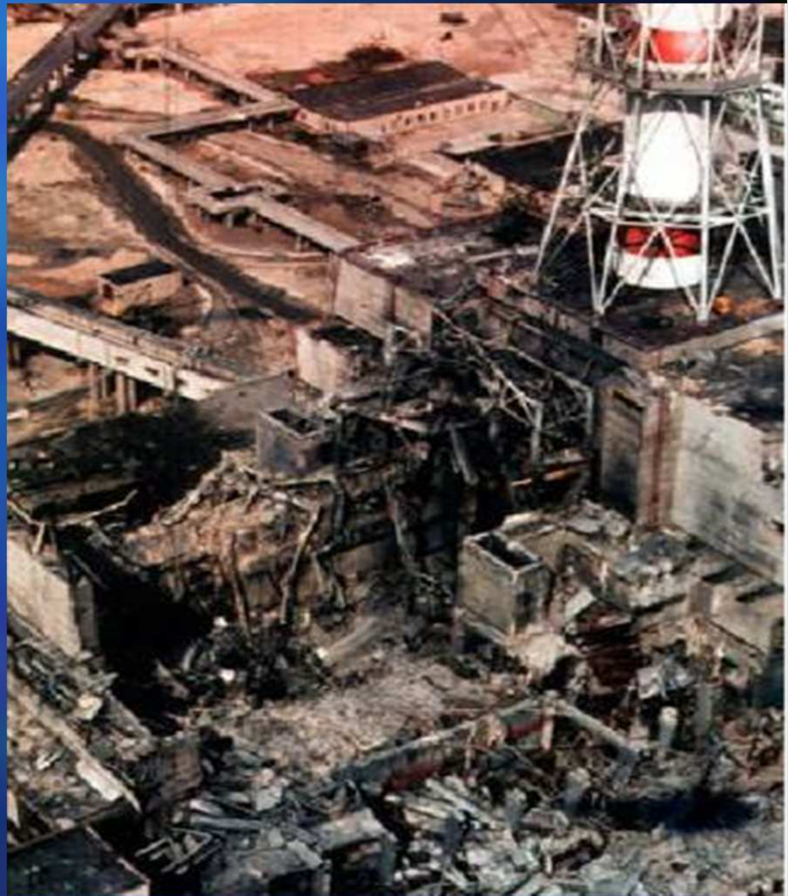


Hiroshima, 6.08.1945
Nagasaki, 9.08.1945

The studies of Japanese bomb survivors began in 1950, and have formed the basis of radiation protection guidelines ever since

Radiation accidents consequences

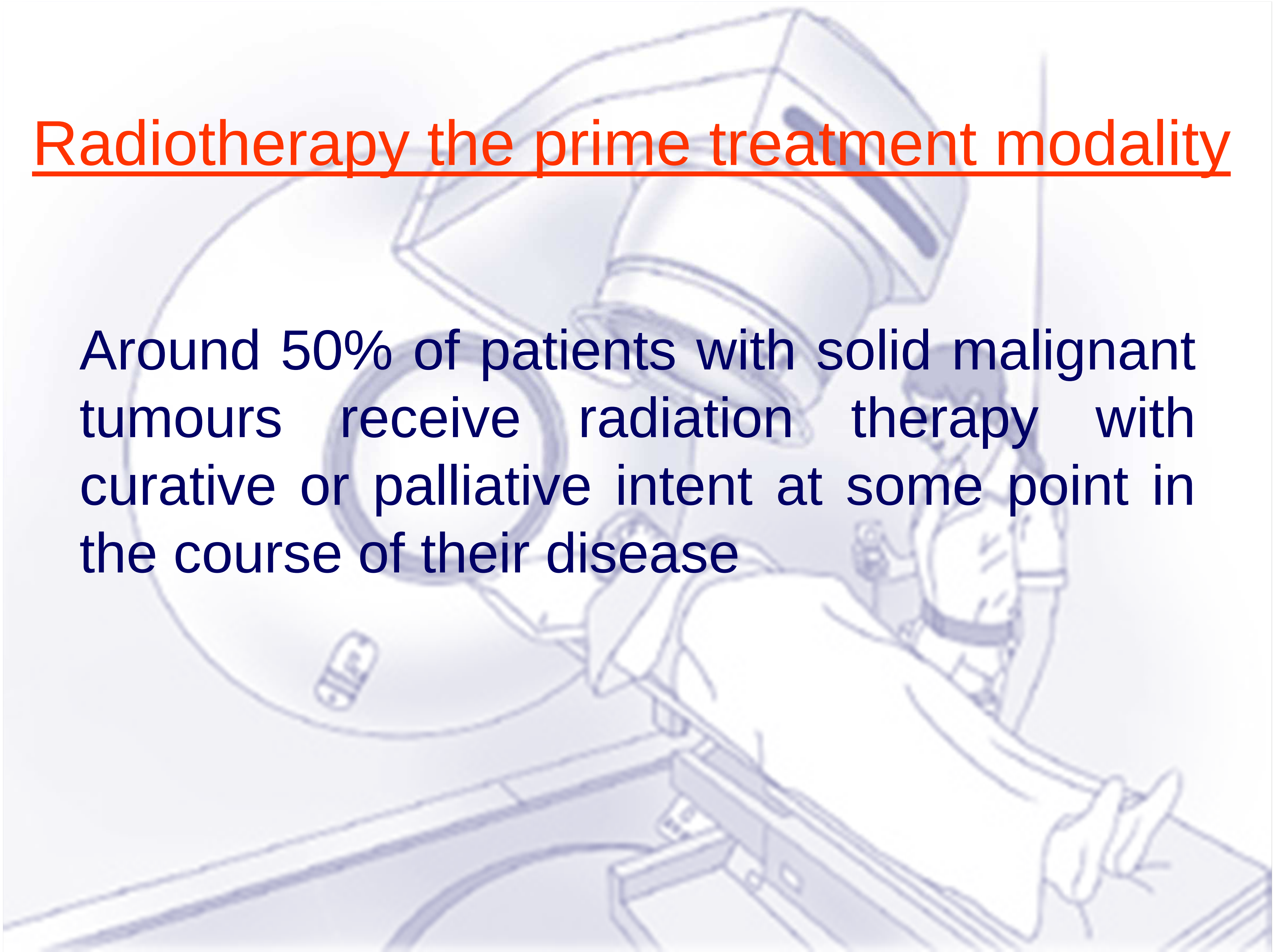
1944-2001 more than 425 radiation accidents



Coiania, Brazil (1987)

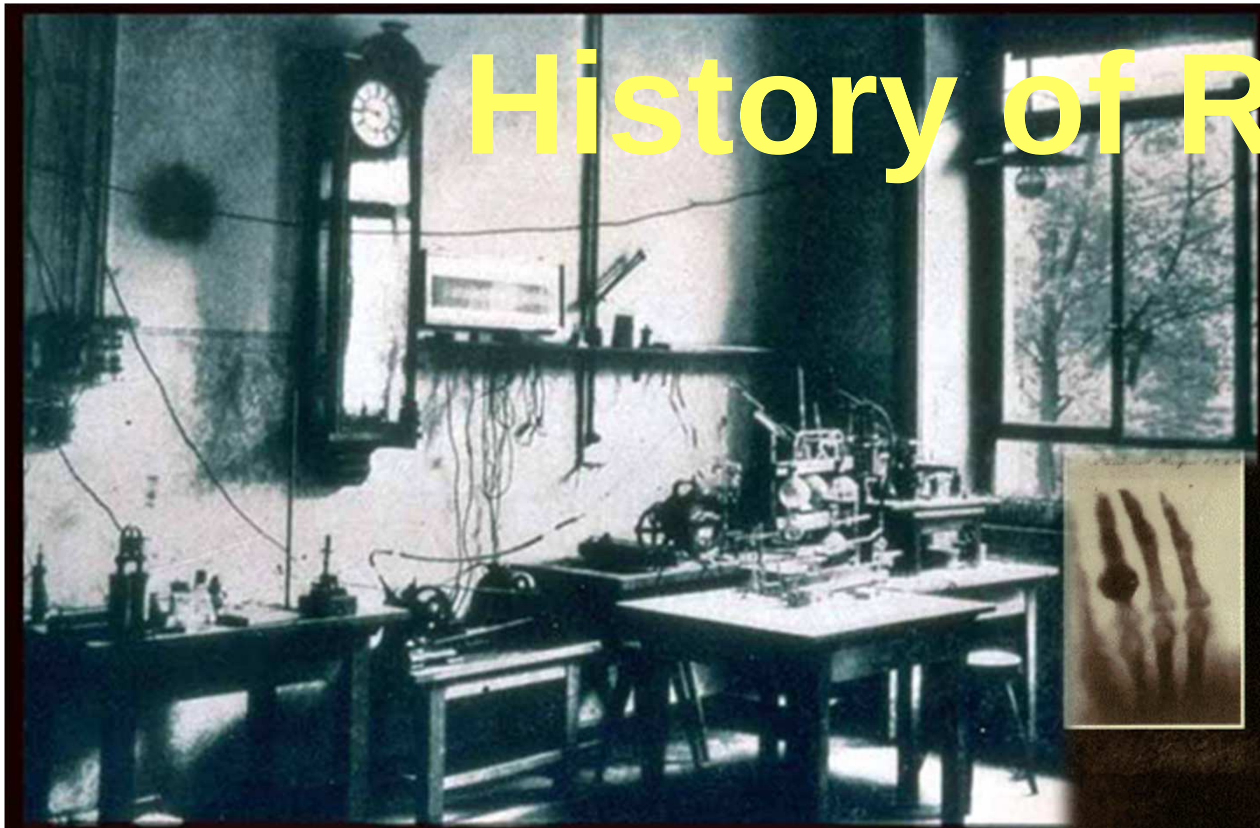
Chernobyl, USSR (1986)

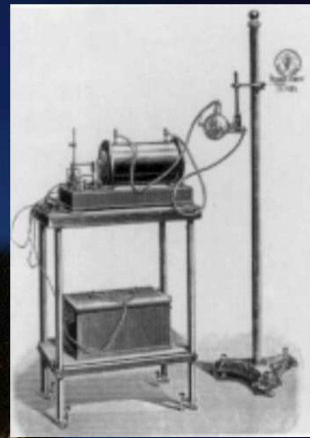
Radiotherapy the prime treatment modality



Around 50% of patients with solid malignant tumours receive radiation therapy with curative or palliative intent at some point in the course of their disease

History of Radiation





Roentgen's Wurzburg Laboratory

On 22 December 1895,
Mr. Roentgen made the first
X-ray photograph
(Mrs. Roentgen’s hand).

Wilhelm Conrad Roentgen

1895 – Discovery of X -rays

1901 – Nobel prize in physics

A great interest was triggered for the therapeutic use of radiation

The Aftermath

- On 1st January 1896, Roentgen announced his discovery to the world.

Application of radiation in medicine:

- 14th February 1896, four days after news of the discovery reached the U.S, X-rays were used to guide surgery in New York.

- In early 1896, the Italian military began using X-rays to diagnose and treat wounded soldiers

At the same time ...

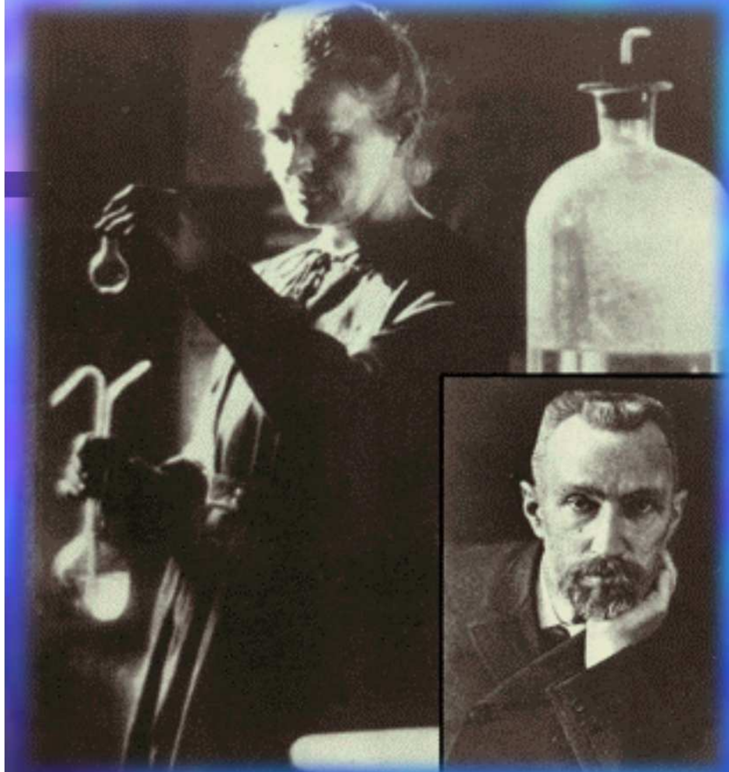
- In February 1896, Henri Becquerel discovered radioactivity.

oStudied fluorescent minerals containing uranium.

oDiscovered that radioactivity occurs in unstable atoms.

oFound that uranium emits radiation without external source.

History of Radiation

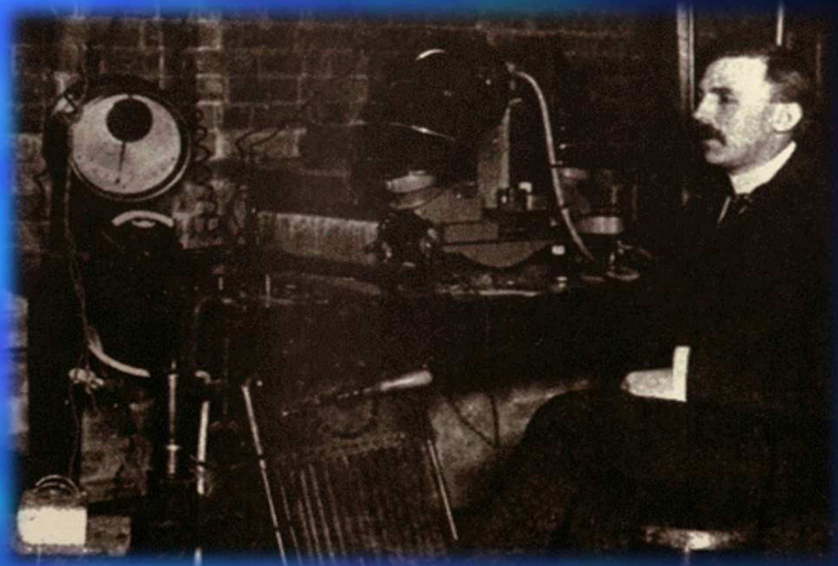


Pierre Curie & Marie Curie

(Discovery of Radium & Polonium – 1898)

1903 - Nobel prize in physics (radioactivity)

1911 - Nobel prize in chemistry (M. Curie)



Ernest Rutherford

1908 - Nobel prize in chemistry

(chemistry of radioactive substances)-

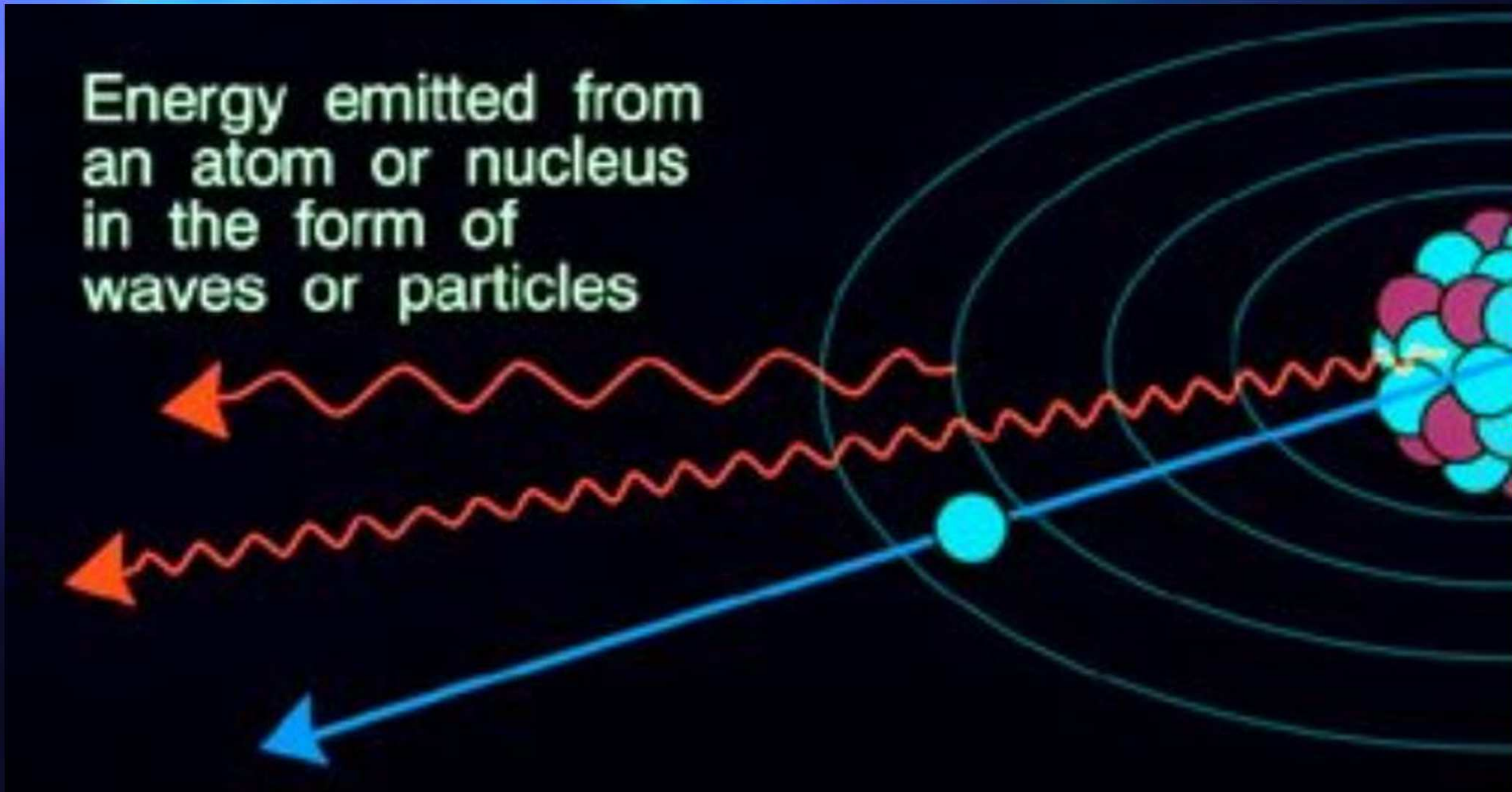
Discovered that elements decay into other elements after emitting nuclear radiation. Called it Nuclear Decay.

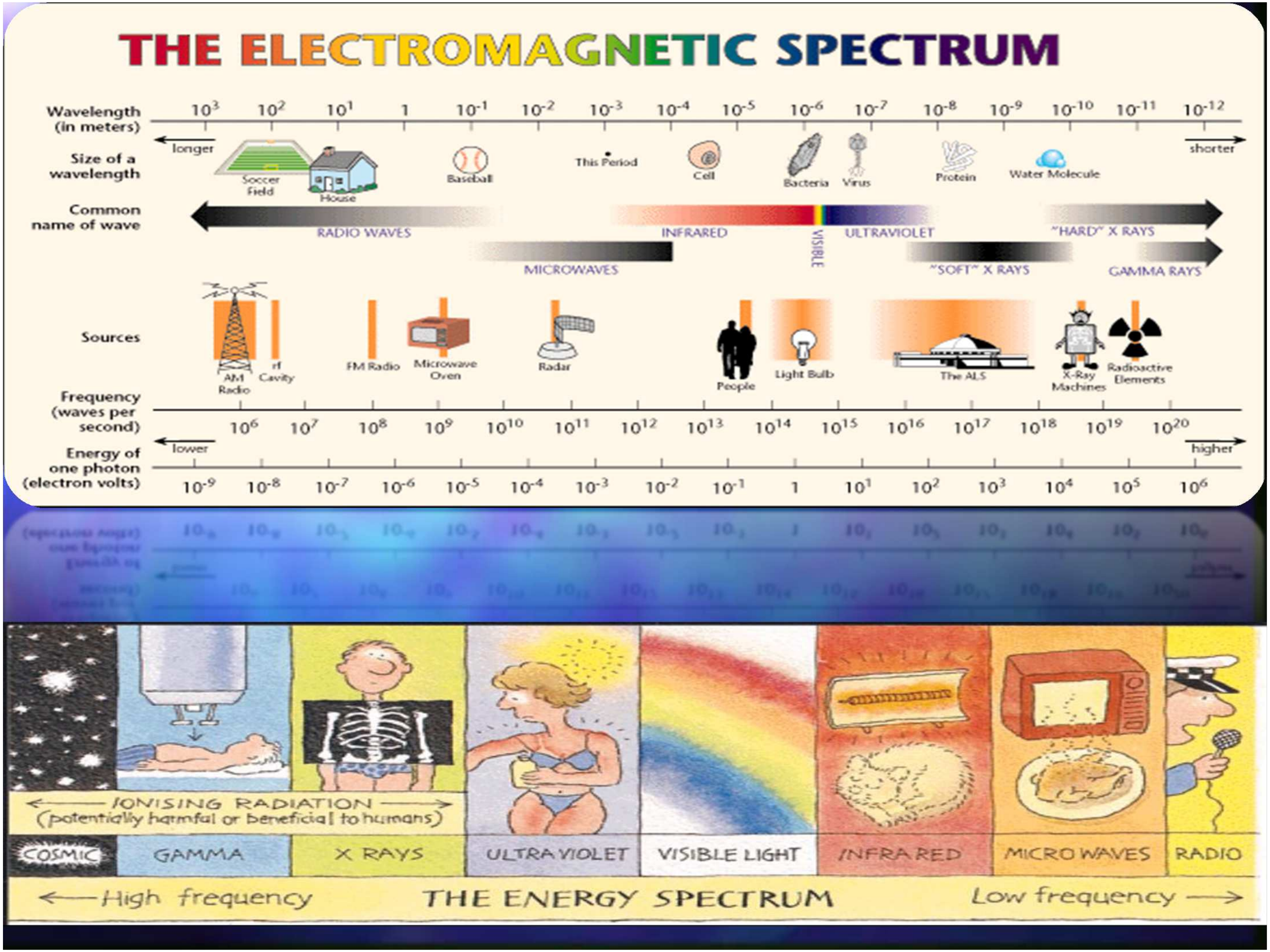
Discovery of harmful effects of ionizing radiation

- **First report about *local radiation injuries* (1896)**
- **First report about *radiation-induced sterility* (1903) and *radiation-induced leukemia* (1911)**

- **1920s: *bone cancer* among radium dial painters**
- **1930s: *liver cancer and leukemia* due to Thorotrast (**thorium dioxide a diagnostic contrast agent **administration-**cerebral angiography)
- **1940 - 50s: excess *leukemia* among first radiologists.**
- Madame and Irene Curie died of leukemia as a result of prolonged exposure of radiation during their studies

What is Radiation?




THE ELECTROMAGNETIC SPECTRUM
Wavelength (in meters)
10^3 10^2 10^1 1 10^-1 10^-2 10^-3 10^-4 10^-5 10^-6 10^-7 10^-8 10^-9 10^-10 10^-11 10^-12
longer
shorter
Size of a wavelength
Soccer Field
House
Baseball
This Period
Cell
Bacteria
Virus
Protein
Water Molecule
Common name of wave
RADIO WAVES
INFRARED
VISIBLE
ULTRAVIOLET
"HARD" X RAYS
MICROWAVES
"SOFT" X RAYS
GAMMA RAYS
Sources
AM Radio
rf Cavity
FM Radio
Microwave Oven
Radar
People
Light Bulb
The ALS
X-Ray Machines
Radioactive Elements
Frequency (waves per second)
10^6 10^7 10^8 10^9 10^10 10^11 10^12 10^13 10^14 10^15 10^16 10^17 10^18 10^19 10^20
lower
higher
Energy of one photon (electron volts)
10^-9 10^-8 10^-7 10^-6 10^-5 10^-4 10^-3 10^-2 10^-1 1 10^1 10^2 10^3 10^4 10^5 10^6
IONISING RADIATION
(potentially harmful or beneficial to humans)
COSMIC
GAMMA
X RAYS
ULTRAVIOLET
VISIBLE LIGHT
INFRARED
MICROWAVES
RADIO
High frequency
THE ENERGY SPECTRUM
Low frequency

Types of radiation

Ionizing Radiation

Type of radiation that produces the ejection of an orbital electron from an atom or molecule and results in the formation of an ion pair.

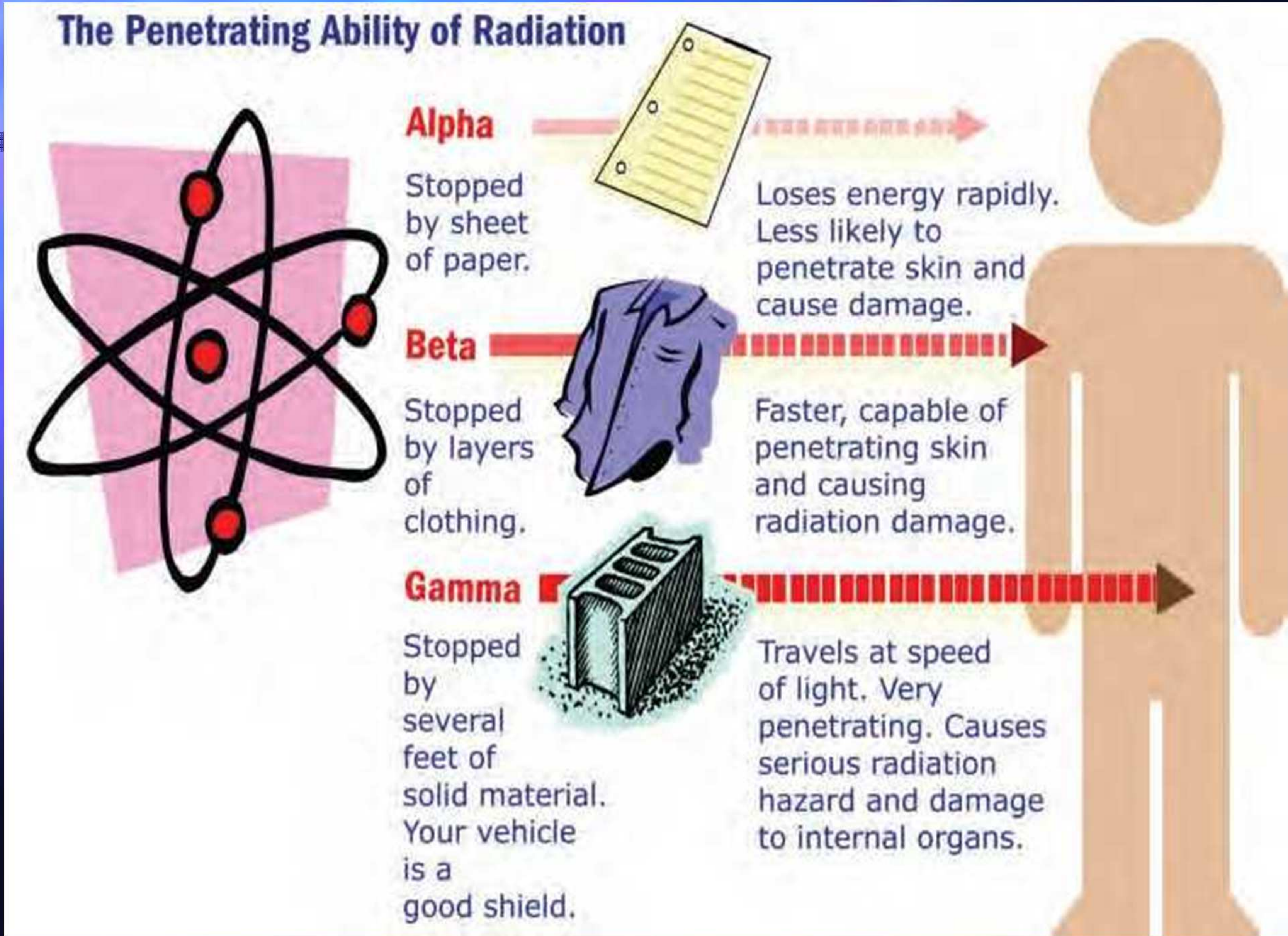
- **Particulate (alphas and betas)**
- **Waves (gamma and X- rays)**

Non-Ionizing Radiation

Deposits insufficient energy and fails to eject electron, but can induce excitation or molecular vibration and heat.

Examples include UV, microwaves, infrared, visible, radar, radio waves, lasers, TV

Ionizing Radiation Types



Background Radiation Is Always Present !

We are constantly exposed & evolved with low levels of background radiation. Background levels can vary depending upon location.

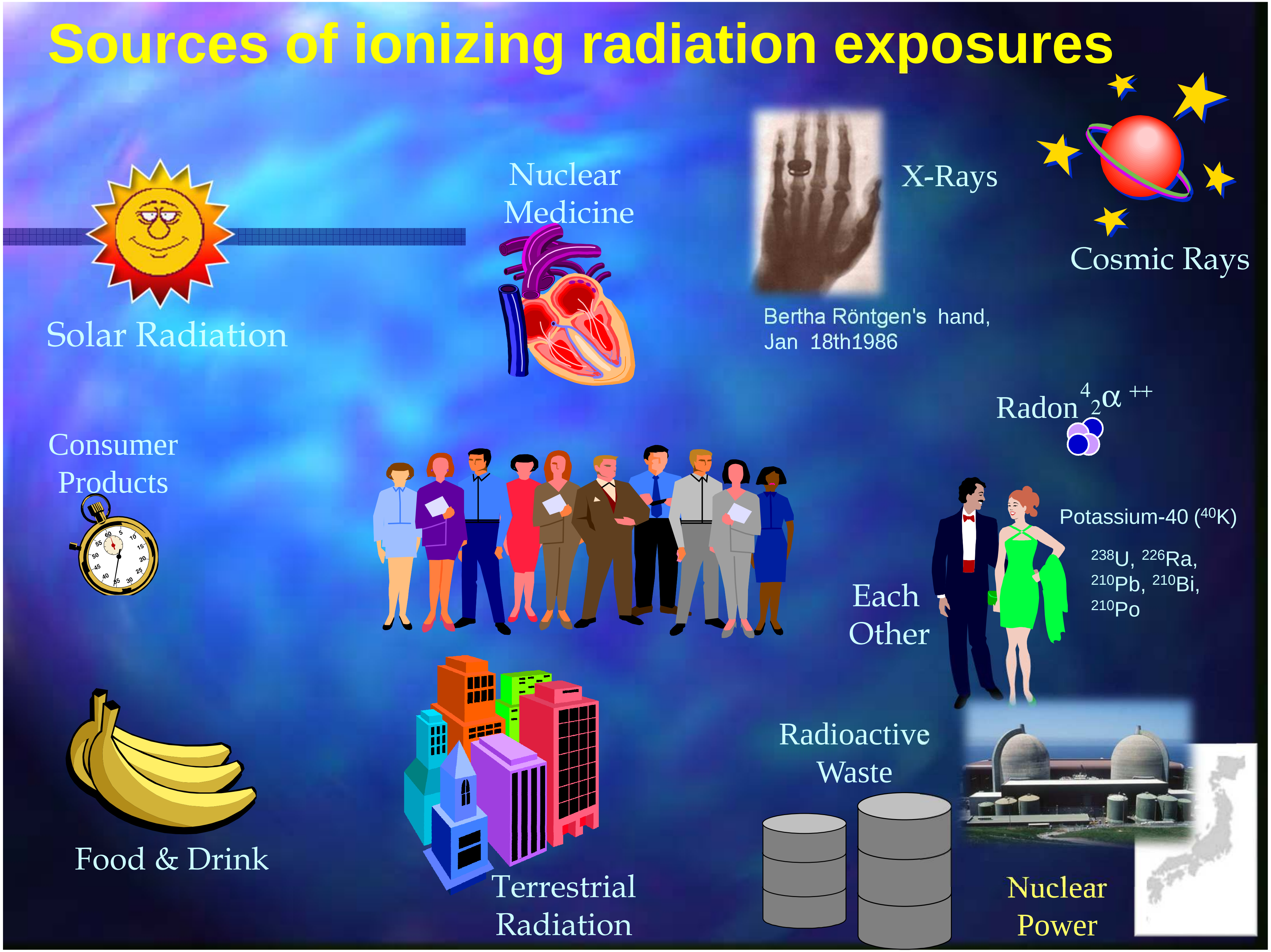
- **Soil : Radon (primary source)- uranium decay**
- **Sunlight : Cosmic Rays**
- **Man-Made: Nuclear, Medical & Industrial**

Radiation Exposure from Various Sources

Source	Exposure
External Background Radiation	60 mrem/yr, US Average
Natural K-40 and Other Radioactivity in Body	40 mrem/yr
Air Travel Round Trip (NY- LA)	5 mrem
Chest X-Ray Effective Dose	10 mrem per film
Radon in the Home	200 mrem/yr (variable)
Man-Made (medical x rays, etc.)	60 mrem/yr (average)

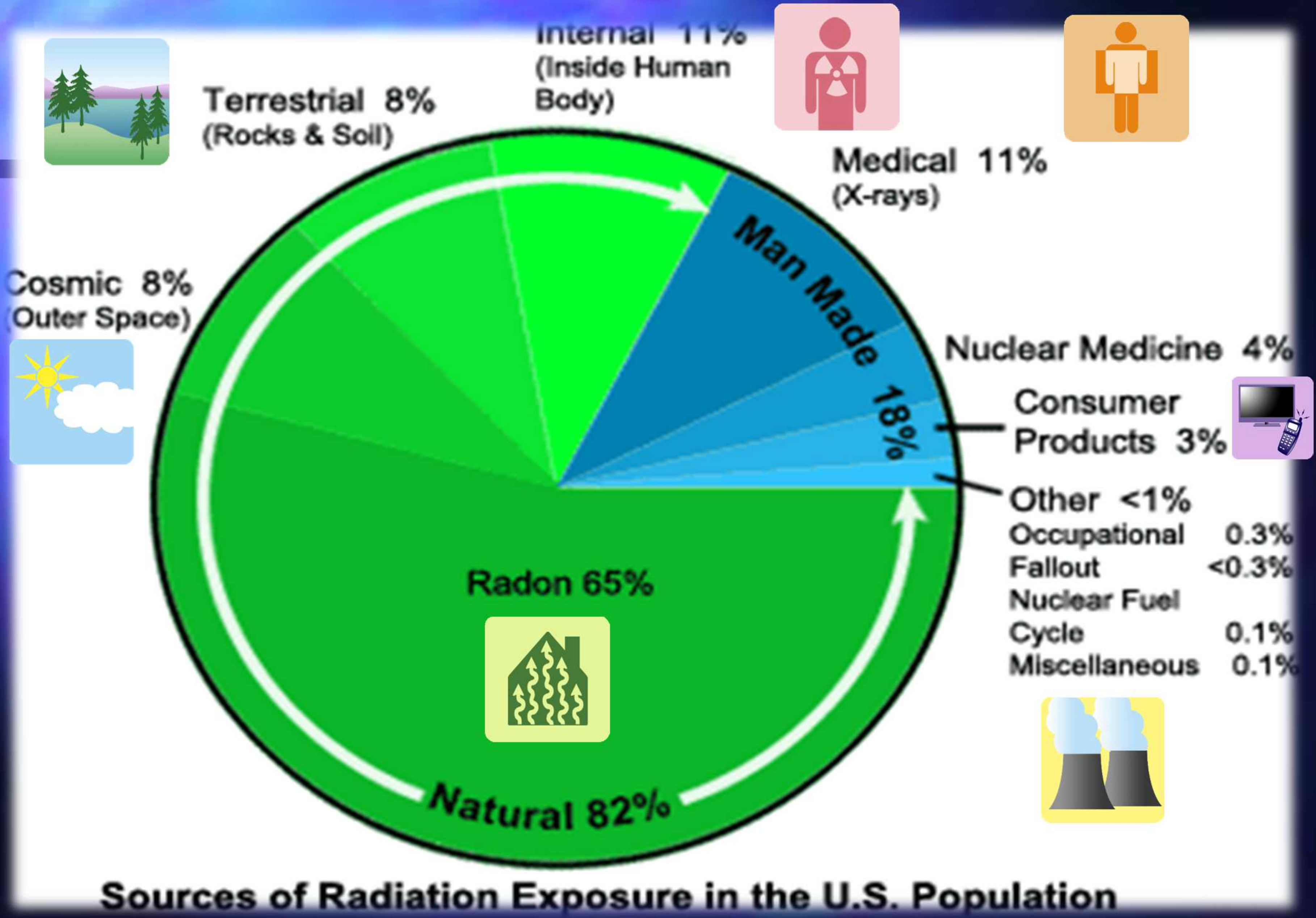
Radiation from Natural Sources

Source	mrem/year
Cosmic rays	28
The earth	26
Radon	200
Natural K-40 and Other Radioactivity The human body	25
Building materials	4



Sources of ionizing radiation exposures
Solar Radiation
Nuclear Medicine
X-Rays
Bertha Röntgen's hand, Jan 18th1986
Cosmic Rays
Radon $^{4}_{2}\alpha^{++}$
Consumer Products
Potassium-40 (^{40}K)
^{238}U, ^{226}Ra, ^{210}Pb, ^{210}Bi, ^{210}Po
Each Other
Radioactive Waste
Food & Drink
Terrestrial Radiation
Nuclear Power

Sources of ionizing radiation exposures



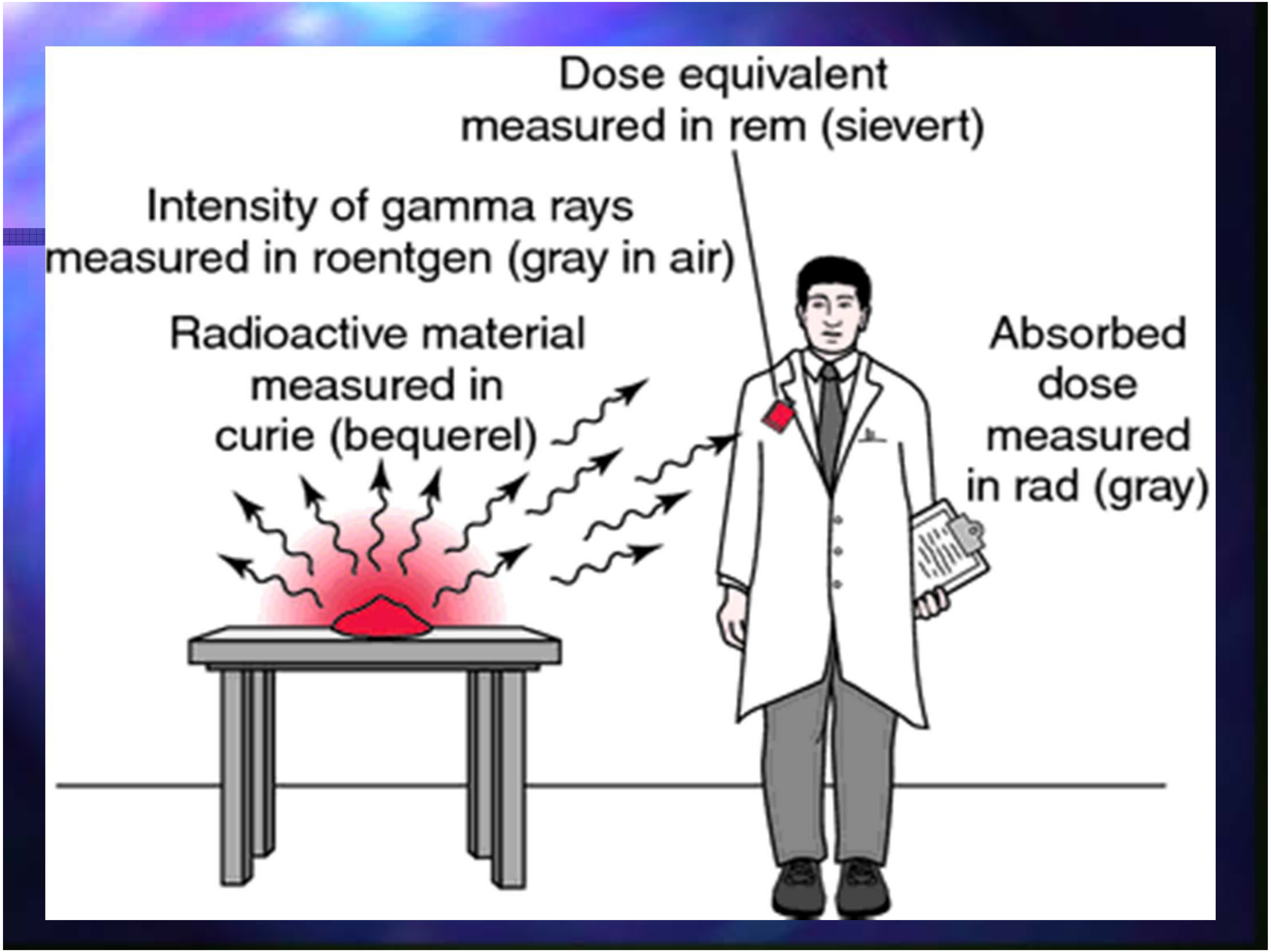
Radiation Units

Measure of	Quantity	Unit
Amount of radioactive material	Activity	curie (Ci)
Ionization in air	Exposure	roentgen (R)
Absorbed energy per mass	Absorbed Dose	rad
Absorbed dose weighted by type of radiation	Dose Equivalent	rem

For most types of radiation **1 R ≈ 1 rad ≈ 1 rem**

Conversion between units

	SI unit	Old unit	Relationship
Activity	Becquerel	Curie (Ci)	1 Ci = 3.7×10^{10} Bq
Exposure	Coulomb/kg	Roentgen (R)	1 C/kg = 3876R
Absorbed dose	Gray (J/kg)	rad	1 Gy = 100 rad
Equivalent dose	Sievert	rem	1 Sv = 100 rem 1 rem = 10mSv
Effective dose	Sievert	rem	1 Sv = 100 rem 1 rem = 10mSv


Dose equivalent measured in rem (sievert)
Intensity of gamma rays measured in roentgen (gray in air)
Radioactive material measured in curie (bequerel)
Absorbed dose measured in rad (gray)

AREA OF RADIATION EXPOSURE

Planned exposures

- **Radiotherapy**
- **Space program**
- **Diagnostic exposure**
- **Reactors maintenance**

Unplanned exposure

- Nuclear warfare
- Nuclear terrorism
- Nuclear industry
- Nuclear accidents
- Nuclear emergencies

Exposure of radiation leads development of various cancer

&

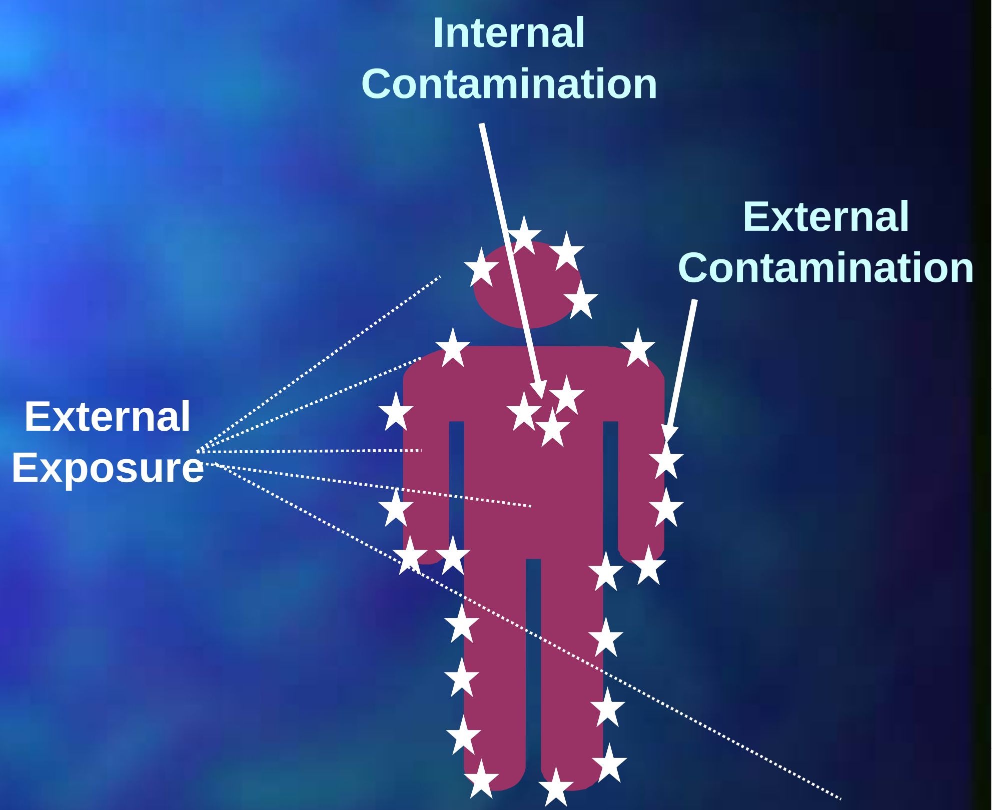
radiation syndromes

Types of Radiation Hazards

- ***External Exposure*** -

  Whole-body or partial-body

- ***Contaminated*** -
  - External radioactive material: on the skin or clothing
  - Internal radioactive material: inhaled, swallowed, absorbed through skin or wounds



Relative hazard of ionizing radiations

The biological hazard varies with type of radiation and if the radiation is internal (ingested, inhaled, or injected) or external.

External	Radiation type	Internal
most damaging	fast neutrons	least damaging
	thermal neutrons	
	x rays and γ rays	
	beta radiation	
least damaging	alpha radiation	**most**
damaging		

Standards & Regulatory Status

US National Council on Radiation Protection (NCRP)

International Council on Radiation Protection (ICRP)

Annual limits of radiation exposure

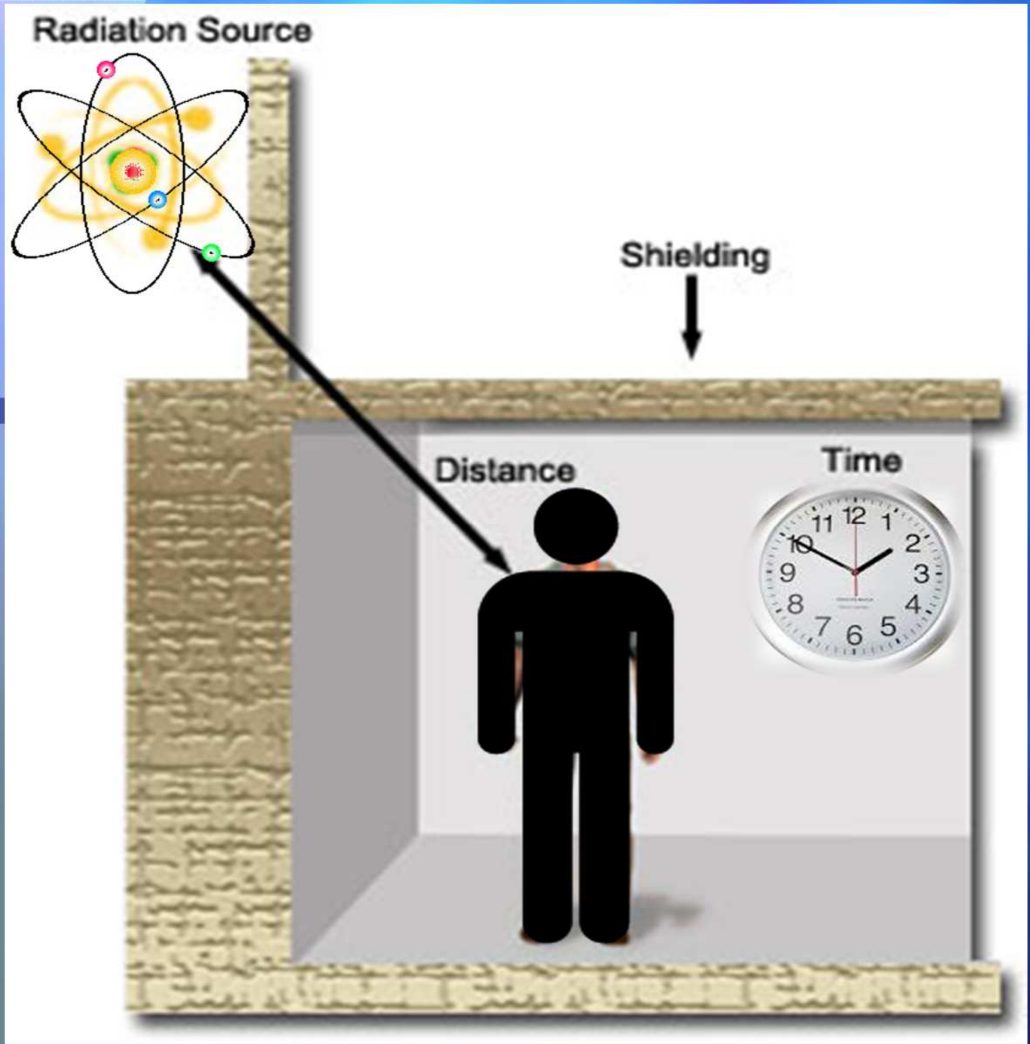
Occupational workers	20 mSv
General Public	1 mSv
LIMIT ON LIFE TIME DOSE	1 Sv

These limits are in addition to exposures from natural and medical sources

A simple chest X-ray gives 0.2 mSv !!!

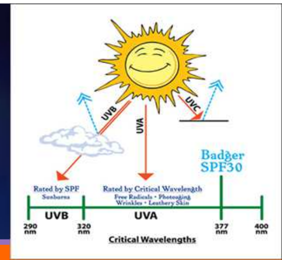
Reducing Exposure

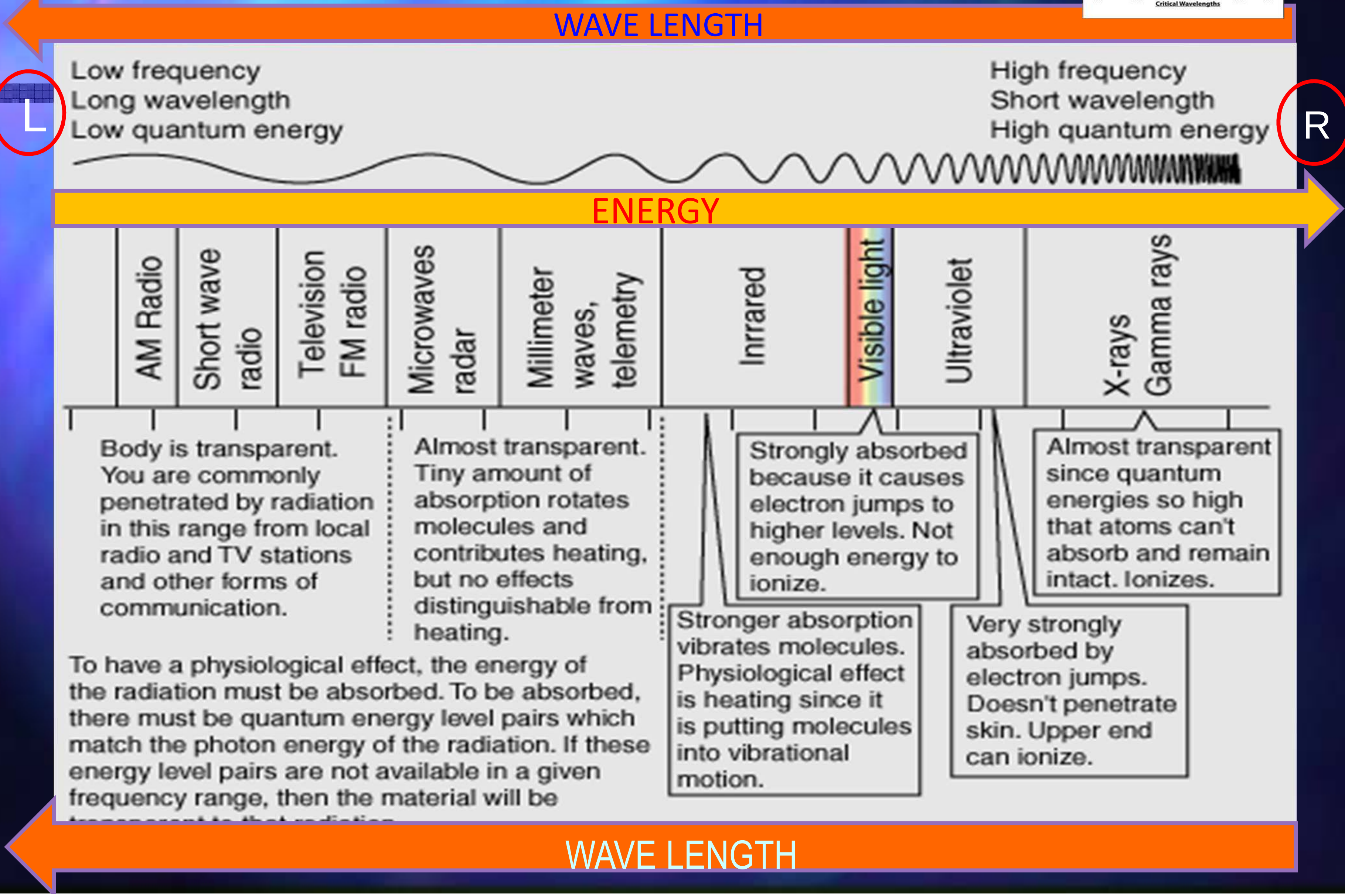
We protect ourselves from radiation exposure by:



Exposure X Time = Dose

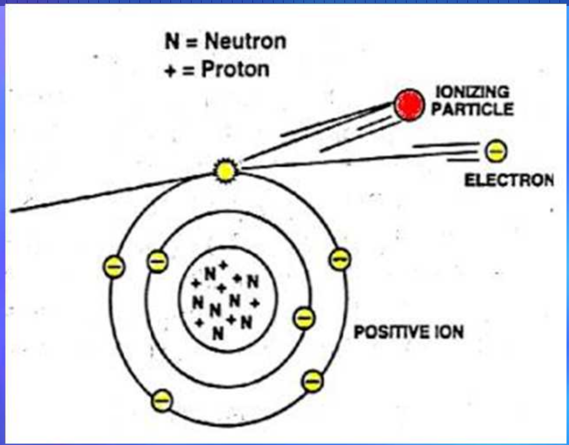
Radiation and the Human Body

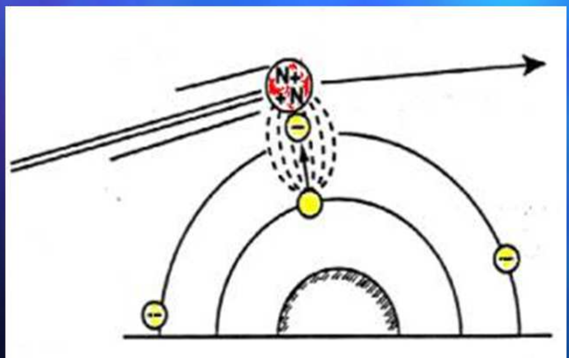




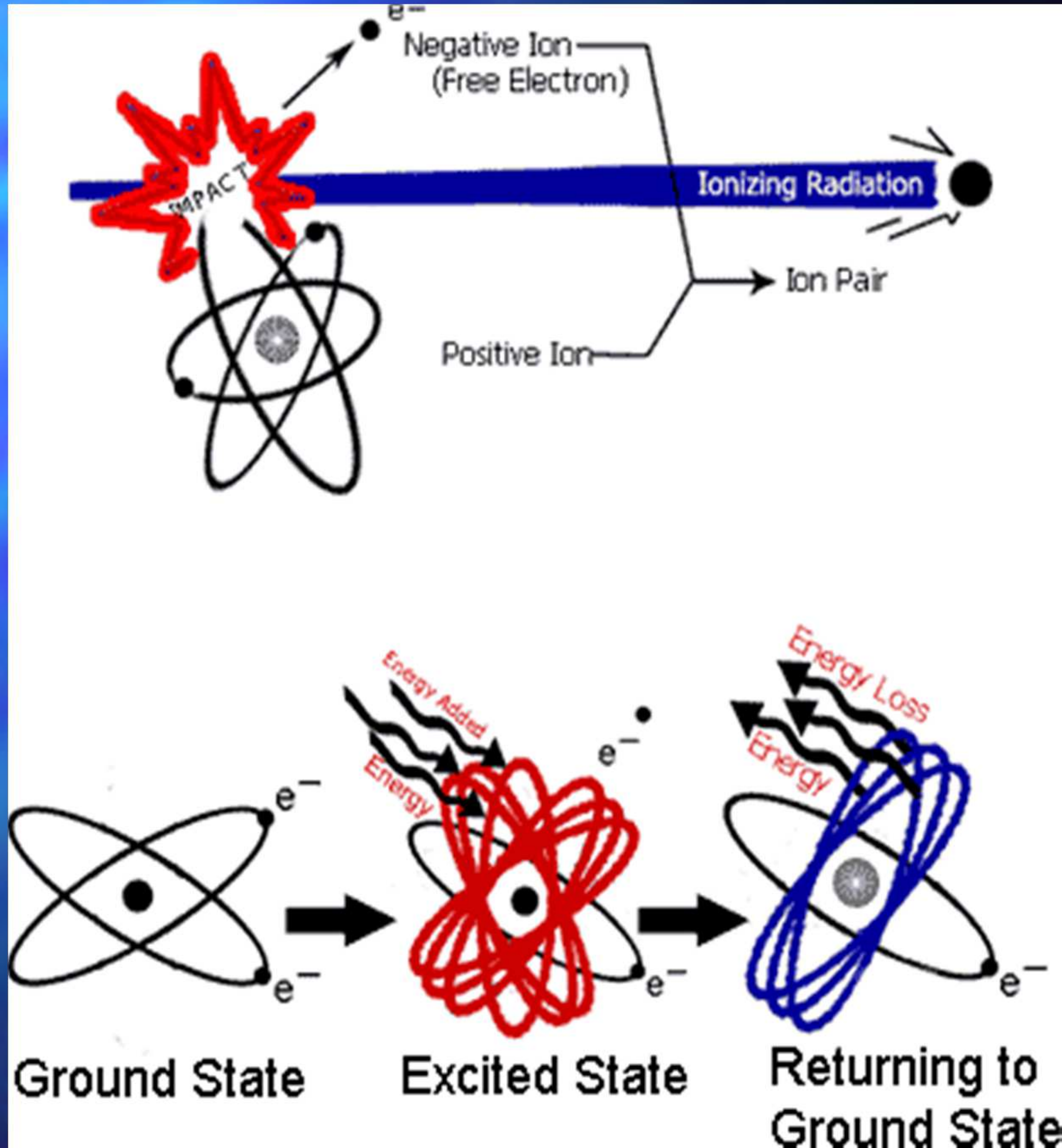
Radiation interaction with matter

- **Ionization**



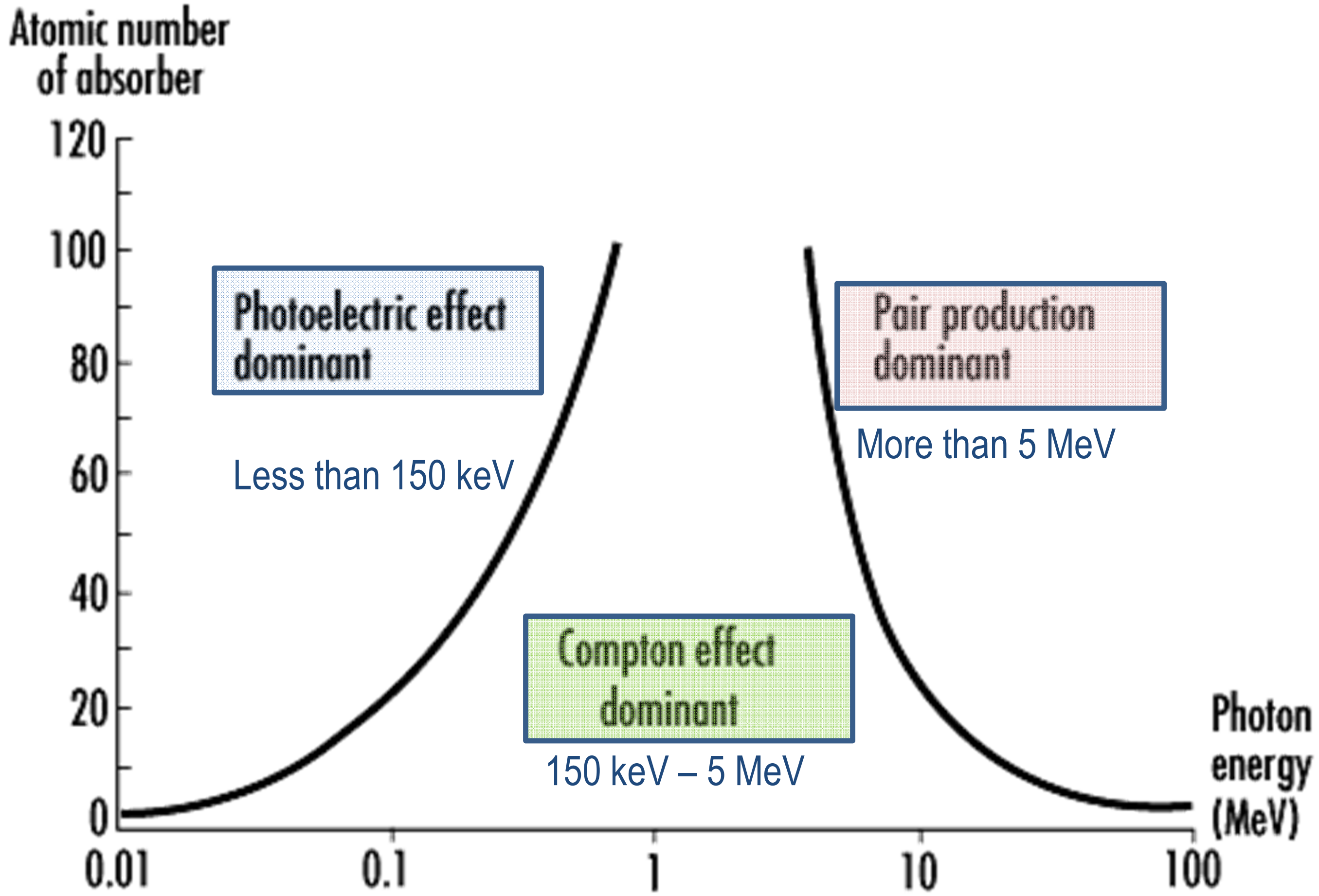


- **Excitation**



Interaction of electromagnetic radiations or X- / gamma radiations with matter

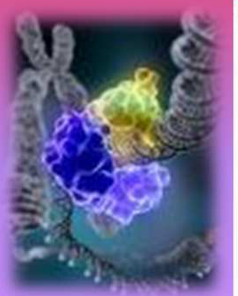
Interaction with matter mainly by three processes

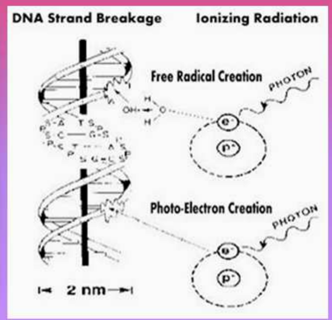


How Does Radiation Interact with Cells?

Past

Hit theory





- Direct ionization
- Indirectly by
  Free radical formation

Present –also by

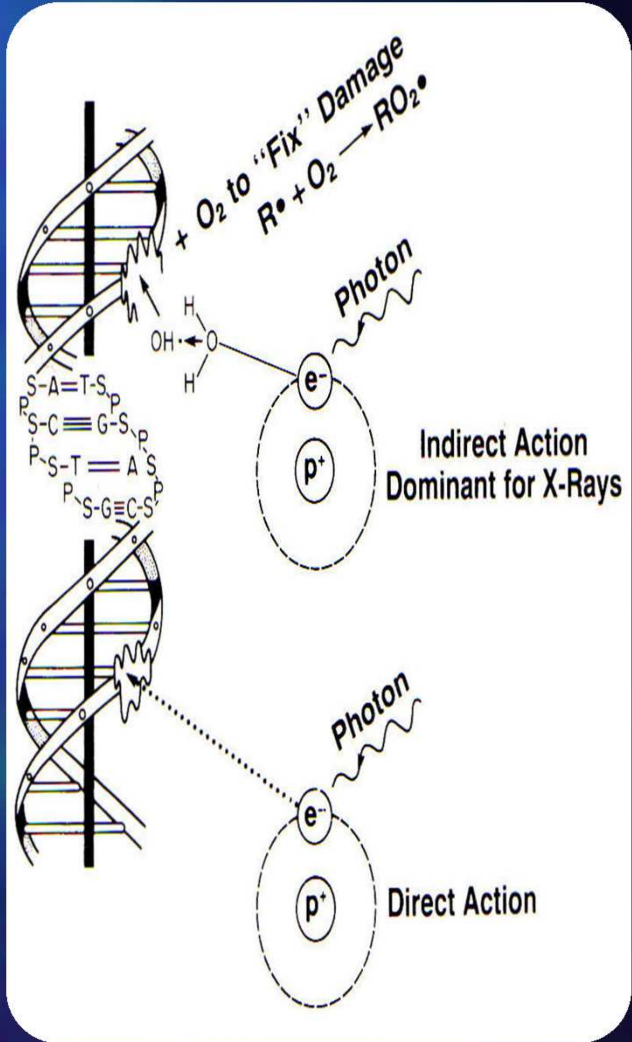
Bystander effects

Phenomenon when unirradiated cells exhibit irradiated effects as a result of signals received from nearby radiation treated cells

- Cell-cell communication
- Cell-matrix communication

Interaction of radiation with bio-molecules: Molecular level (Example: DNA)

For every one DNA molecule, there are 1.2X10^7 water molecules



- **Direct Action:** When the atoms of the target itself are ionized by the radiation. It is the dominant process for high LET radiation.

- **Indirect Action:** When the radiation interacts with other cellular molecules (e.g. water) to produce free radicals that migrate to and damage the target. About 2/3 of x-ray damage is due to indirect action.

Sequence of Radiation Effects

Incident X-ray photon

↓

Photon absorption via Compton effect

↓

Formation of free radicals

↓

Radical induced DNA damage

↓

Biological effect (mutation, cancer, etc.)

Time interval between radiation exposure and manifestation of biological effects can be divided into six stages

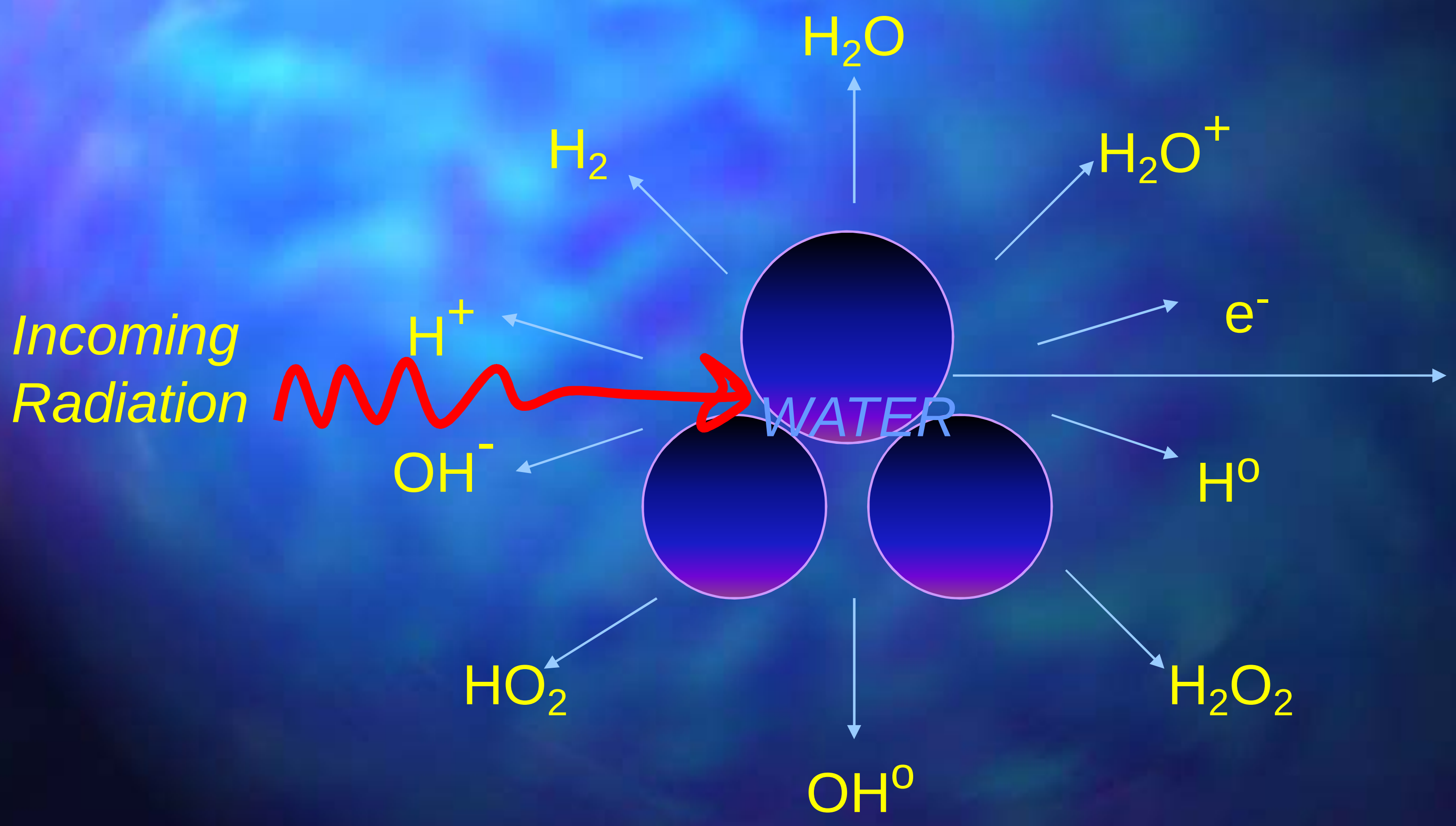
Phase	Events and Processes	Time Scale (secs)
Physical	Energy absorption, Ionisation and excitation	10^{-18} -10^{-15}
Physico-Chemical	Formation of radicals, rearrangement of excited ionized molecules	10^{-15} -10^{-8}
Chemical	Molecular alterations, formation of bio-radicals by indirect action	10^{-8} -10^{-3}
Bio-chemical	Enzymatic reactions, Repair, Fixation of damage	10^{-3} -10^{4}
Cellular Level	Cell death, Tissue repair, Mutation	10^{4} -10^{7}
Systematic (Multi-cellular Organisms)	Hormonal Effects, immune reactions, Functional impairment carcinogenesis, death	10^{8} -10^{10}

Radiolysis of Water

- Free Radical: An atom or molecule that contains an unpaired electron (chemically highly reactive).
- Hydrated Electron: A free electron surrounded by a shell of water molecules.

Radiation Induced decomposition of water within a cell

Most abundant molecule within humans: Water (70 -80%)



Production of free radicals within the cell can result in indirect effects

Radiolysis of Water

Primary reactions

$$H_2O \xrightarrow{\text{ionising radiation}} H_2O^{+\bullet} + e^-$$ ionisation

$$H_2O \xrightarrow{\text{ionising radiation}} H_2O^*$$ excitation

Secondary reactions

$$e^- + n\,H_2O \longrightarrow e^-_{aq}$$

$$H_2O^{+\bullet} + H_2O \longrightarrow H_3O^+ + OH\bullet$$

$$H_2O^* \longrightarrow H\bullet + OH\bullet$$

The main radical species produced are OH•, H• and e^-_{aq} of which OH• are the most reactive

Secondary Products

- Hydrogen peroxide:
  - $°OH + °OH \rightarrow H_2O_2$

- Inactivation of H_2O_2 in cells:
  - $H_2O_2 + H_2O_2 \rightarrow 2H_2O + O_2$ (catalase)

- Activation of H_2O_2:
  - $H_2O_2 + Fe(II) \rightarrow °OH + OH^- + Fe(III)$ (Fenton Reaction)
  - $Fe(III) + O_2^- \rightarrow Fe(II) + O_2$
  - $H_2O_2 + °O_2^- \rightarrow °OH + OH^- + O_2$ (Haber-Weiss reaction)

Effect of Oxygen

- Enhances production of H_2O_2 and the superoxide radical anion $°O_2^-$ and the hydroperoxy radical $°HO_2$

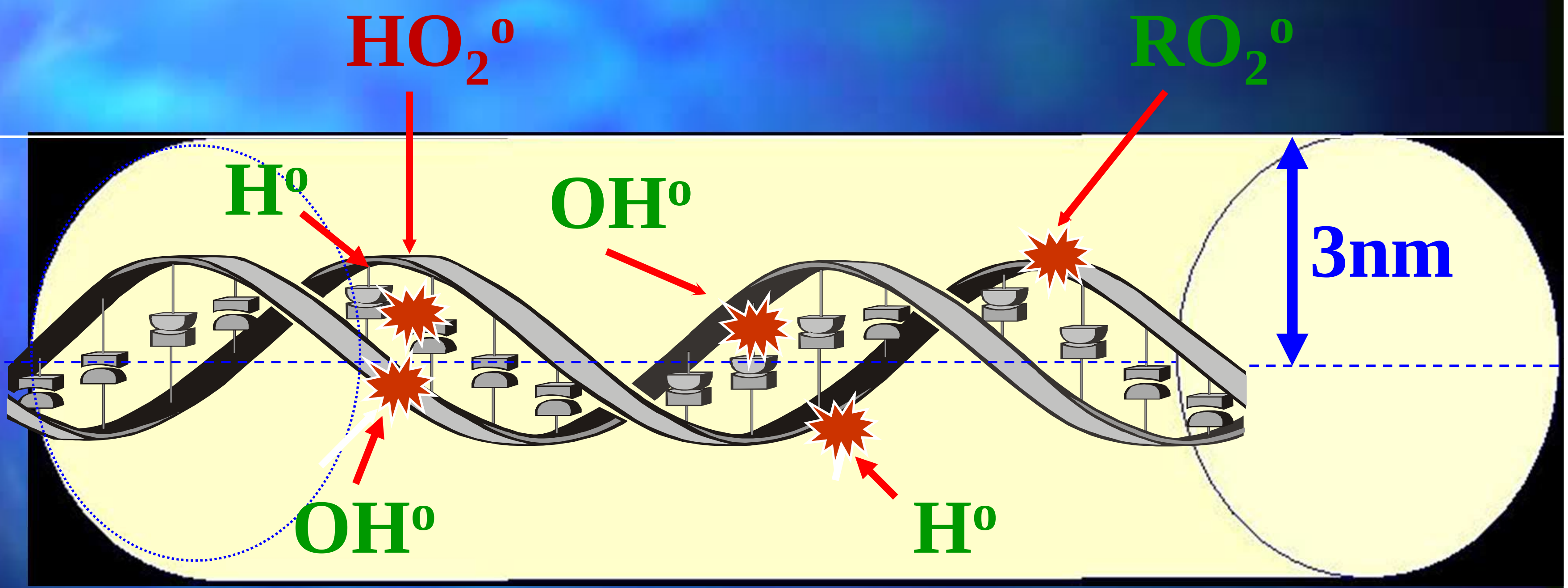
  - $°H + O_2 \rightarrow °HO_2$

    $\uparrow\downarrow \quad + \ H^+$
  - $e^-_{aq} + O_2 \rightarrow °O_2^-$

- Besides scavenging of $°H$ and e^-_{aq} , oxygen reacts rapidly with the more long lived radicals produced in biomolecules to produce peroxide radicals and hydroperoxides:
  - $X° + O_2 \rightarrow XO_2° \rightarrow XO_2H$

  This process is referred to as DAMAGE FIXATION.

Lifetimes of free radicals

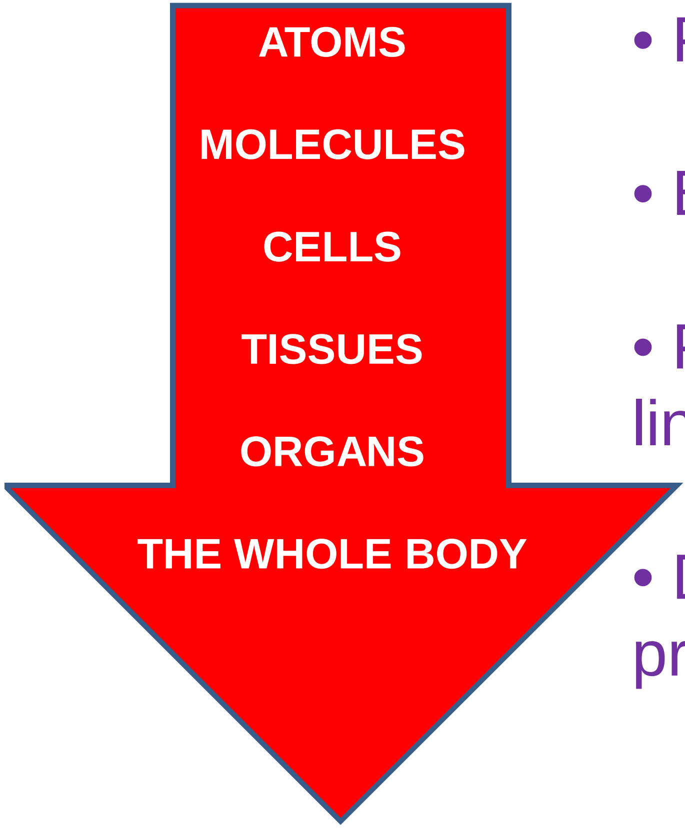


Because short life of simple free radicals (10^{-10}sec), only those formed in water column of 2-3 nm around DNA are able to participate in indirect effect

Mechanisms of radiation damage

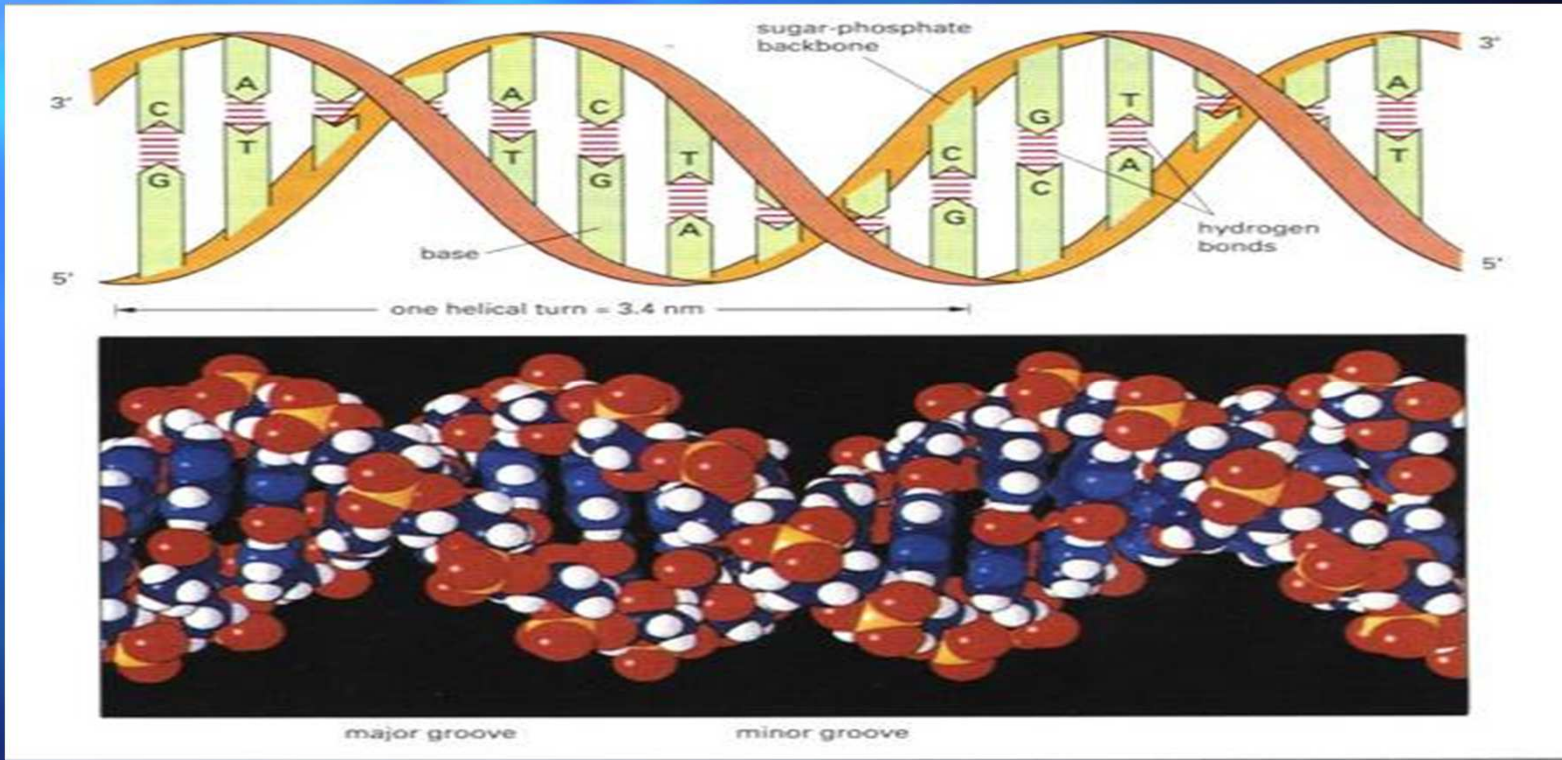
Injury to cells/ tissues results from the transfer of energy to atoms and molecules.

Atoms and molecules may be exited or ionized depending upon the energy and these excitation and ionizations can:



- Produce free radicals
- Break chemical bonds
- Produce new chemical bonds and cross linkage between macromolecules
- Damage molecules that regulate vital processes (DNA, RNA & Protein synthesis)

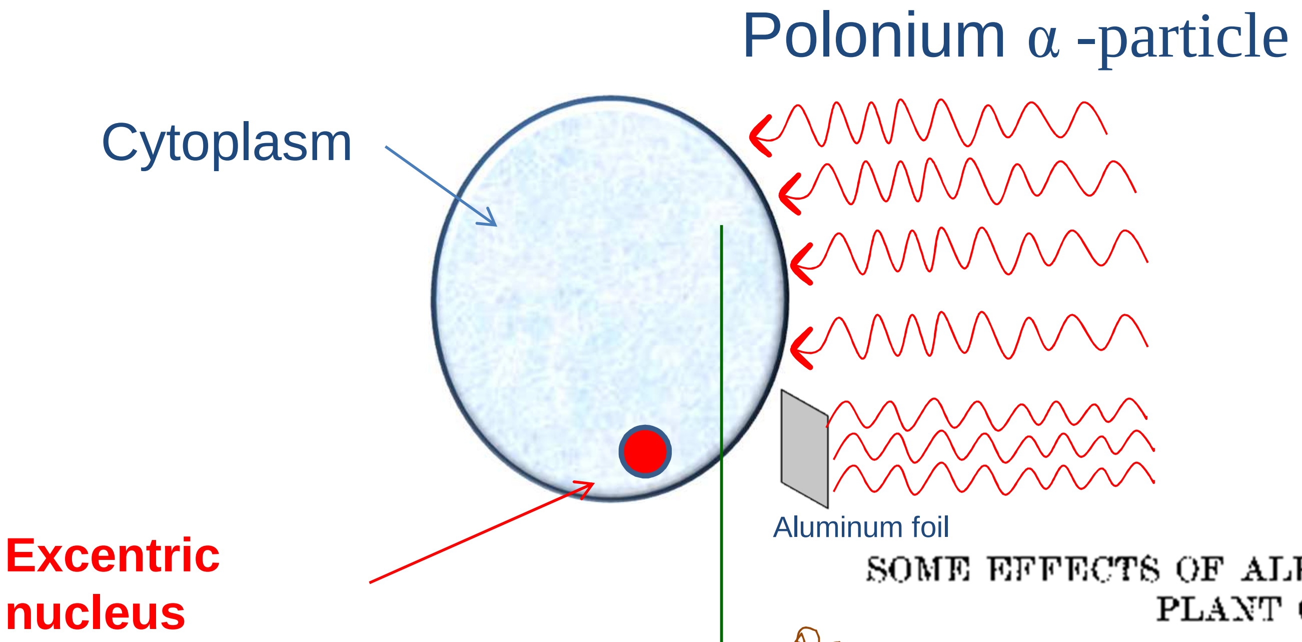
Biochemical reactions with ionizing radiation



- DNA is primary target for cell damage from ionizing radiation

Pteris longifolia (fern spore)

– Raymond E. Zircle



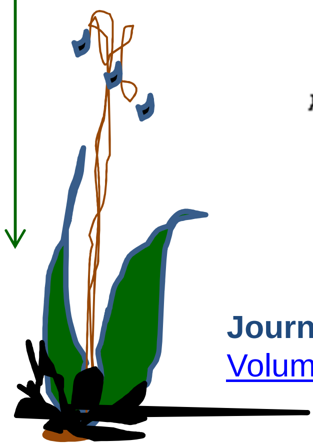
SOME EFFECTS OF ALPHA RADIATION UPON PLANT CELLS[1]

R. E. ZIRKLE
Department of Botany, University of Missouri

TEN FIGURES

(Received for publication, October 14, 1932)

Journal of Cellular and Comparative Physiology
Volume 2, Issue 3, pages 251–274, December 1932



Germination

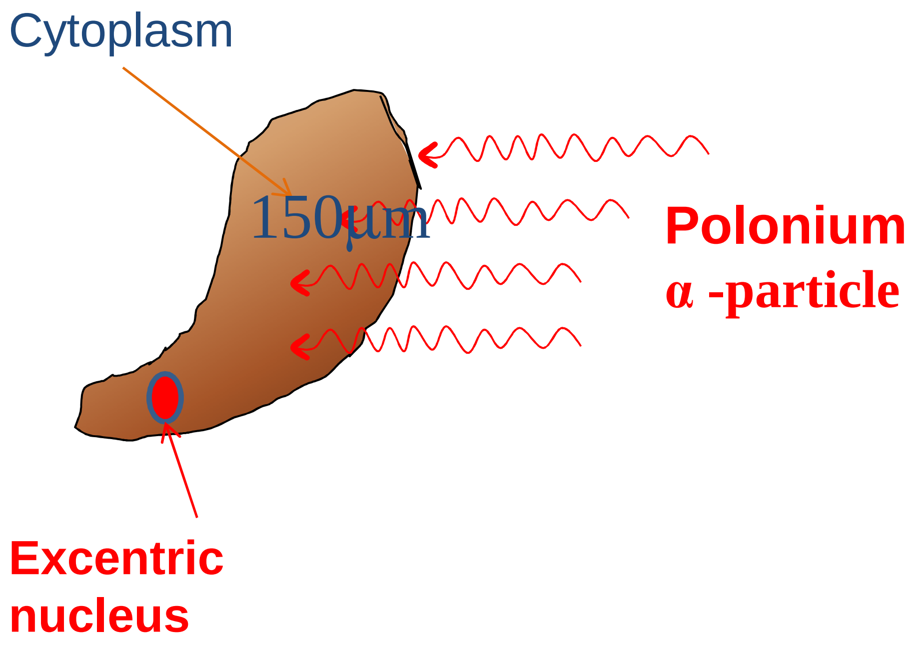
WITH SMALL DOSES OF RADIATION TO THE NUCLEUS

- Inhibition of germination
- Chlorophyll development
- Cracking of spore coats

Fertilized habrabracon egg (parasitic wasp egg)

R.W. Rogers & R. C. Von Borsel

Fertilized habrabracon egg



Observations

1 α –particle to nucleus -
No hatching

17.6 x 10^6 α –particle to cytoplasm
50 % - Hatching
+
50% - KILLED

RADIATION RESEARCH 7, 484–490 (1957)

Alpha-Particle Bombardment of the *Habrobracon* Egg.

I. Sensitivity of the Nucleus

R. W. ROGERS[1] AND R. C. VON BORSTEL

Biology Division, Oak Ridge National Laboratory,[2] Oak Ridge, Tennessee, and Department of Zoology, Florida State University, Tallahassee, Florida

RADIATION RESEARCH 8, 248–253 (1958)

Alpha-Particle Bombardment of the *Habrobracon* Egg

II. Response of the Cytoplasm

R. C. VON BORSTEL AND R. W. ROGERS[1]

Biology Division, Oak Ridge National Laboratory,[2] Oak Ridge, Tennessee, and Department of Zoology, Florida State University, Tallahassee, Florida

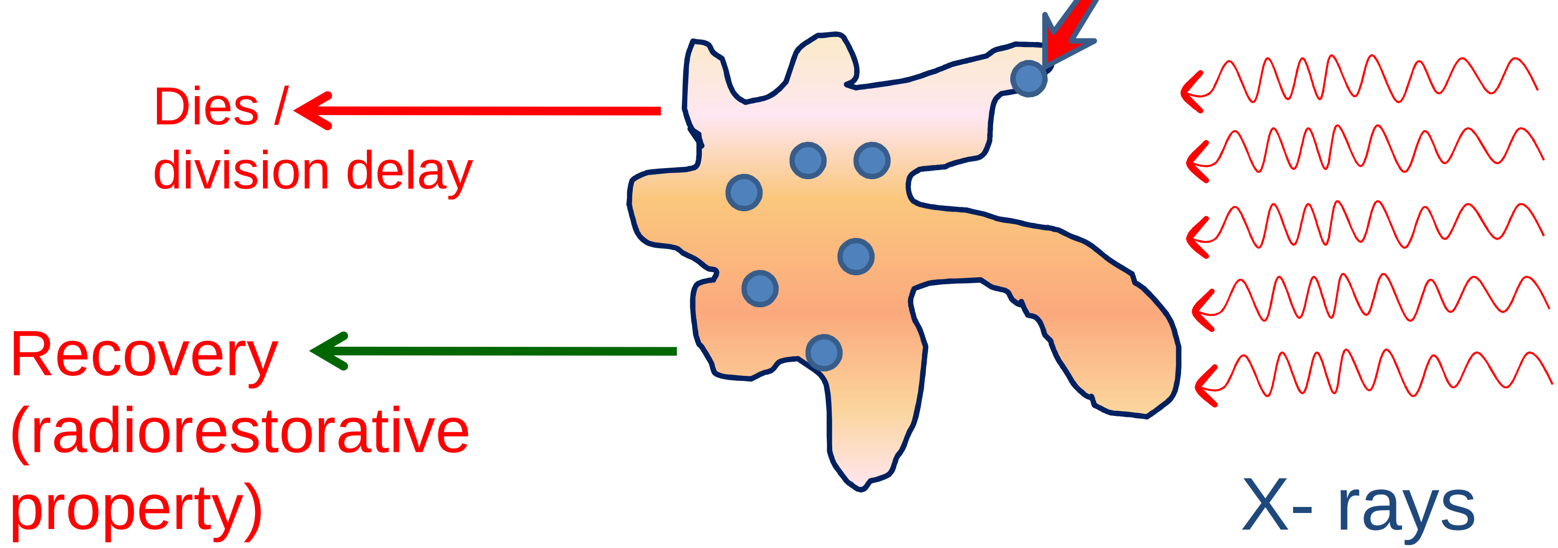
The Site of Damage in Amoebae Exposed to X-Rays

By M. J. ORD AND J. F. DANIELLI
(*From the Zoology Department, King's College, Strand, London, W.C. 2*)

SUMMARY

The technique of nuclear transfer was used to study the extent to which X-rays damage nuclei and cytoplasms of *Amoeba proteus*. Results showed that cytoplasm was directly damaged by the radiations. Cytoplasmic damage with doses below 280,000 r was reversible, though damaged cytoplasm could lethally damage normal nuclei. Damage with doses above 300,000 r caused lethal damage and death occurred without division in 0–3 days. Damage to nuclei was probably a combination of a direct action of the radiations and exposure to reversibly damaged cytoplasm. Nuclei were 2·4 times as sensitive as cytoplasms, the LD_{50} doses being approximately 120,000 r for nuclei and 290,000 r for cytoplasm. Death due to nuclear damage generally occurred without division within 3 to 6 weeks. Nuclear damage cannot be interpreted in terms of the 'target' theory.

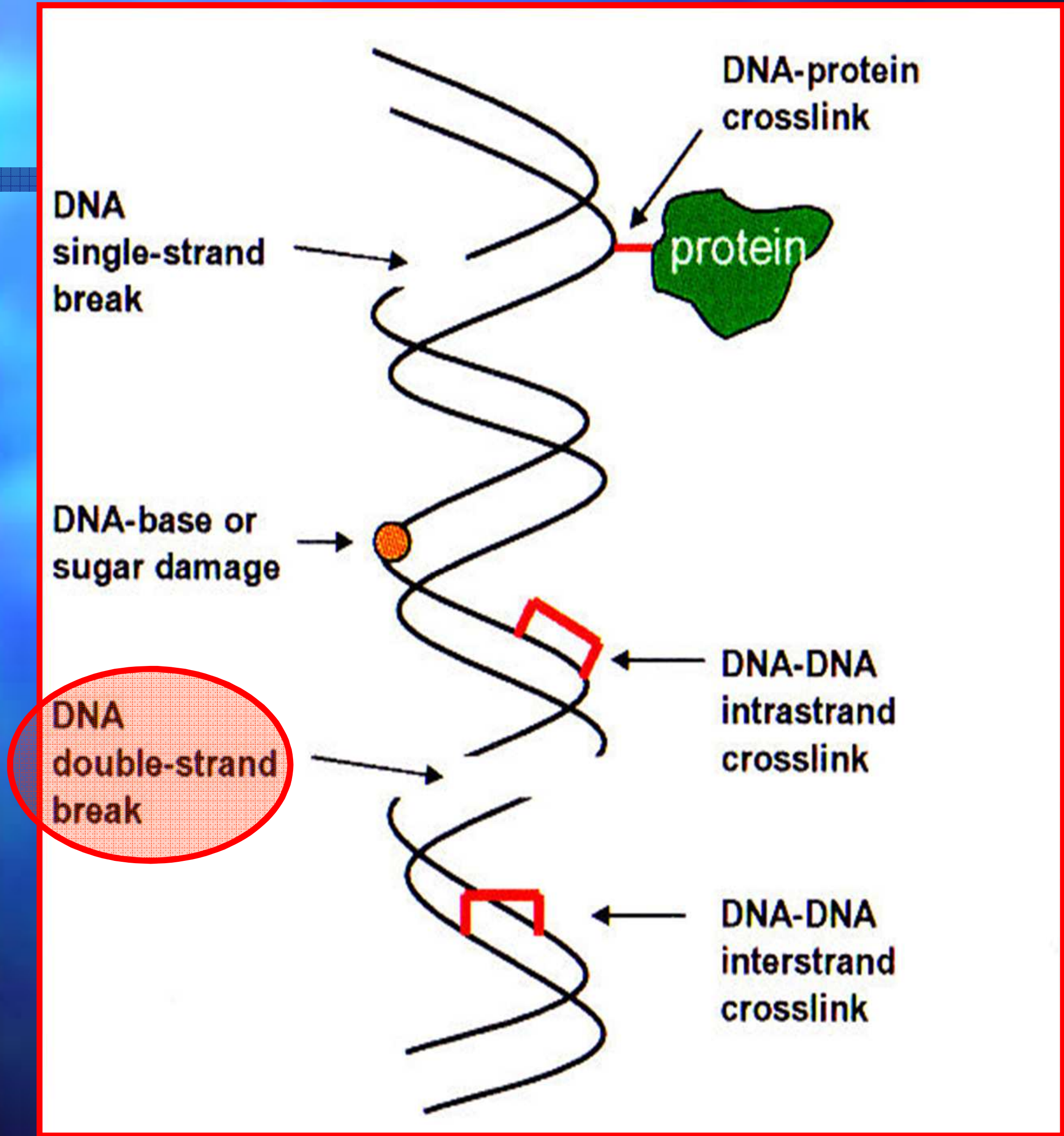
[Quarterly Journal of Microscopical Science, Vol. 97, part 1, pp. 29-37, March 1956.]



Other Evidence for Chromosomes (DNA) As Primary Target in Cell Killing

- Cells killed by radioactive tritiated thymidine incorporated into DNA
- Structural analogues of thymidine when incorporated substantially increase radiosensitivity of cells
- Transplantation of irradiated nucleus into unirradiated cell is lethal at doses that an unirradiated nucleus can survive

Types of Radiation induced DNA damage



Damage in a mammalian cell nucleus
(1 Gy of low-LET radiation)

Initial physical damage

Ionizations in cell nucleus	~ 100 000
Ionizations directly in DNA	~ 2 000
Excitations directly in DNA	~ 2 000

Selected biochemical damage (Ward 1988)

DNA strand breaks DNA	~ 1 000
8-Hydroxyadenine	~ 700
Diol de thymine	~ 200
DNA double-strand breaks	~ 40
DNA-proteins crosslinks	~ 150

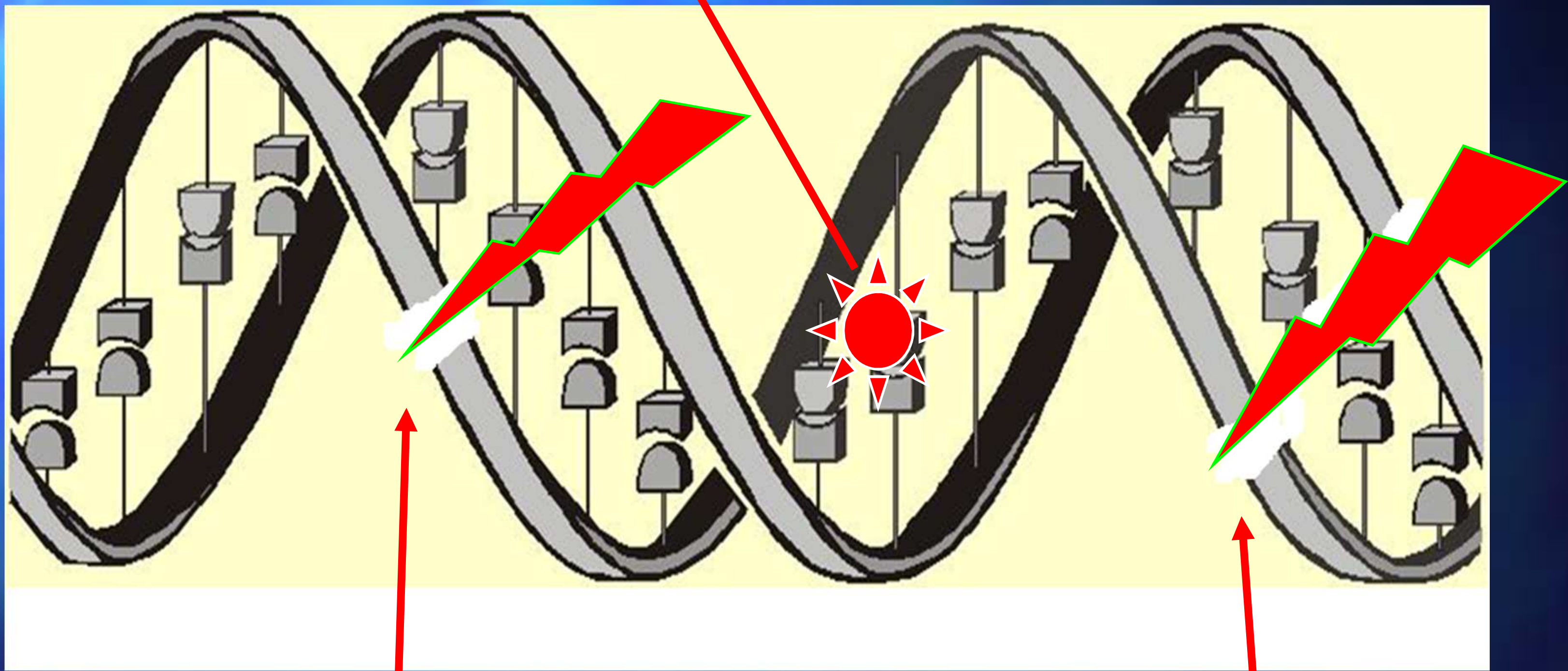
Selected cellular effect

Lethal events	~ 0.2-0.8

D.T. Goodhead, IJRB, 65, 7-17 1994

The most important types of radiation induced lesions in DNA

Base damage: 1000-2000 per 1 Gy

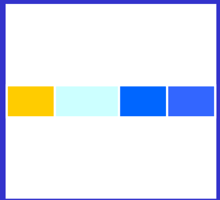


Single-strand breaks
500-1000 per 1 Gy

Double strand breaks
40-50 per 1 Gy

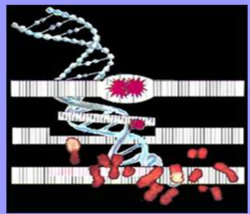
DNA is the most important molecule that can be changed by radiation

Effects of DNA Damage



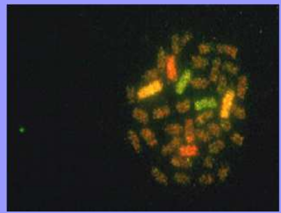
[Gene Expression]

A gene may respond to the radiation by changing its signal to produce protein. This may be protective or damaging.



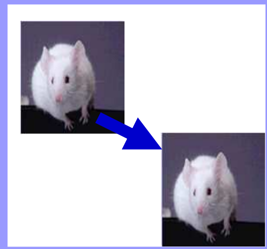
[Gene Mutation]

Sometimes a specific gene is changed so that it is unable to make its corresponding protein properly



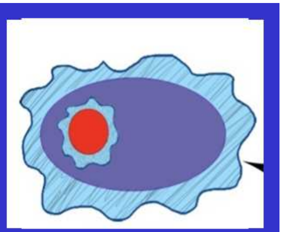
[Chromosome Aberrations]

Sometimes the damage effects the entire chromosome, causing it to break or recombine in an abnormal way. Sometimes parts of two different chromosomes may be combined



[Genomic Instability]

Sometimes DNA damage produces later changes which may contribute to cancer.

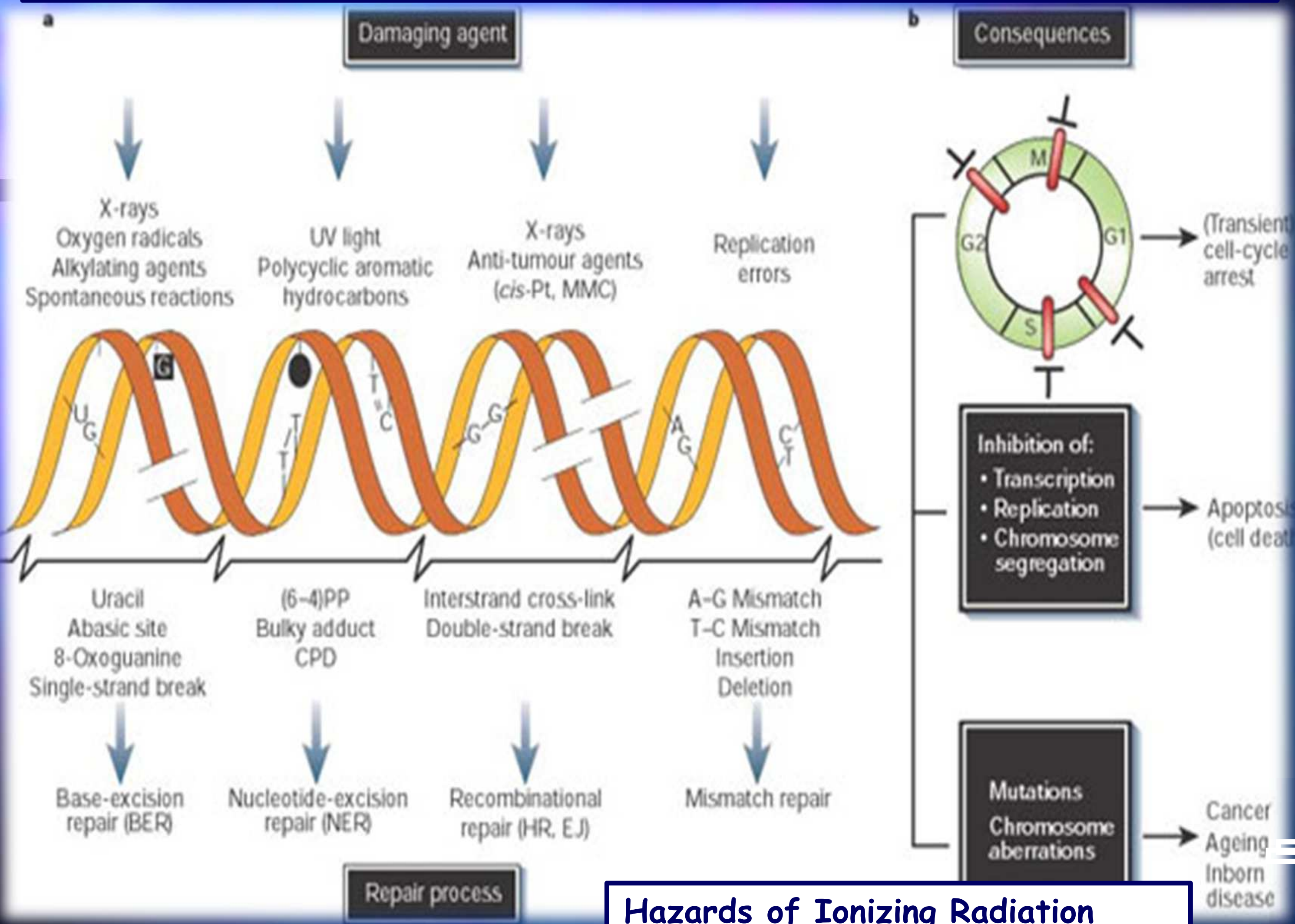


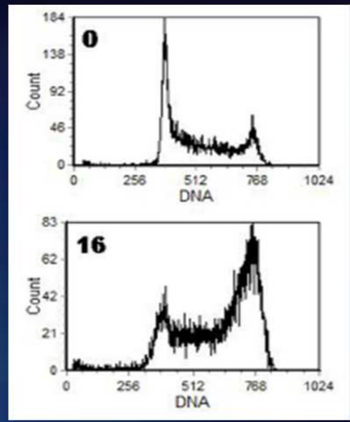
[Cell Killing]

Damaged DNA may trigger apoptosis, or programmed cell death.
If only a few cells are affected, this prevents reproduction of damaged DNA and protects the tissue.

Studies have shown that most radiation-induced DNA damage is normally repaired by the body

Radiation effect on DNA: CONSEQUENCES





Hazards of Ionizing Radiation

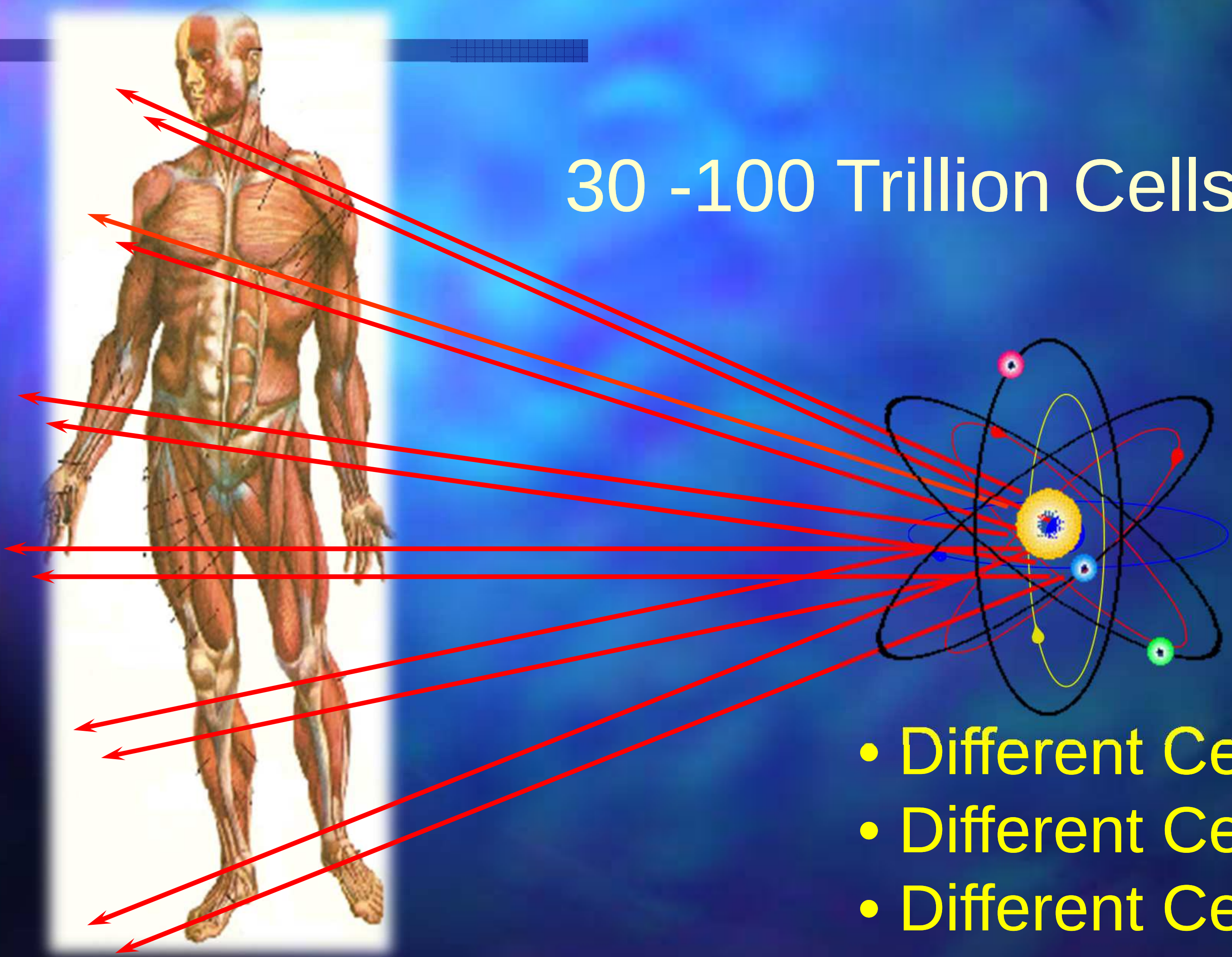
Genetic effects

Carcinogenic effects

Effects on the developing embryo/fetus

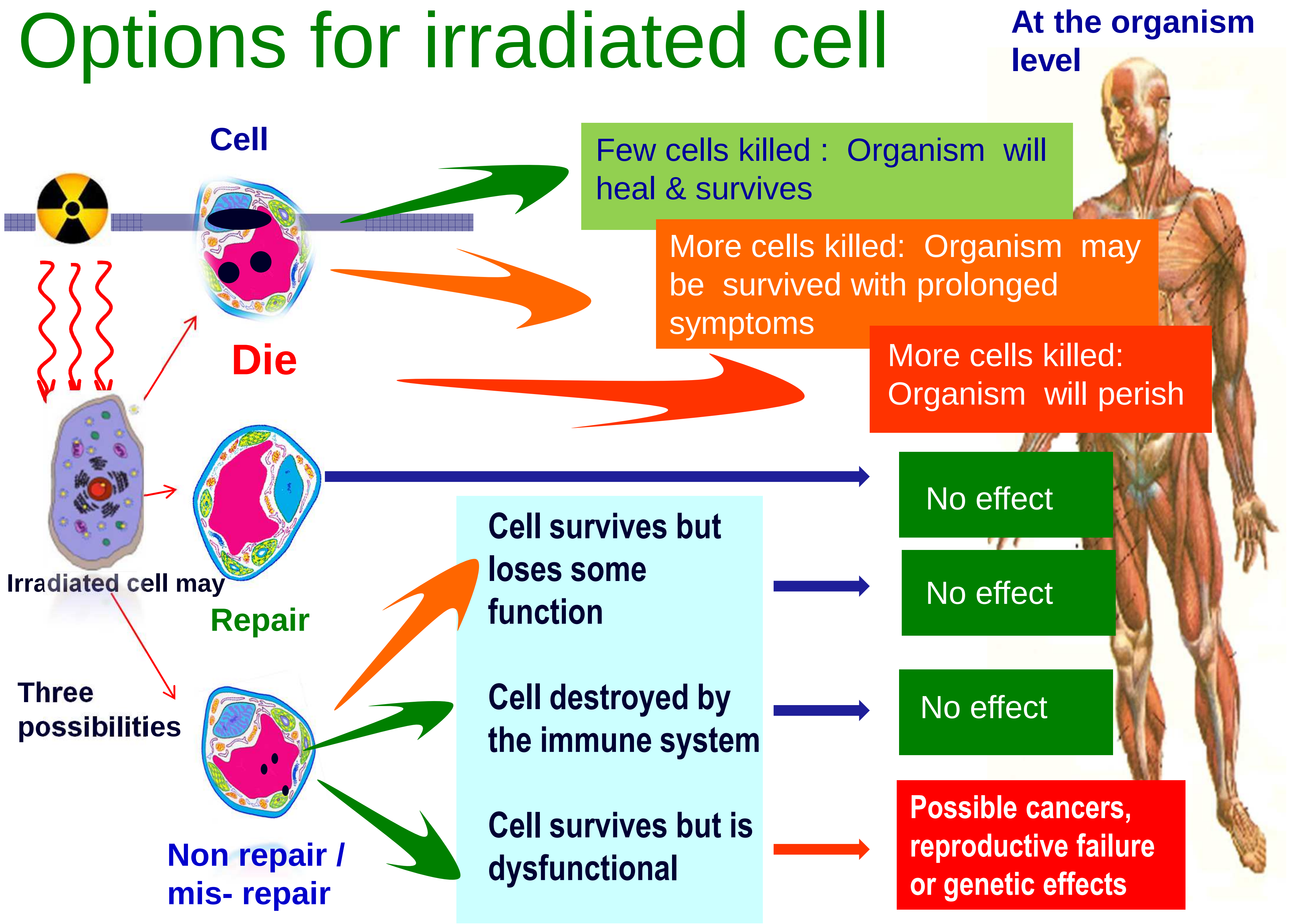
HUMAN EXPOSURE

30 -100 Trillion Cells at Risk



- Different Cell Types
- Different Cell Cycle
- Different Cell Targets

Options for irradiated cell



Cellular radiosensitivity
Law of Bergonie' and Tribondeau

"*The radiosensitivity of a population of cells is directly proportional to their reproductive activity and inversely proportional to their degree of differentiation*."

Cells tend to be radiosensitive if they have three properties:

- Cells that have high division rate
  (the time between divisions)
- Cells that have long dividing future
  (immature cells in early cellular life)
- Cells that are unspecialized
  (cells which have a widely diverse future)

Relative Sensitivity of Cells and Tissue Types

MOST SENSITIVE

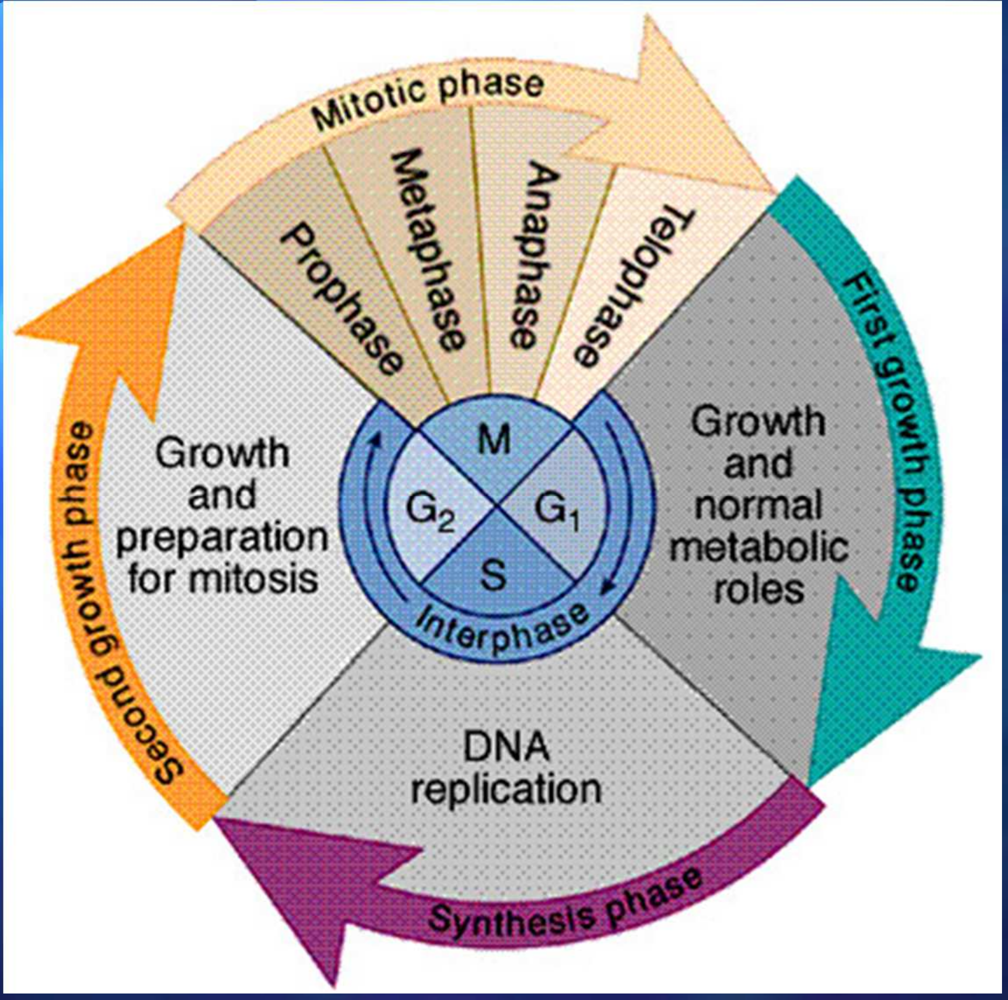
Lymphocytes
Spermatogonia
Hematopoietic (Blood Forming)
Intestinal Epithelium
Skin
Nerve Cells
Muscle Tissue
Bone

- Cells most affected:
  - Rapidly dividing cells: (small intestines, bone marrow, fetus)
- Cells least affected:
  - Slowly dividing cells: (brain, nerves)

LEAST SENSITIVE

The Cell Cycle

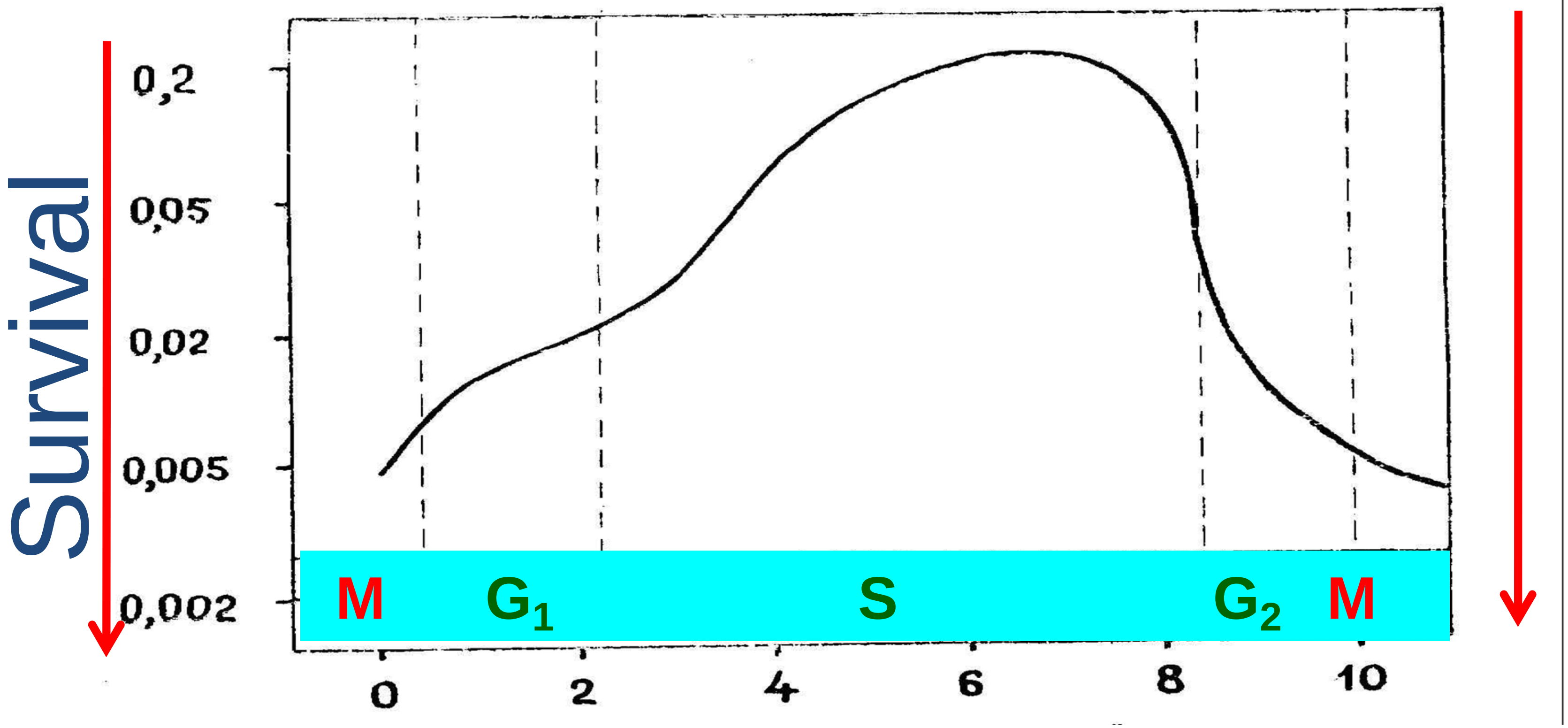
(Ordered set of events, culminating in cell division into two daughter cells)



Radiosensitivity & Mitotic Cycle

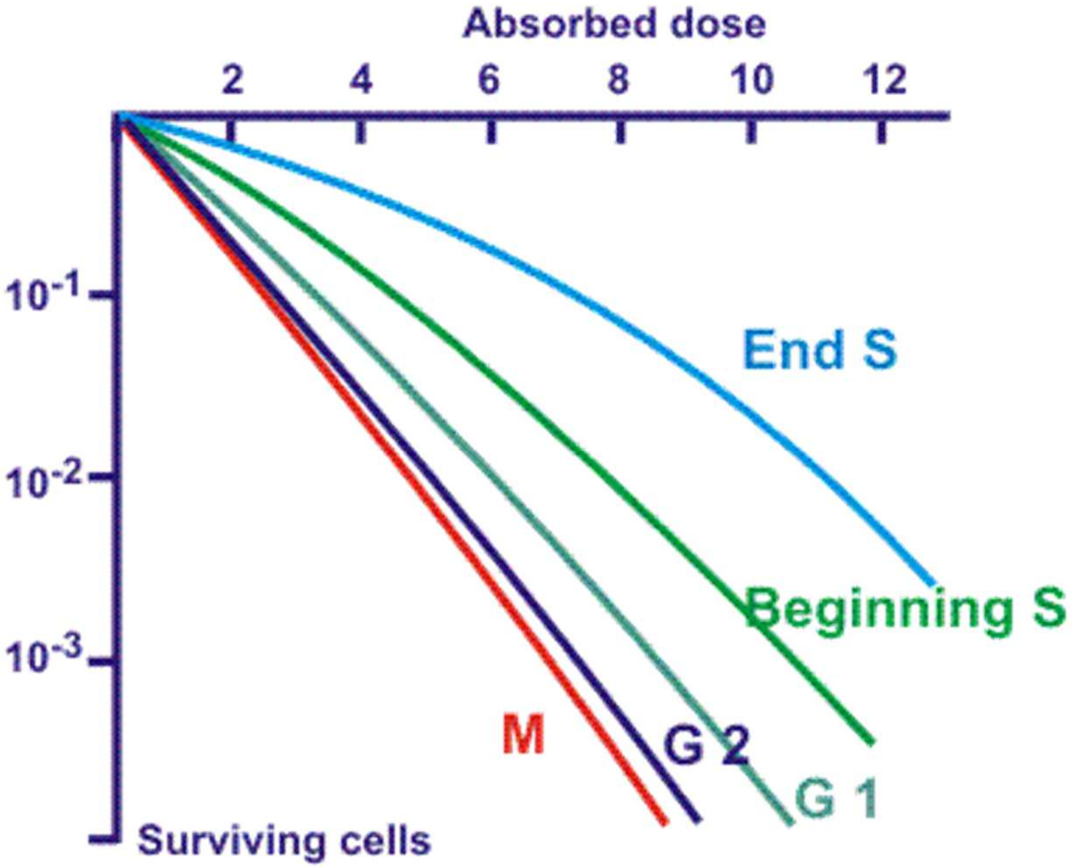
- Sensitivity
  - Cells most sensitive – Mitotic and close to mitosis
  - Resistance greatest in latter part of S
  - For long G_1's, there is an early resistance period followed by sensitive one at the end of G_1
  - $G_2 \sim M$ in sensitivity

Radiosensitivity of cells during cell cycle



Relative survivability of cells irradiated in different phases of the cell cycle: synchronised cells in late G_2 and in mitosis (M) showed greatest sensitivity to cell killing

Cell cycle & RADIOSENSITIVITY



Survival curve of Chinese hamster cells irradiated at various cycle phases after cellular blocking and synchronizing. There is a greater sensitivity to radiation at phase M, G2 and G1 and a lesser sensitivity during phase S.

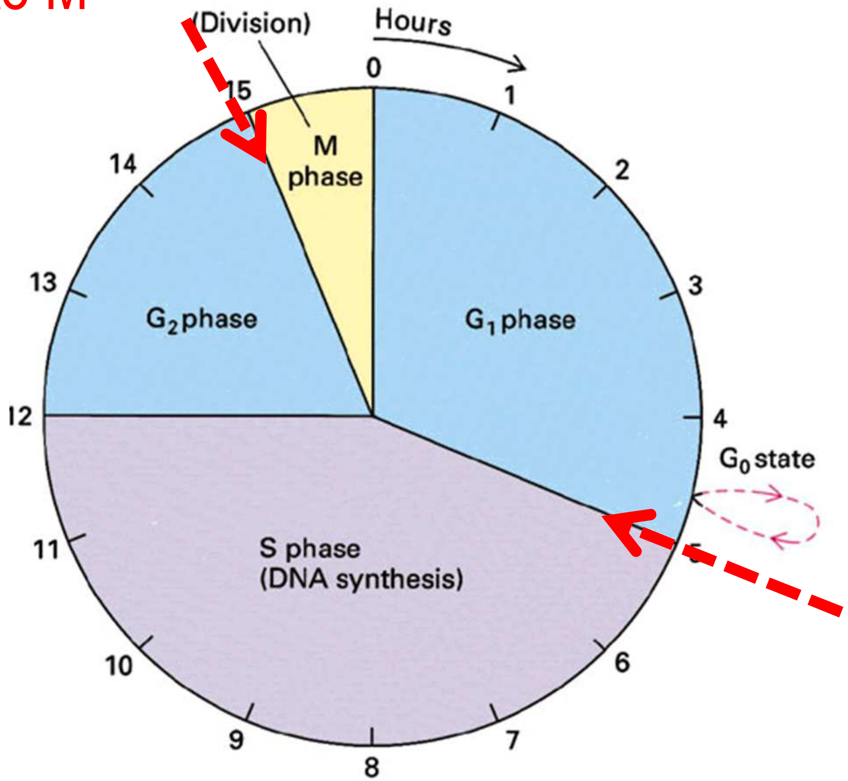
(From Sinclair, W.K., Radiat. Res., 33, 620, 1968)

Effect of radiation on cell cycle

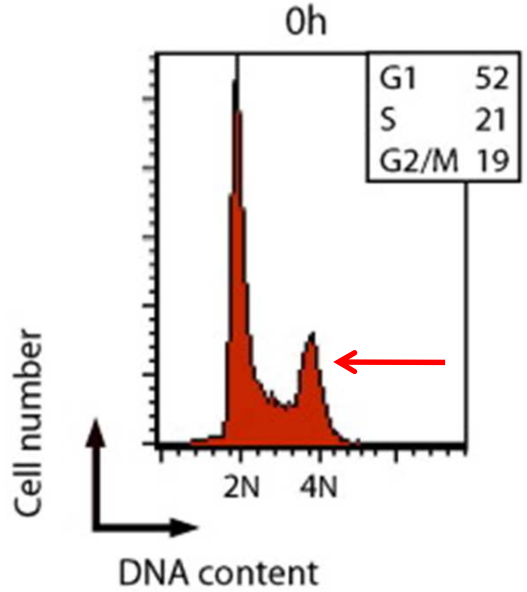
Perturbation in the cell cycle

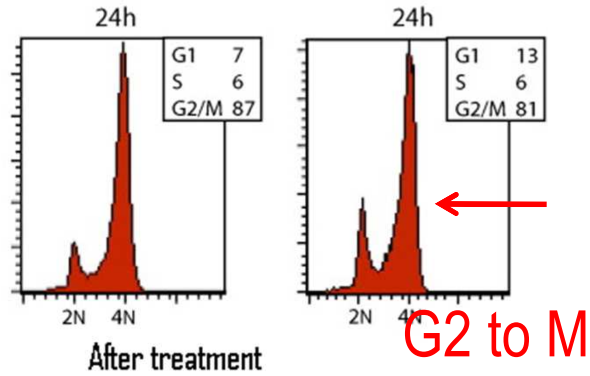
Mitotic delay, cell cycle delay, G_2–block

Blocking progression of cells from G1 to S & G2 to M



DNA histograms





Biological effects of radiation

Distinguished as:

Somatic – affect the individual- (Complex molecules, Sub-cellular/cellular, Tissue, Whole organism)

Somatic effects can be:

Deterministic (Non- Stochastic) – There is a threshold of damage. All early effects, and most normal tissue late effects. The severity depends on dose.

Stochastic – There is no threshold. The <u>effect</u> (e.g. cancer) is independent of dose but its <u>probability</u> *is* dose dependent.

Genetic – affect descendents - → long-term damage – can affect populations

Radiation effects

Early (deterministic only) < 3 months

Local

Radiation injury of individual organs: functional and/or morphological changes within hrs-days-weeks

Common

Acute radiation syndrome

Late (> 3 months /years)

Deterministic

Radiation dermatitis
Radiation cataract
Teratogenic effects

Stochastic

Tumours
Leukaemia
Genetic effects

Radiation-induced Mutagenesis

- Radiation *DOES NOT* produce new, unique mutations, but increases the incidence of the same mutations that occur spontaneously.
- Mutation incidence in humans is *DOSE* and *DOSE-RATE* dependent.
- A dose of 1 rem (10 mSv) per generation increases 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.

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. Solid 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.

TISSUE SENSITIVITY

Radiation sensitivity of a tissue is:

- Proportional to the rate of proliferation of its cells
- Inversely proportional to the degree of cell proliferation

Most sensitive: Blood forming organs

Reproductive organs

Skin

Bone and teeth

Muscles

Least sensitive: Nervous system

Developing embryo: - Most sensitive (early stages of differentiation, more sensitive during first trimester than in later trimesters

Human Populations in which Radiation Effects have Been Observed

Population

- Radiologists
- Atomic bomb survivors
- Radiation accident victims
- Uranium miners
- Radium watch dial painters
- Patients treated with ^{131}I
- Children treated for enlarged thymus
- Irradiation *in utero*

Effects

- Childhood malignancy
- Leukemia,
- Reduced life span
- Malignant disease
- Acute lethality
- Thyroid cancer
- Lung cancer
- Bone cancer
- Fertility impairment

Types of Radiation Response – after human exposure

- If the response to radiation happens in minutes or days it is referred to as **early effects of radiation.**

- If the responds is not observed for six months or more, it is termed to be **late effects of radiation.**

Early Responses to Radiation in Humans

- Acute radiation syndrome
  - Hematological Syndrome - Hematological depression
  - Gastrointestinal Syndrome
  - Central Nervous System Syndrome
- Local tissue damage
  - Skin
  - Gonads
  - Extremities

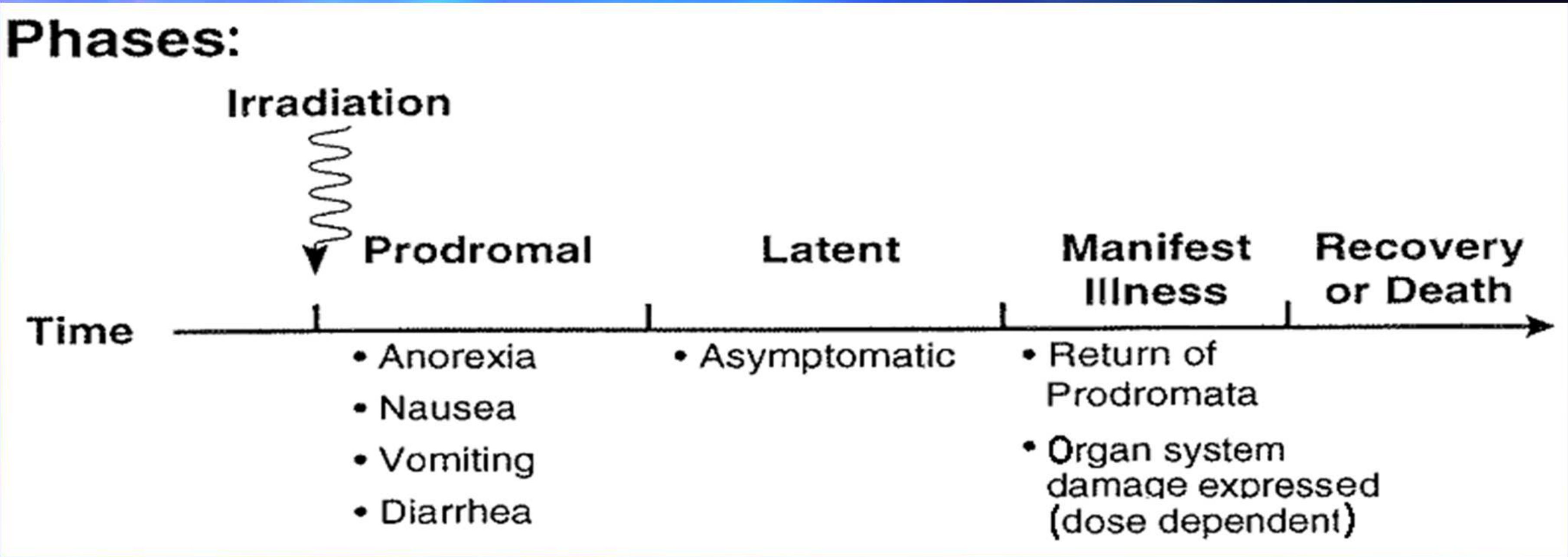
Late Responses to Radiation in Humans

- Leukemia
- Other malignant disease
  - Bone Cancer
  - Lung Cancer
  - Thyroid Cancer
  - Breast Cancer
- Local tissue damage
  - Skin
  - Gonads
  - Eyes
- Shortened life span
- Genetic damage

Effects of Fetal Irradiation in Humans

- Prenatal death
- Neonatal death
- Congenital malformations
- Childhood malignancy
- Diminished growth and development.

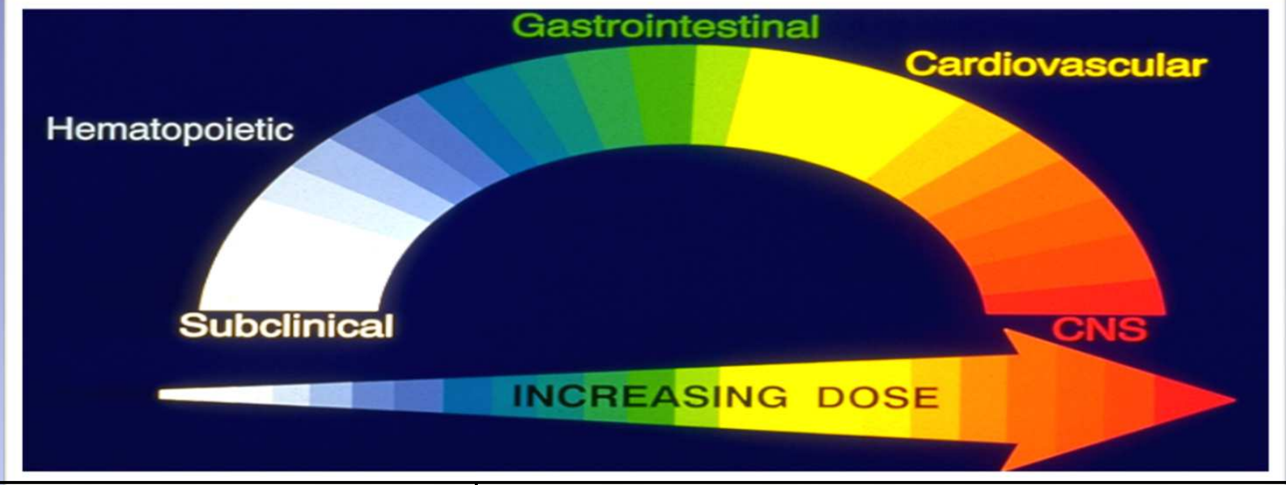
Acute Radiation Syndrome



Dose Levels and Lethal Effects:

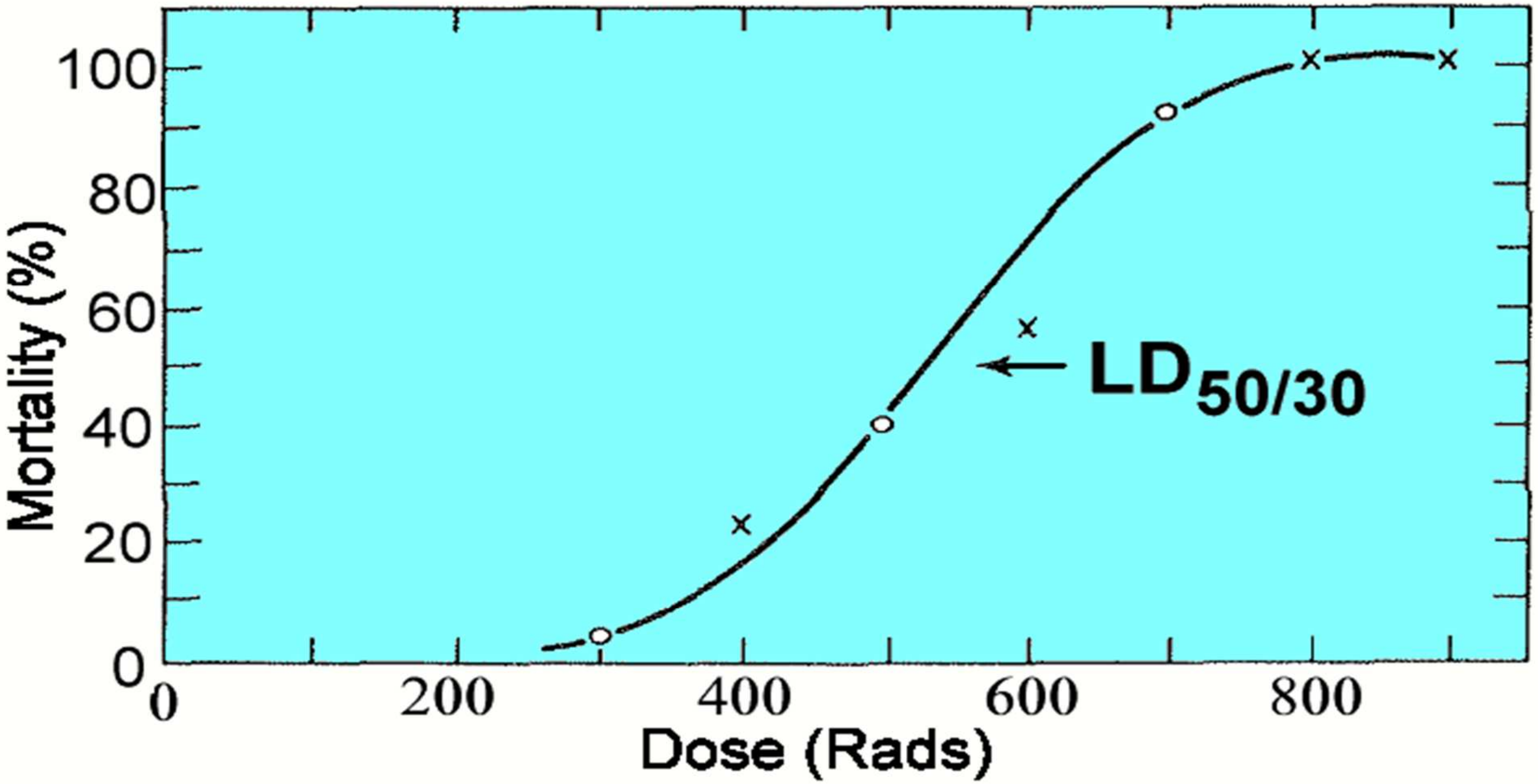
- **>50 Gy:** Cerebrovascular syndrome (system collapse)
- **> 5 Gy:** Gastrointestinal death (crypt cells destroyed)
- **3-5 Gy:** Hematopoietic death (stem cell destruction)

SPECTRUM OF RADIATION INDUCED SYNDROME



Dose (Gy)	Name of the radiation syndrome	Symptoms & consequences
1 - 2	Nausea, vomiting, diarrhea (NVD) syndrome	Nausea, vomiting, diarrhea, anorexia, giddiness, and loss of appetite
2 - 6	Haematopoetic syndrome	Bone marrow, spleen and thymus gets affected. Approximate time of death varies between 10- 30 days.
8 - 15	Gastrointestinal (GI) syndrome	Damage to intestinal crypt takes place resulting in loss of absorption of nutrient, dehydration, loss of weight, severe electrolyte imbalance and low blood pressure. Death occurs usually within 3 – 5 days.
> 25	Central Nervous System (CNS) syndrome	Irritability, hyper excitability response, epileptic type fits and coma. Symptoms are irreversible. Death usually occurs within 48 hrs.

Whole Body Dose and LD_{50} (30/60)



Mortality of Rhesus Monkeys at 30 days after single whole-body exposure to x-rays

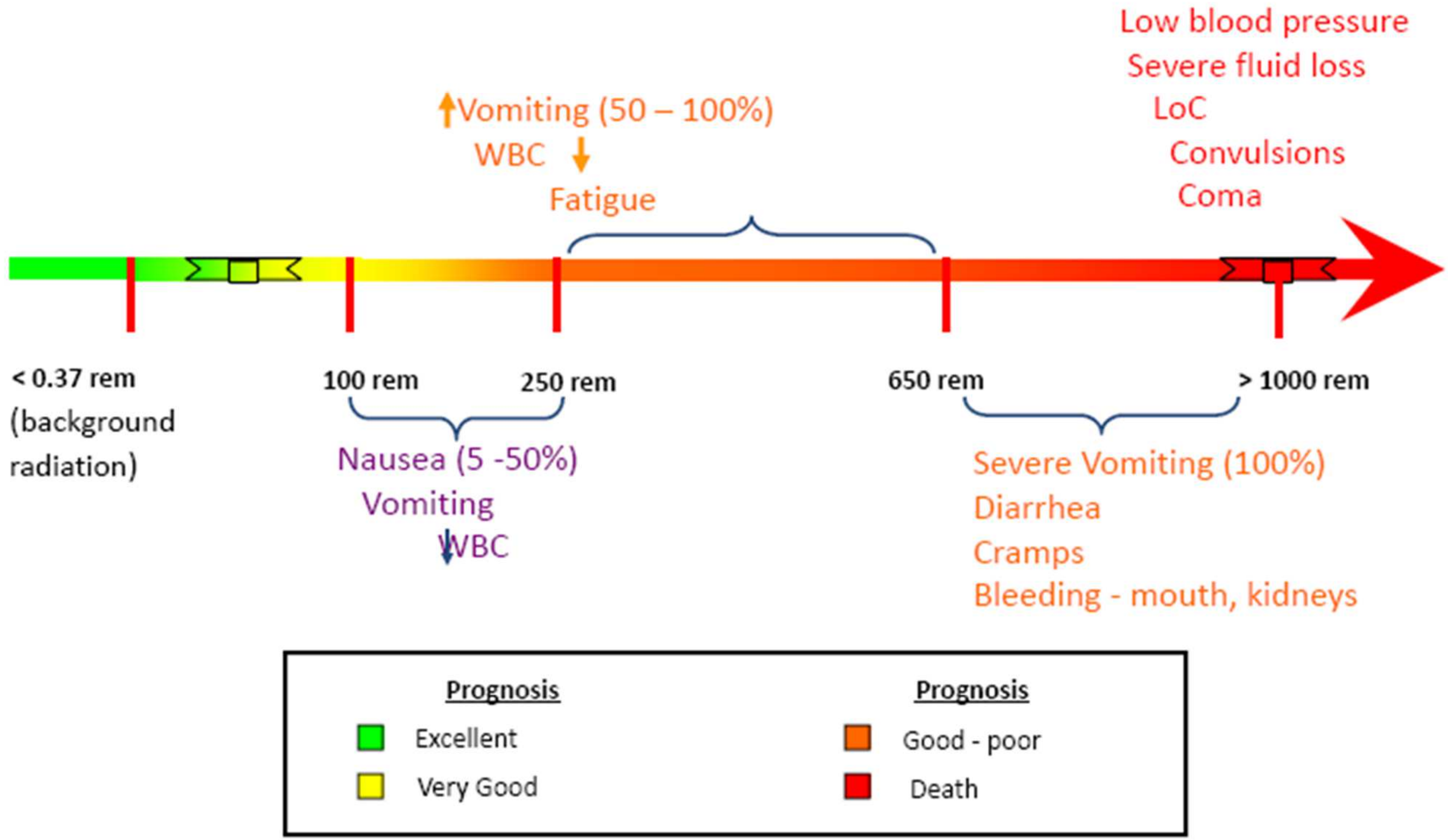
LD_{50}

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

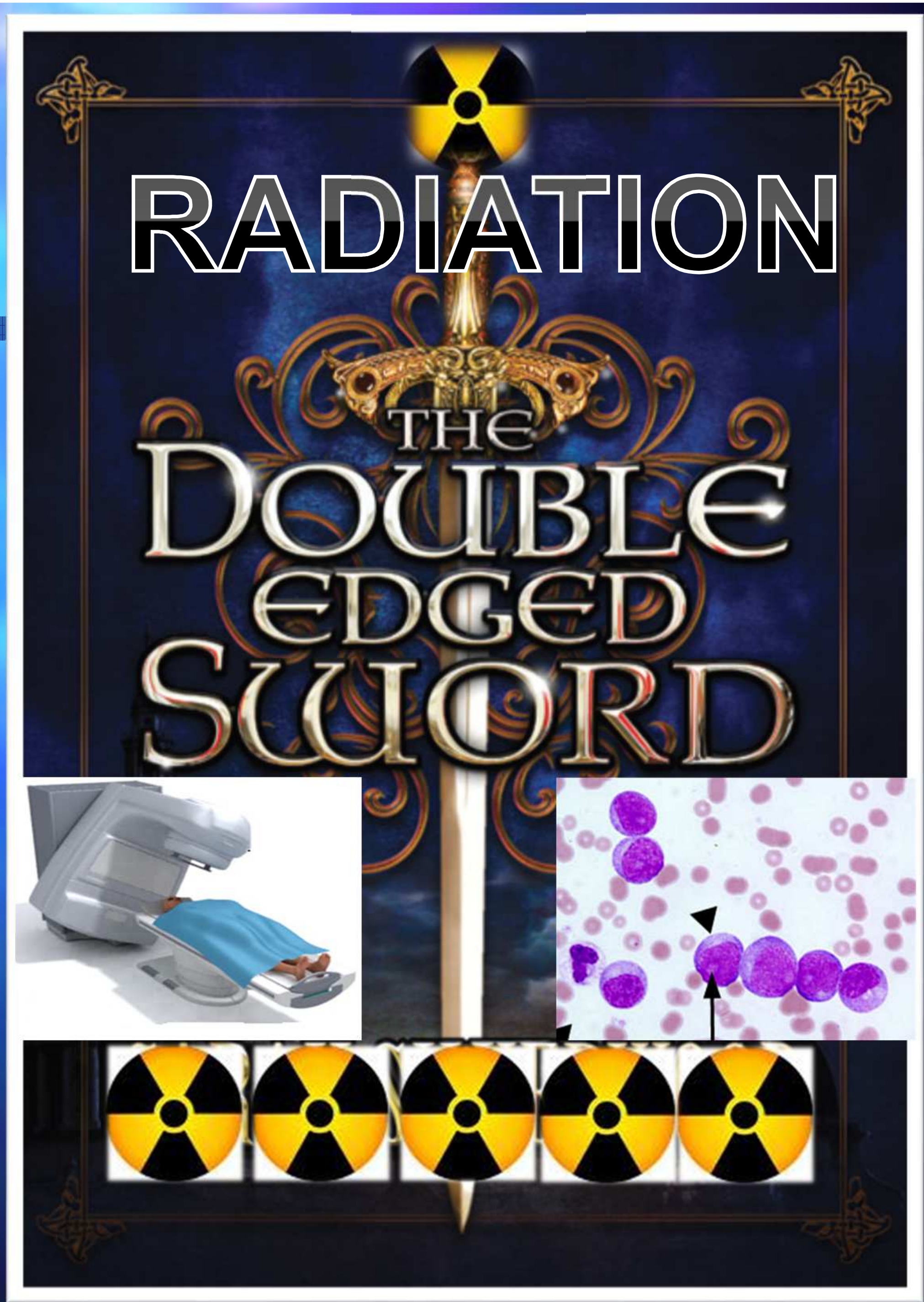
Species	Average Body Weight in kg	LD_{50} in Gy Total-Body Irradiation	Rescue Dose per kg $\times 10^{-8}$	Relative Hematopoietic Stem Cell Concentration
Mouse	0.025	7	2	10
Rat	0.2	6.75	3	6.7
Rhesus monkey	2.8	5.25	7.5	7.3
Dog	12	3.7	17.5	1.1
Humans	70	4	20	1

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

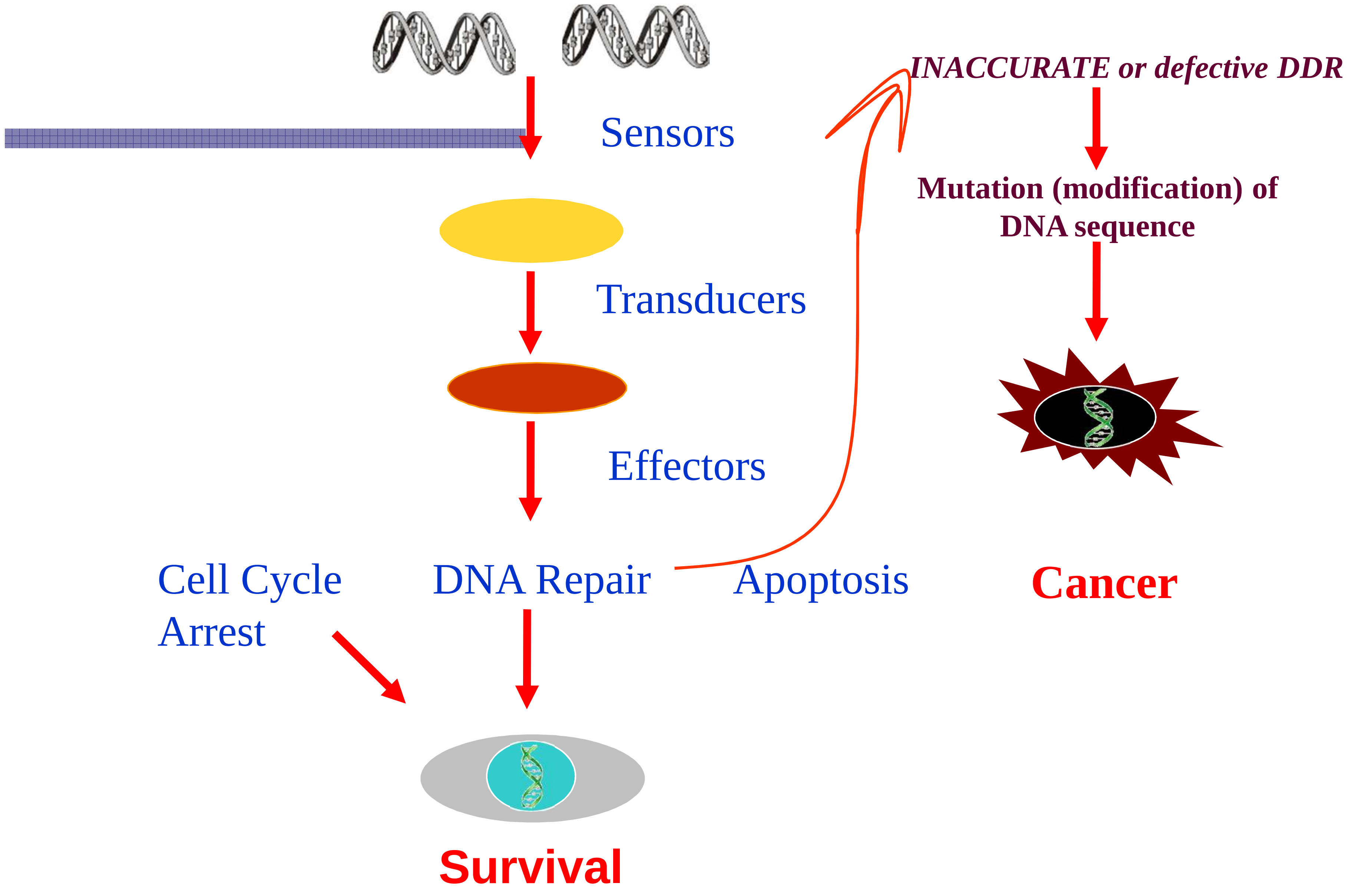
Clinical Symptoms as an Estimator of Radiation Dose

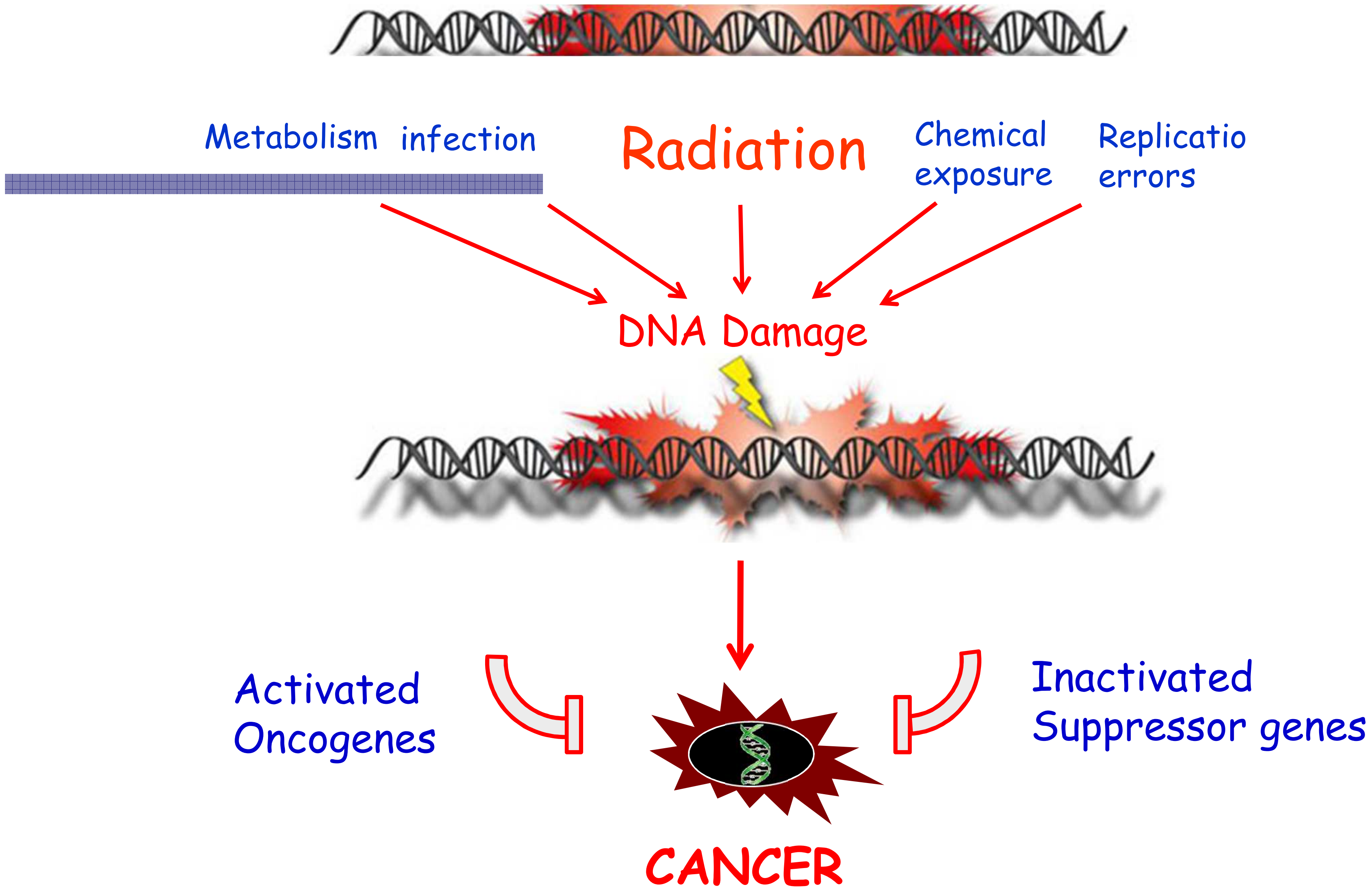


Severity and onset correlate directly with dose and inversely with prognosis


RADIATION
THE
DOUBLE
EDGED
SWORD

Cellular Response to DNA Strand Breaks




Metabolism
infection
Radiation
Chemical exposure
Replicatio errors
DNA Damage
Activated Oncogenes
Inactivated Suppressor genes
CANCER

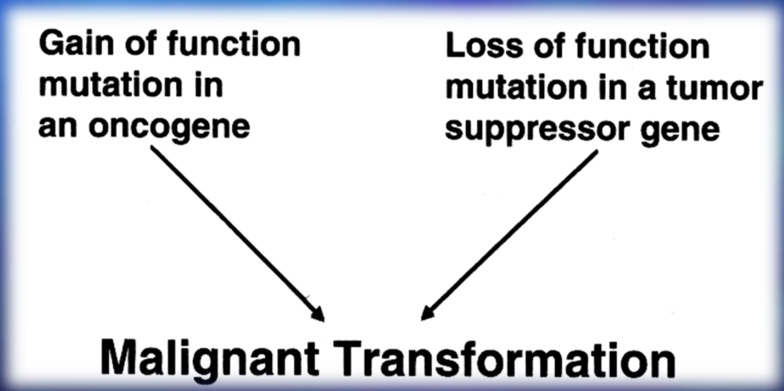
What types of radiation cause cancer?

Ionizing radiations, both photon and particle radiations, induce cancers.

How does radiation cause cancer?

A multi-step induction over 10-20 yrs

- The transformation of a cell from normal to malignant may result from activation of **oncogenes**
- The transformation of a cell from normal to malignant may also result from loss of **tumor-suppressor genes**

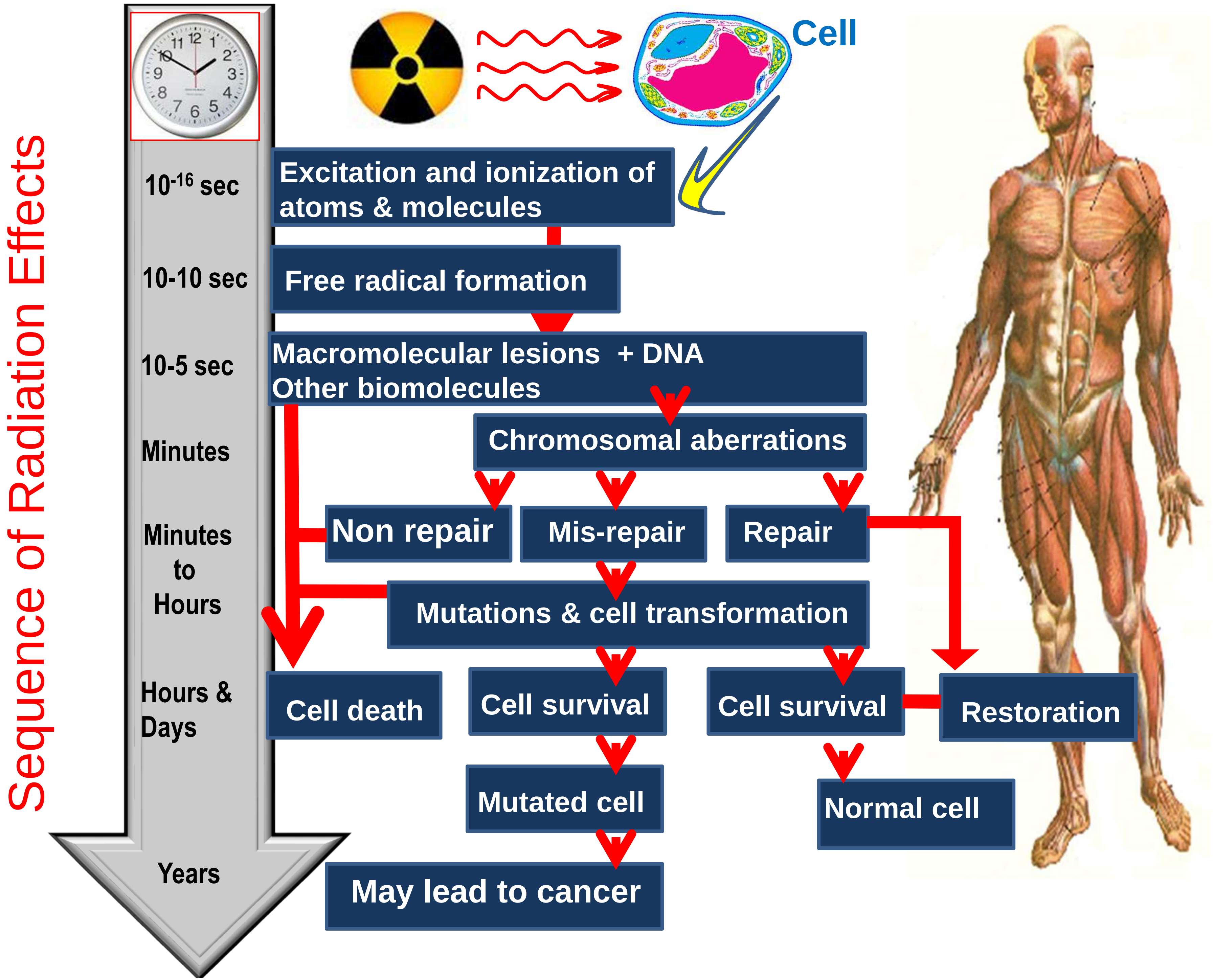


Radiation & Oncogenes

- An oncogene is a gene that contributes to cancer formation when mutated or inappropriately expressed
- Oncogenes can be activated via transformation by radiation, various chemicals, viruses, etc.
- Oncogenes appear to be associated with about 10 - 15% of all cancers
- The *ras* family of oncogenes are the most common

Tumor suppressor genes

- Tumor suppressor genes are normally present in cells and suppress their neoplastic potential
- Missing or mutated tumor suppressor genes can lead to transformation from normal to malignant
- There are over a dozen tumor suppressor genes that have been identified and related to certain cancers



Sequence of Radiation Effects
Cell
10^{-16} sec
10-10 sec
10-5 sec
Minutes
Minutes to Hours
Hours & Days
Years
Excitation and ionization of atoms & molecules
Free radical formation
Macromolecular lesions + DNA Other biomolecules
Chromosomal aberrations
Non repair
Mis-repair
Repair
Mutations & cell transformation
Cell death
Cell survival
Cell survival
Restoration
Mutated cell
Normal cell
May lead to cancer

Conclusion

EFFECTS OF RADIATION

Our knowledge of radiation effects derives primarily from groups of people who have received high doses.

The risk associated with large radiation doses is relatively well established.

However, the risks associated with doses under about 200 mSv are less obvious because of the large underlying incidence of cancer caused by other factors.

Radiation protection standards assume that any dose of radiation, no matter how small, involves a possible risk to human health.

However, available scientific evidence does not indicate any cancer risk or immediate effects at doses below ~ 100 mSv a year.

At low levels of exposure, the body's natural repair mechanisms seem to be adequate to repair radiation damage to cells soon after it occurs.


Thank You!