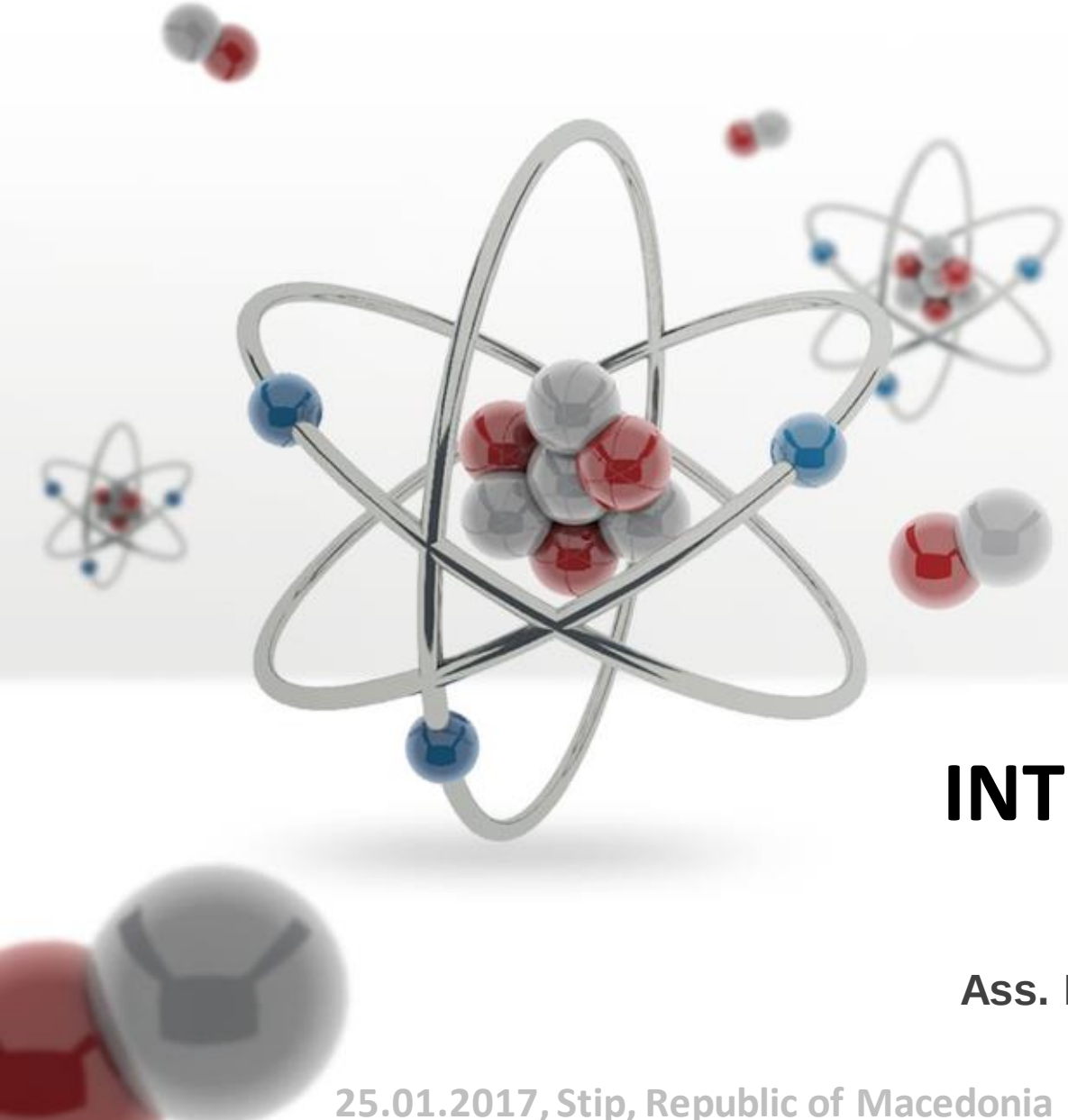
УНИВЕРЗИТЕТ
„ГОЦЕ ДЕЛЧЕВ“
ШТИП

IAEA
International Atomic Energy Agency



INTRODUCTION TO RADIOBIOLOGY

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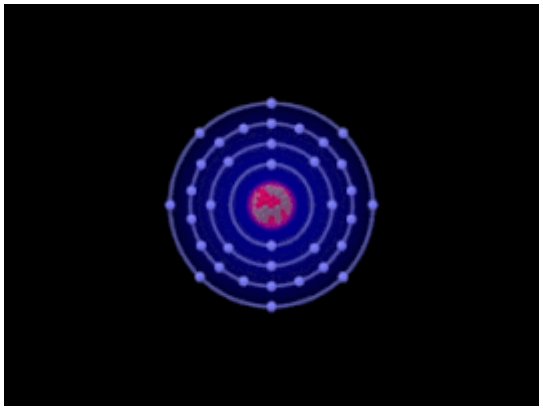
25.01.2017, Stip, Republic of Macedonia

Radiobiology

effects of ionizing radiations on living systems

- mechanism of radiation damage
- radiosensitivity of cells and tissues
- different types of effect on living matter
- risks of cancer and genetic effects from radiation exposure



Sources of ionizing radiation

AVERAGE ANNUAL EFFECTIVE DOSE OF IONIZING RADIATION TO INDIVIDUALS AS IN YEAR 2000

Source	Dose (mSv)	Range (mSv)
Natural background		
External exposure		
Cosmic	0.4	0.3 – 1.0
Terrestrial	0.5	0.3 – 0.6
Internal Exposure		
Inhalation (mainly radon)	1.2	0.2 – 10.
Ingestion	0.3	0.2 – 0.8
Total	2.4	1 - 10
Man-made (artificial)		
Medical	0.4	0.04 – 1.0
Nuclear Testing		0.15 – decreasing trend
Chernobyl accident	0.002	0.04 – decreasing trend
Nuclear power production	0.0002	Decreasing trend
Total	**2.8**	**1 - 10**

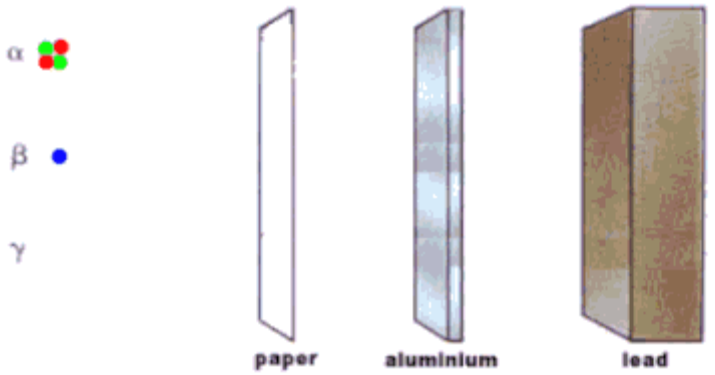
Physics and chemistry of radiation interactions with matter

- Types of radiation (arbitrary)
  - Ionizing

    α, β, γ, X-rays → electromagnetic radiation (X-rays and γ rays)

    α, β, γ, X-rays → particulate radiation (neutrons, alpha and beta particles).

  - Nonionizing (visible, IR- light, radiowaves, microwaves, etc.)



Radiation dose and units

Exposure

- ability to produce ionization in air under standard temperature and pressure
- SI unit Coulombs/kg in air

(old unit: Roentgen , 1 R = 2.58 x 10-4 C/kg air)

cannot be used to describe dose to tissue

Absorbed dose

- The amount of energy absorbed per mass - energy absorbed per unit mass of tissue
- SI units **Gray 1 Gy = 1 J/kg**

(old unit rad, 100 rad = 1 Gy)

Radiation dose and units

Equivalent dose

- to compare the biological effectiveness of different types of radiation to tissues
- **SI dose equivalent in Sievert (Sv)** is the product of the absorbed dose in the tissue multiplied by a radiation weighting factor, (quality factor)

includes the effects of irradiation of tissue by more than one type of radiation

- Unit rem (radiation equivalent man) was used to compare doses received by different types of radiations (100 rem = 1 Sv).

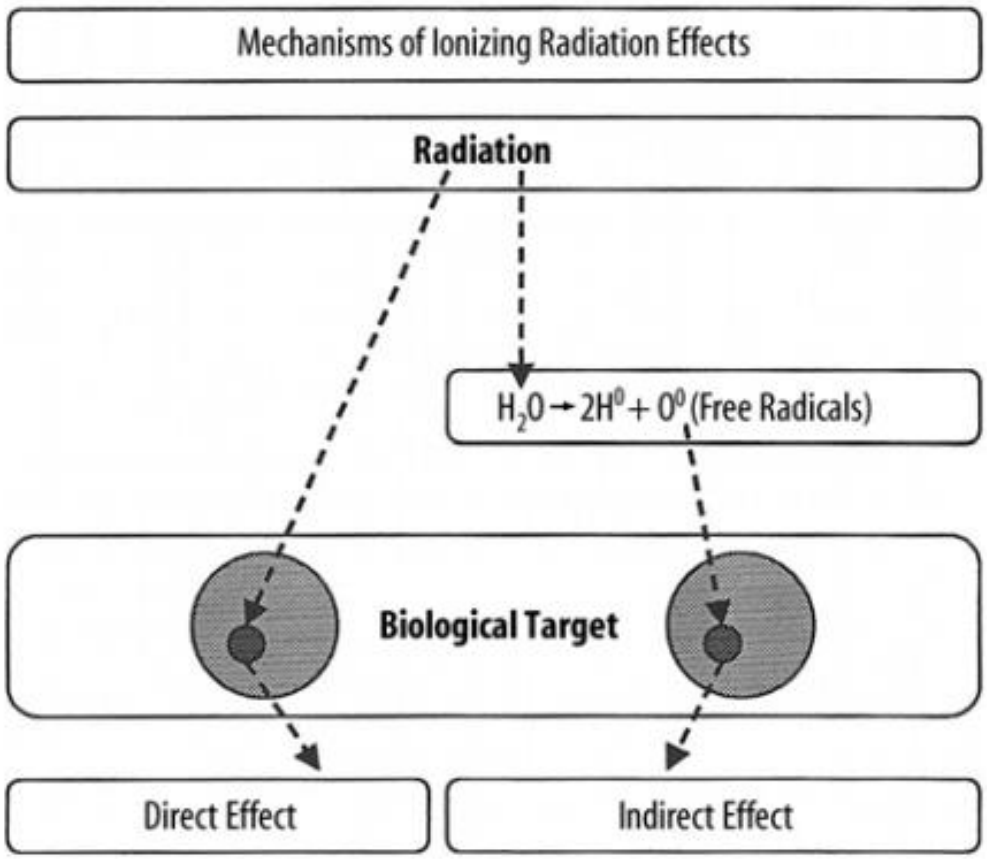
In low LET radiations 1 Sv = 1 Gy.

Effective dose – Unit *Sv,* to estimate the risk of radiation in humans

Collective dose dose received per person in Sv multiplied by the number of persons exposed per year i.e. man-sievert per year

Water radiolysis

depends on the pH and LET of the radiation



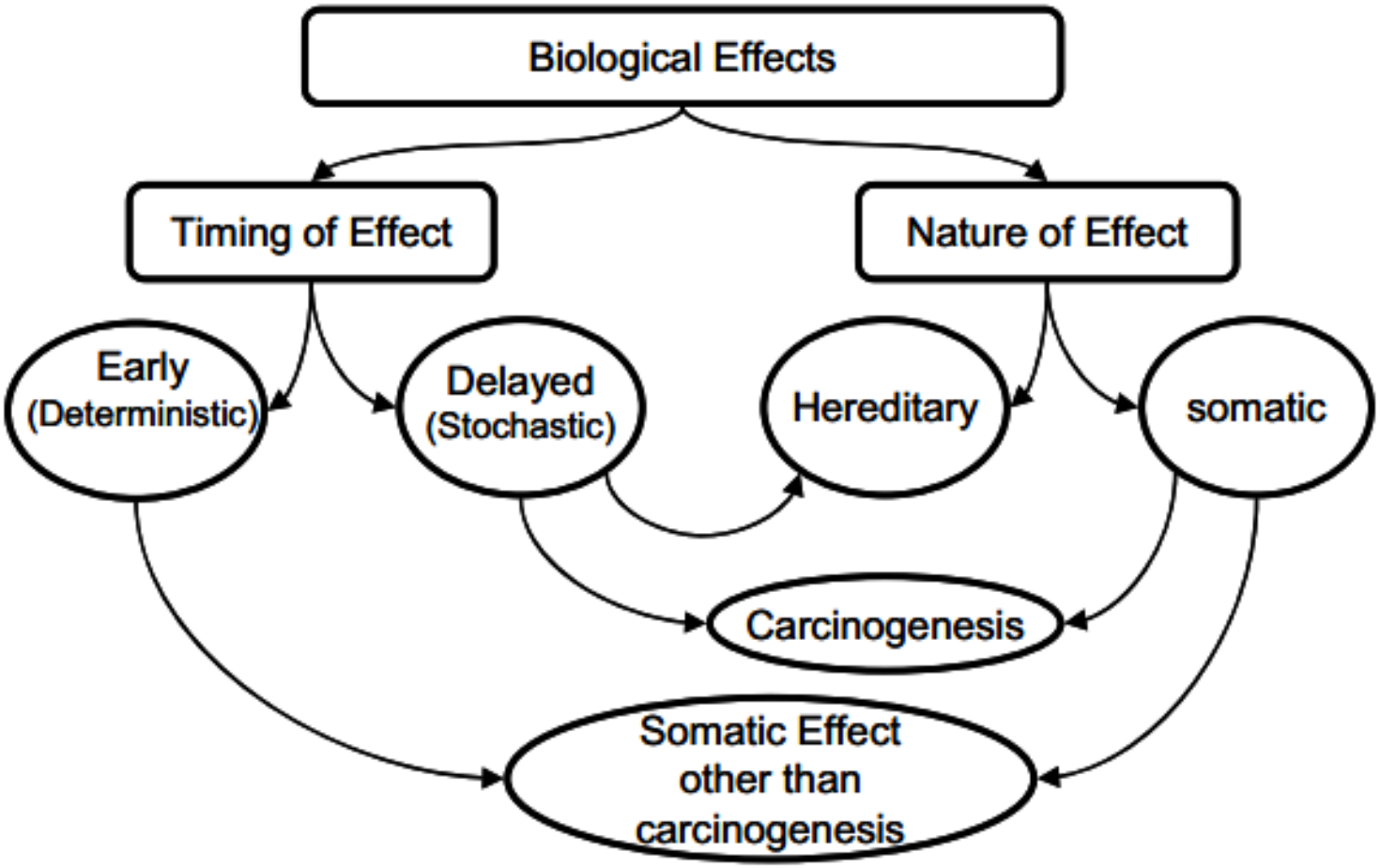
$$H_2O + \text{energy} \rightarrow H_2O^+ + e^-$$
$$H_2O + e^- \rightarrow HOH^-$$
$$H_2O^+ \rightarrow H^+ + OH\bullet \text{ (free radical)}$$
$$HOH^- \rightarrow OH^- + H\bullet \text{ (free radical)}$$
$$H^+ + OH^- \rightarrow H_2O$$
$$H\bullet + OH\bullet \rightarrow H_2O$$
$$OH\bullet + OH\bullet \rightarrow H_2O_2$$
$$H\bullet + O_2 \rightarrow HO_2\bullet \text{ (perhydroxyl radical)}$$

- Free radicals of biomolecules can be restituted by hydrogen donating compounds, such as thiols and cysteine = **repair**
- Alternatively, they can be fixed by reaction with oxygen or oxygen mimicking compounds = **permanent damage**

Biological effects of ionizing radiation

- Biological effects of ionizing radiation depend on several factors that make them variable and inconsistent

- The effects are classified based on their nature and timing after exposure
  - early or delayed (stochastic or deterministic)
  - somatic or hereditary


Biological Effects
Timing of Effect
Nature of Effect
Early
(Deterministic)
Delayed
(Stochastic)
Hereditary
somatic
Carcinogenesis
Somatic Effect
other than
carcinogenesis

Molecular and cellular radiobiology

Radiation lesions in DNA

- Loss of a base
- Cleavage of the hydrogen bond between bases
- Breakage of one strand of the DNA molecule in the phosphodiester linkage (single strand)
- Breakage of both strands of the DNA molecule in opposing sites (double strand)
- Crosslinks (protein-DNA, protein-protein) involving nuclear proteins such as histones and non-histone proteins.

Radiation lesions in DNA

The number of mutations increases with increasing radiation exposure

- In low-dose exposures, the breaks are single stranded and can be repaired by joining the broken components in the original order.
- In higher exposures, double strand breaks occur and the odds for repair decrease.

high-LET radiations cause more damage

How are changes repaired?

Altered base

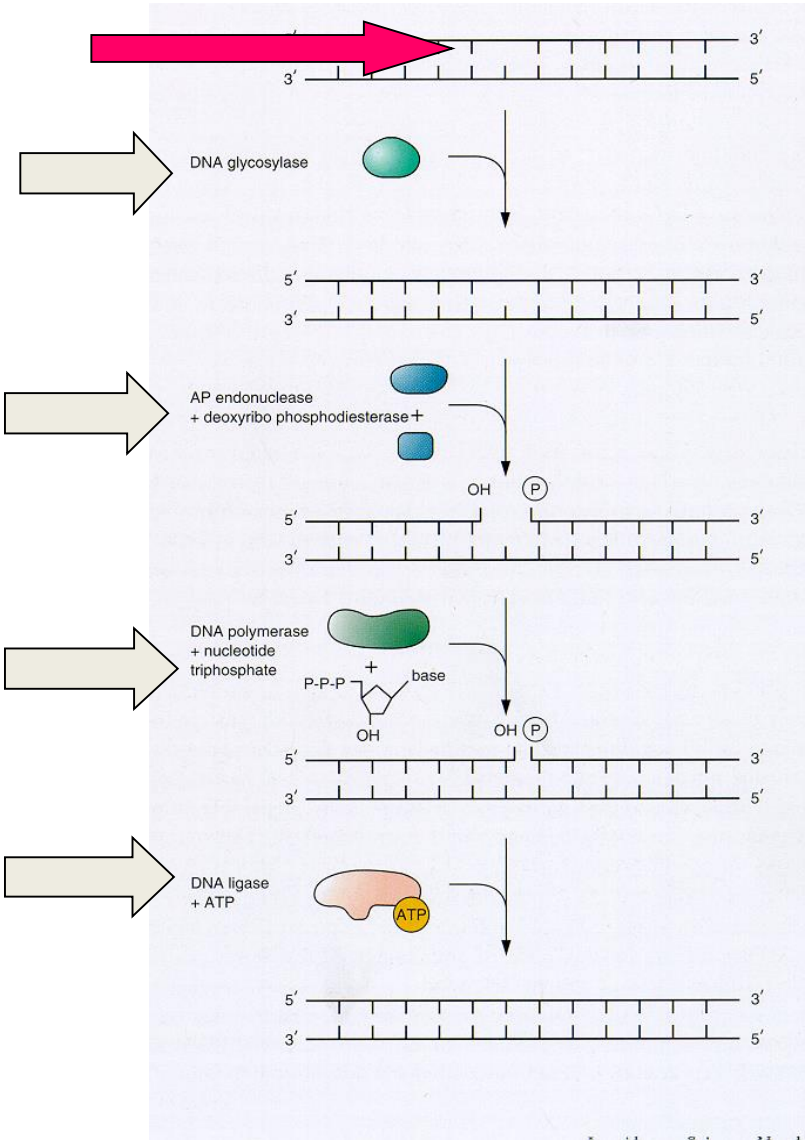
Glycosylases **recognizes lesion and release damaged base**

AP-endonuclease **makes incision and releases remaining sugar**

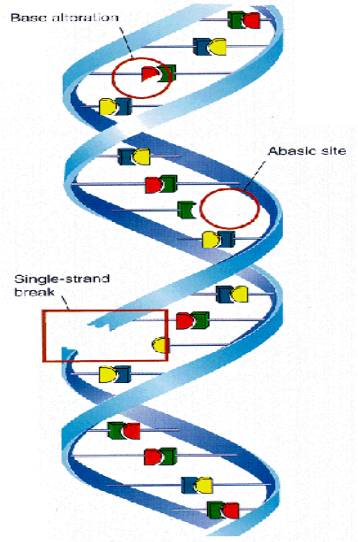
DNA-polymerase **fills resulting gap but nick remains**

DNA ligase **seals the nick. Repair completed.**

DNA has been repaired with no loss of genetic information

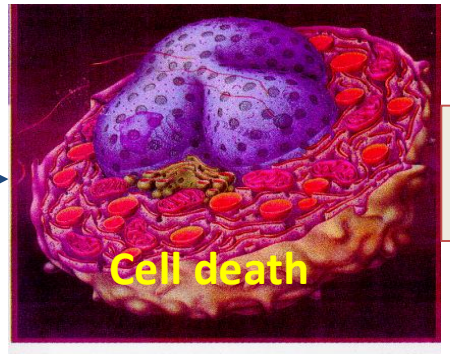


Outcomes after cell exposure

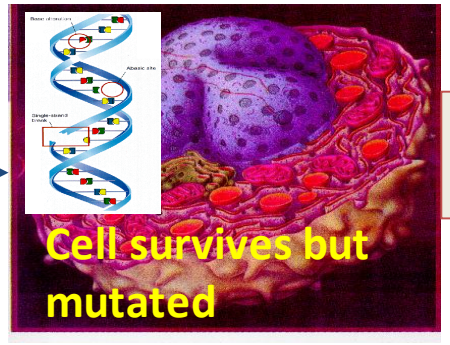


DNA Mutation

Viable Cell



Unviable Cell



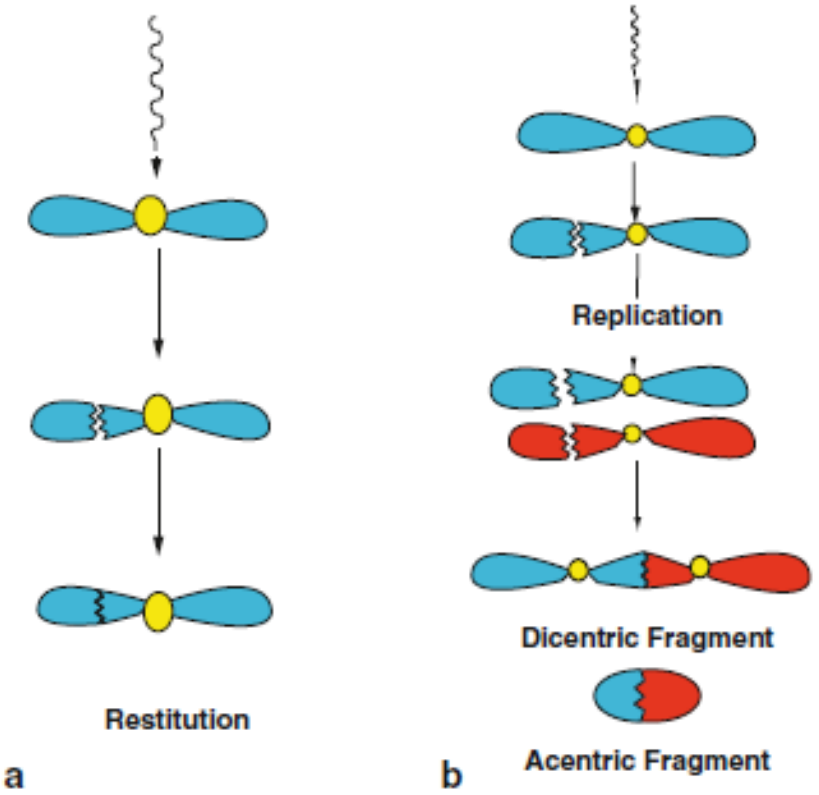
Cancer?

Influence to chromosomes

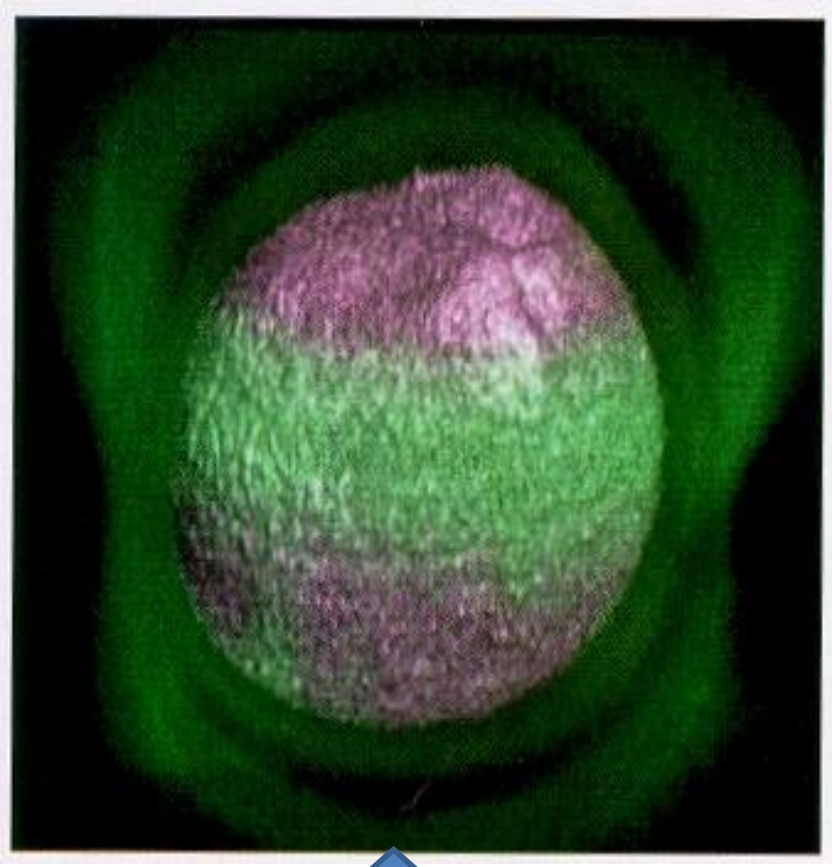
Chromosomal aberrations

- Chromatid aberrations, irradiation occurs after DNA synthesis **prior to mitosis** and only one chromatid is affected.
- Chromosome aberrations, irradiation occurs **after mitosis prior to DNA synthesis** and the broken chromatids are duplicated producing daughter cells with damaged chromosomes.

Outcome?

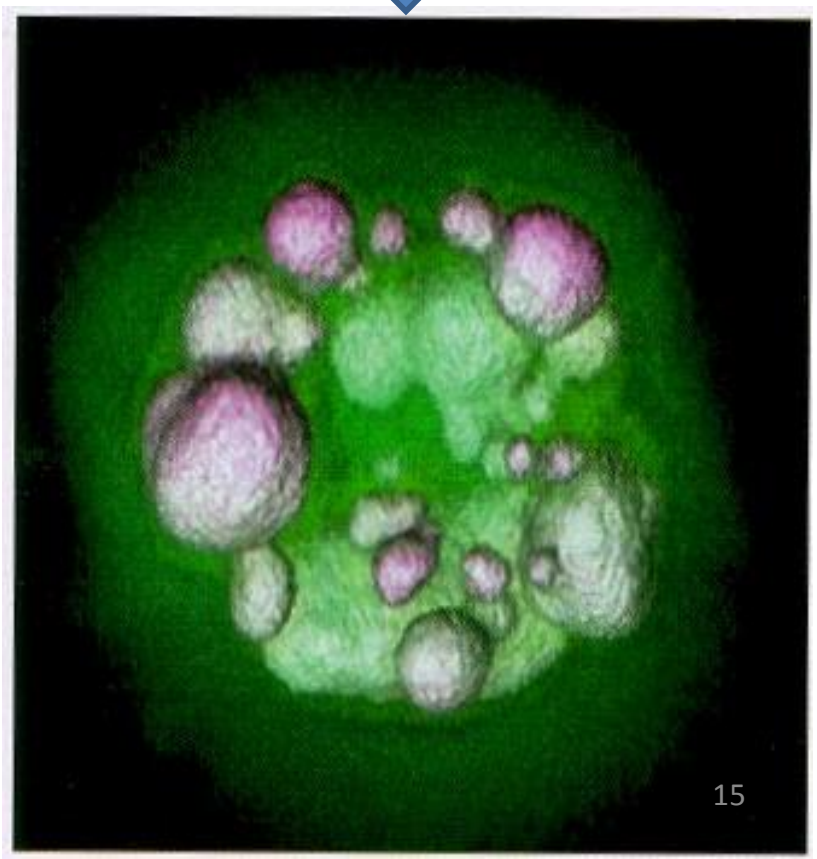


Repair **Genetic mismatch**



Normal human lymphocyte: chromosomes uniformly distributed

Apoptotic cell: Chromosomes and nucleus fragmented and collapsed into apoptotic bodies



Repair of chromosomes after irradiation

Depends on:

- sites of break in the DNA/ chromosome
- total radiation dose
- the dose rate
- LET of the radiation

Radiosensitivitiy of cells

- **Undifferentiated cells** that are undergoing active mitosis are most sensitive to radiation (law of Bergonièe and Tribondeau)
- Differenttiated and mature cells are least effected (loss of cellular function)

Types of cells[a]		Radiosensitivity
VIM	Mature lymphocytes Erythroblasts Spermatogonia	Highly sensitive
DIM	Myelocytes Intestinal crypt cells Basal cells of epidermis	Relatively sensitive
MCT	Osteoblasts Spermatocytes Chondroblasts Endothelial cells	Intermediate sensitivity
RPM	Spermatozoa Granulocytes Erythrocytes Osteocytes	Relatively resistant
FPM	Nerve cells Muscle cells Fibrocytes	Highly resistant

[a] *VIM* vegetative intermitotic, *DIM* Differentiating intermitotic, *MCT* multipotential connective tissue, *RPM* reverting postmitotic, *FPM* fixed postmitotic.

Cell survival curve

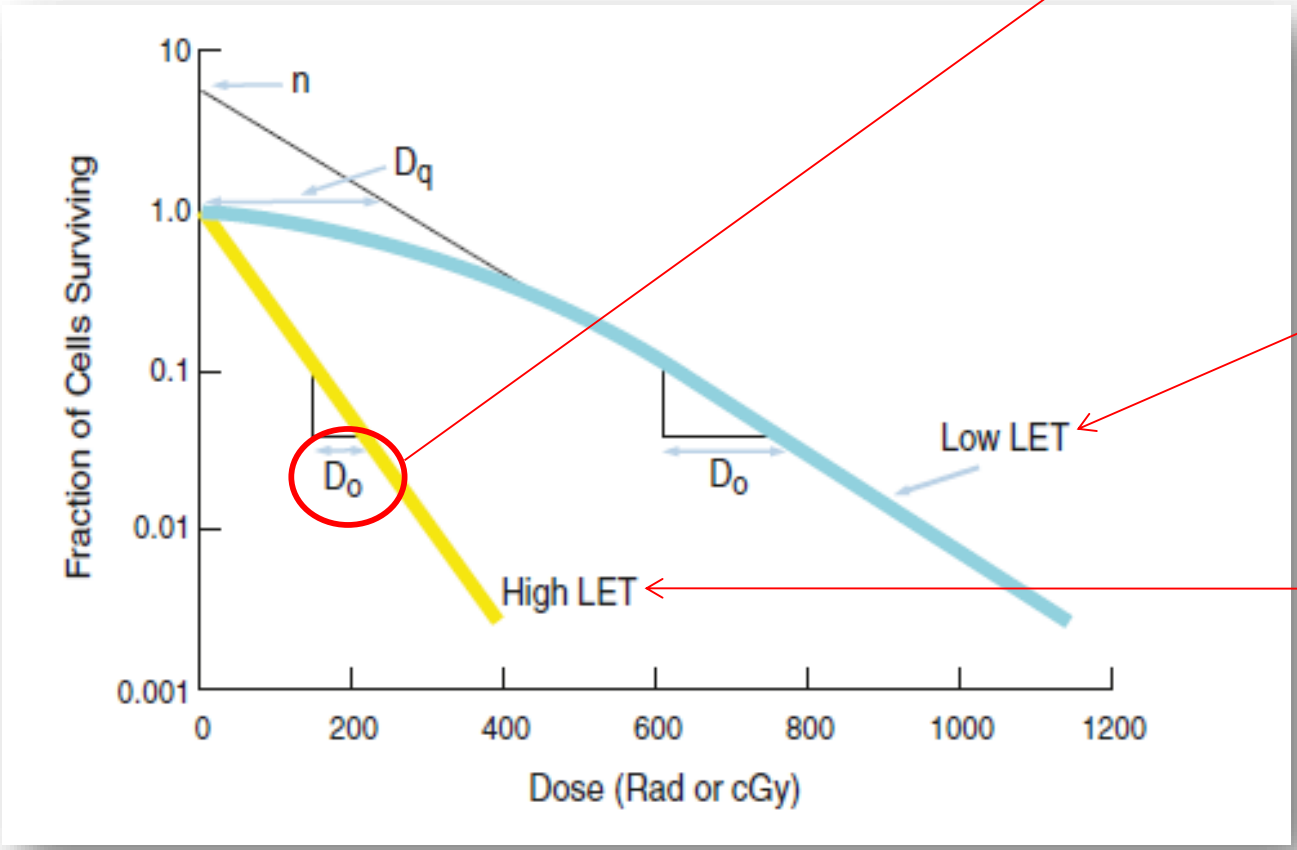
- cellular response to radiation is illustrated by *cell survival curves*

$\log_e n = D_q/D_0$

D_0 -dose at which 37 % of cells survive
n - extrapolation number
D_q - quasithreshold dose

Measure of radiosensitivity of a given cell type

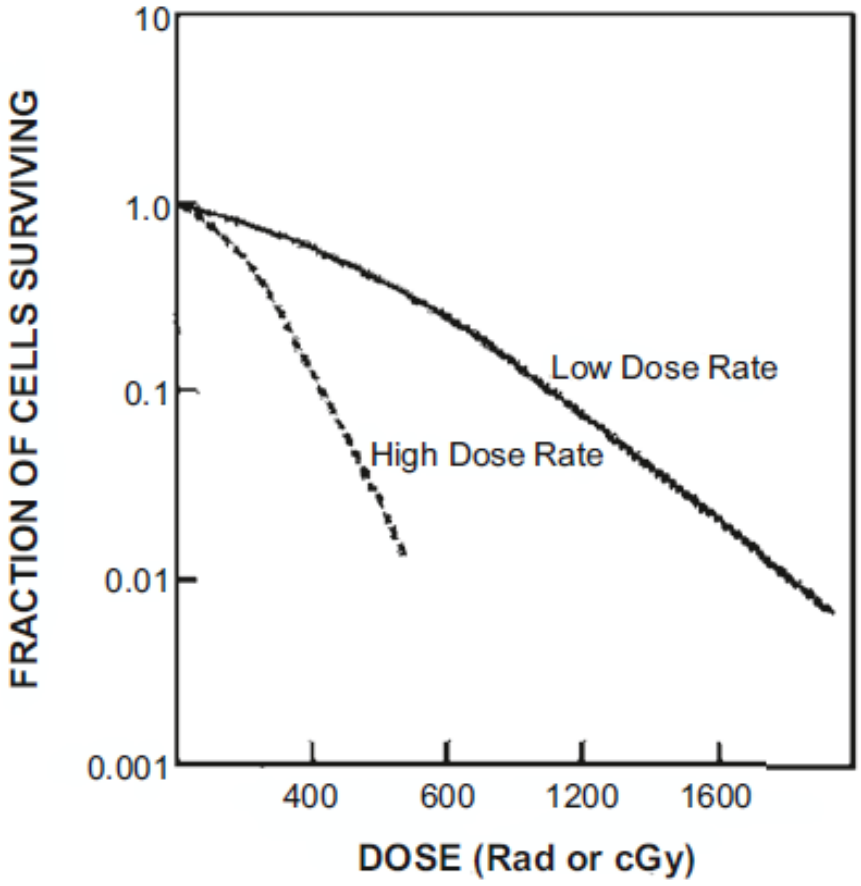
multitarget model



X and γ-rays

α- particles neutrons

Cell survival and dose rate



Dose-rate effect is very important in radiation therapy

When a total dose is given to a patient in fractions over a period of time, it should be kept in mind that the interval between fractional doses should be short enough to keep repair of damage to abnormal cells to a minimum

Chemicals influencing radiosensitivity

Radiosensitizers

Oxygen: hypoxic cells are resistant to radiation, and oxygenated cells are highly radiosensitive (*oxygen effect*)

Pyrimidines

Halogenated pyrimidines, 5-chlorodeoxyuridine (ClUDR), 5-bromodeoxyuridine (BUDR), and 5-iododeoxyuridine (IUDR)

Other substances: actinomycin D, puromycin, methotrexate, and 5-fluorouracil, metronidazole, mesonidazole, etanizadole

Radioprotectors

- Substances containing sulfhydryl groups (-SH), such as cysteine

and cysteamine

- WR-638 and WR-2721 (amifostine) the -SH group is protected by a phosphate group

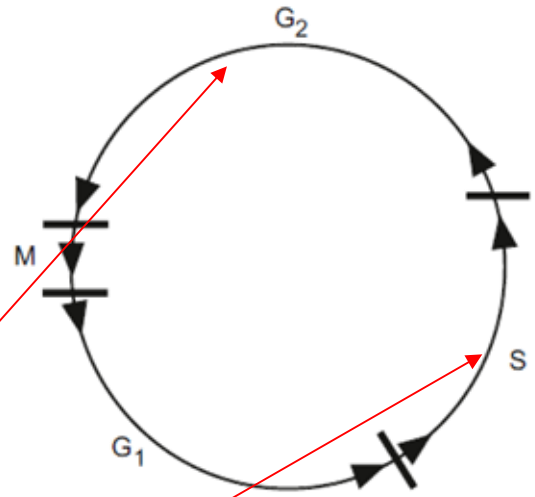
Stage of cell cycle and radiosensitivity

The stage of the cell cycle determines the extent of radiation damage.

- Radiation damage mostly occurs during the period of mitosis, the M phase
- Least damage occurs during the DNA synthesis, the S phase.

Exposure of cells to

- 100–1000 rad (100–1000 cGy) causes delay in the G2 phase to M phase transition.
- 1000 rad (1000 cGy) inhibits the progression of the S phase cells by 30 %, whereas the S phase to G2 phase transition is not affected by such an exposure



S - DNA synthesis phase.
M - mitosis
G1 - is the period between the telophase and *S,*
G2 - is the period between *S and the prophase.*

Classification of cell damage

Based on the degree of lethality induced by radiation:

1. **Lethal damage**, which causes irreversible death
2. **Sublethal damage (SLD),** which normally repairs in hours, and thus avoids cellular death, unless followed by another sublethal damage

Important in radiation therapy (radiation therapy is given in intervals)

4 mechanisms of SLD repair : repair, redistribution, regeneration, and reoxygenation

3. **Potentially lethal dose (PLD)**, which can potentially kill the cell but can be modified to repair under specific physicochemical conditions.

Radiation effects on biological systems

Stochastic effects

✓ Occur randomly

↑ probability with increasing dose *without a threshold*

e.g. radiation-induced hereditary effects, cancer

Deterministic (non-stochastic) effects

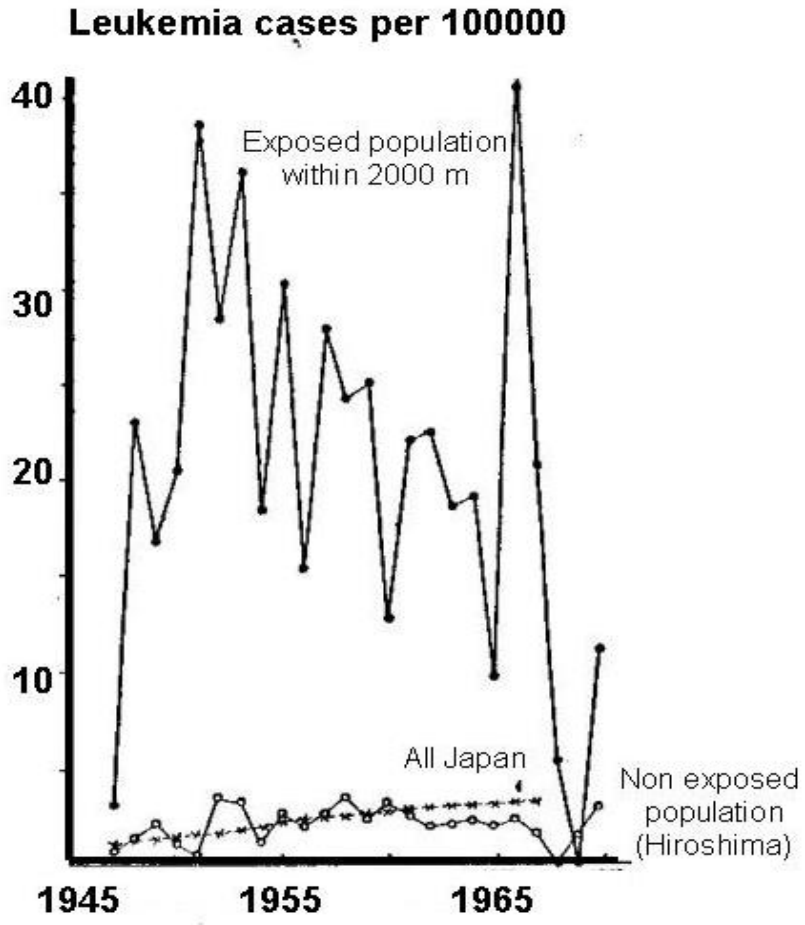
✓ Induced by high radiation doses

severity of the damages increases with the dose

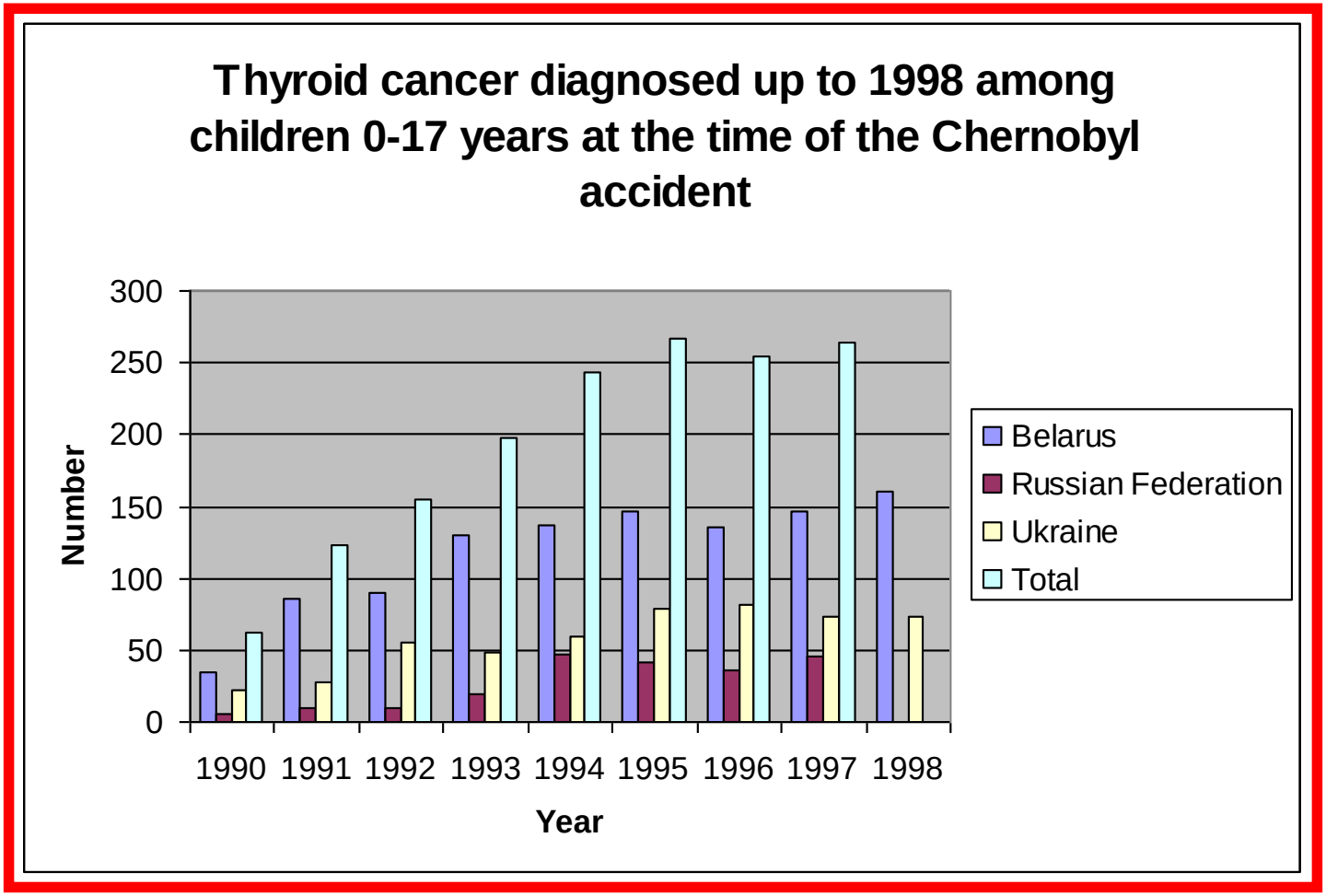
threshold dose (below which no damage is evident)

e.g. cataracts, skin erythema, sterility

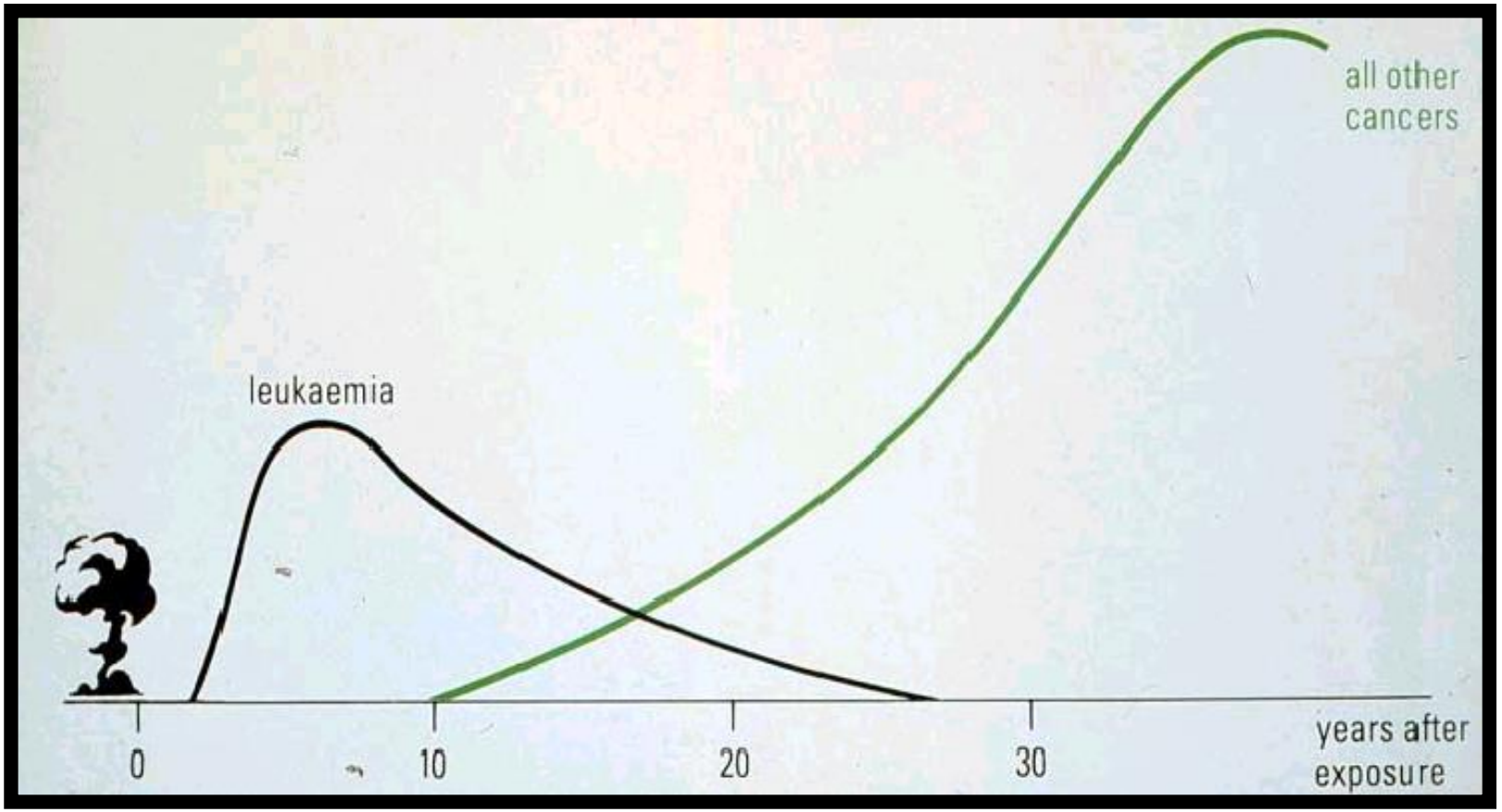
Stochastic (delayed) effects of ionizing radiation



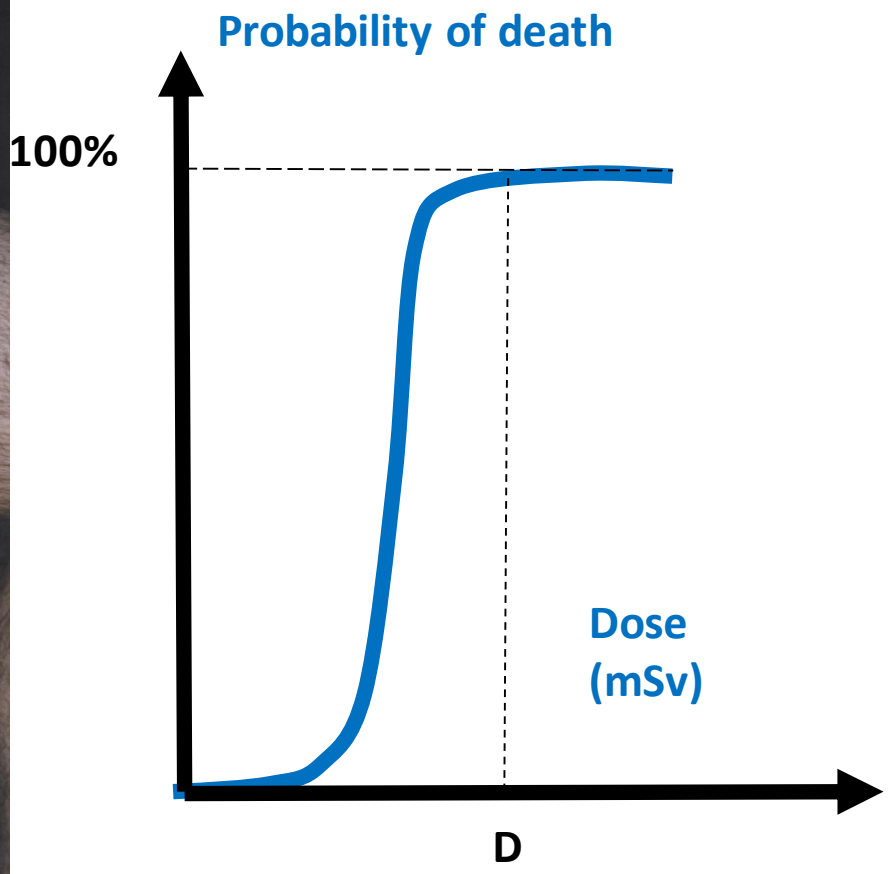
Stochastic effects of ionizing radiation



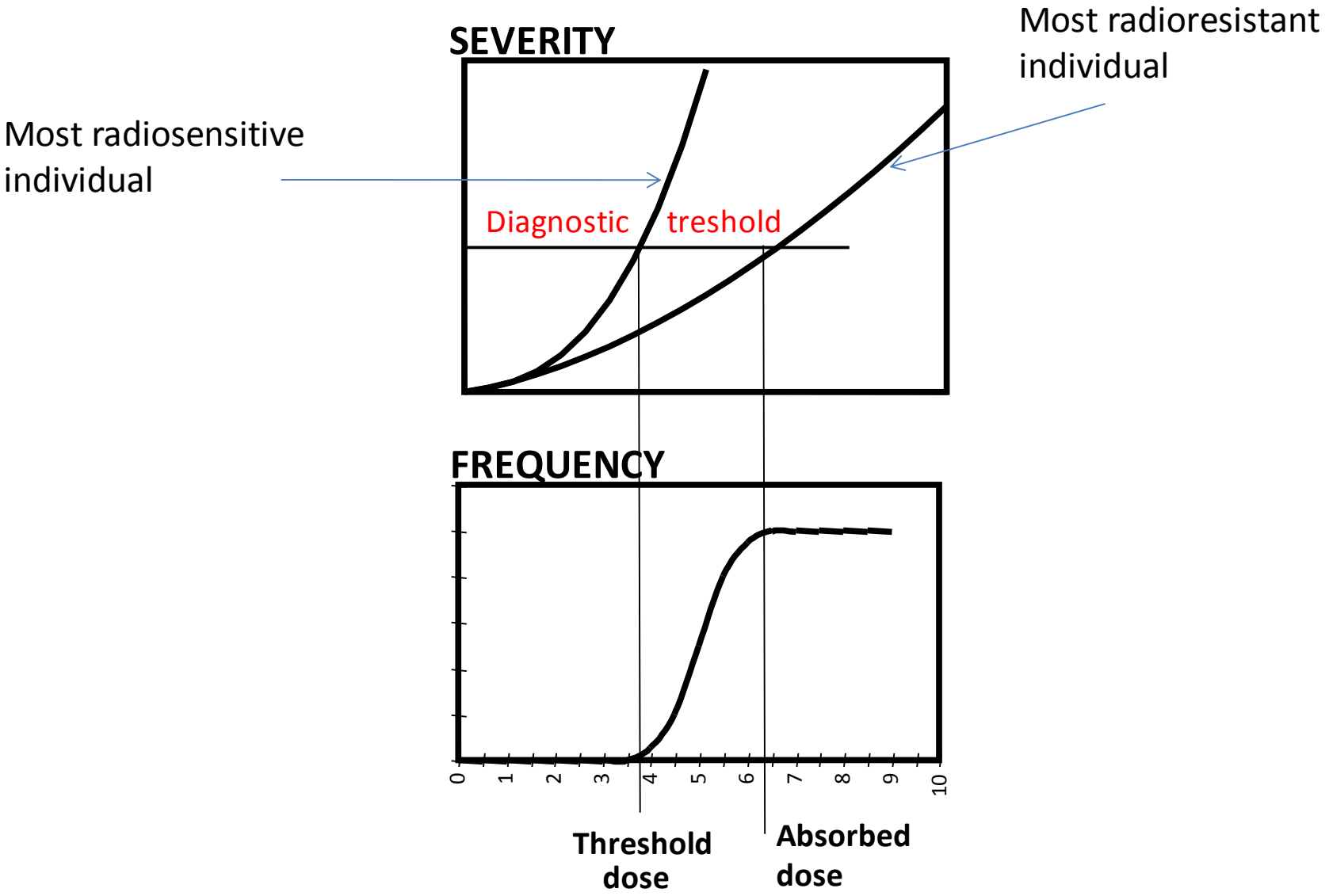
Variation of Cancer Incidence with time following the A-Bombs



Deterministic (early) effects



Deterministic Effects



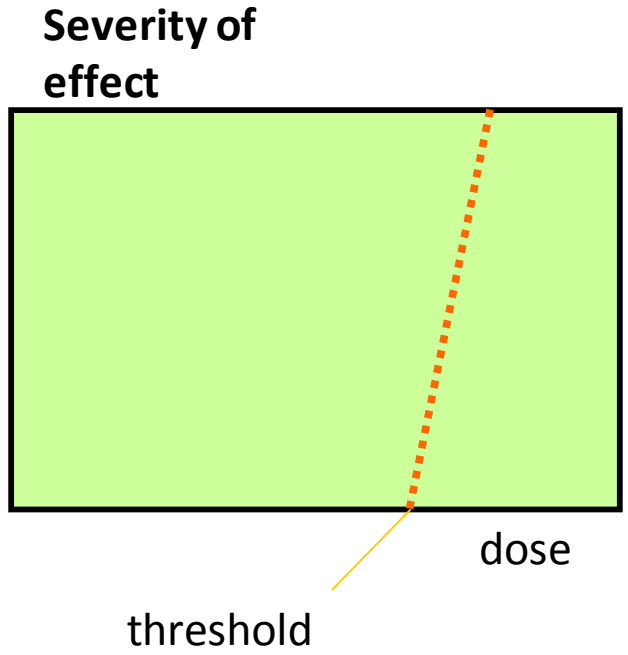
Threshold dose is the absorbed dose that is needed to create a clinically observed injury in the most radiosensitive individual

Threshold doses for deterministic effects

- Cataracts of the lens of the eye 0.5 Gy

[ICRP statement on tissue reactions (http://www.icrp.org/docs/icrp%20statement%20on%20tissue%20reactions.pdf)]

- Permanent sterility
  - males 3.5-6 Gy
  - females 2.5-6 Gy
- Temporary sterility
  - males 0.15 Gy
  - females 0.6 Gy



Note on threshold values

- Depend on dose delivery mode:
  - single high dose most effective
  - fractionation increases threshold dose in most cases significantly
  - decreasing the dose rate increases threshold in most cases
- Threshold may differ in different persons

Systemic effects

- Effects may be morphological and/or functional

Factors:

  - Which Organ
  - How much Dose

Effects

  - Immediate (usually reversible): < 6 months e.g.: inflammation, bleeding.
  - Delayed (usually irreversible): > 6 months e.g.: atrophy, sclerosis, fibrosis.

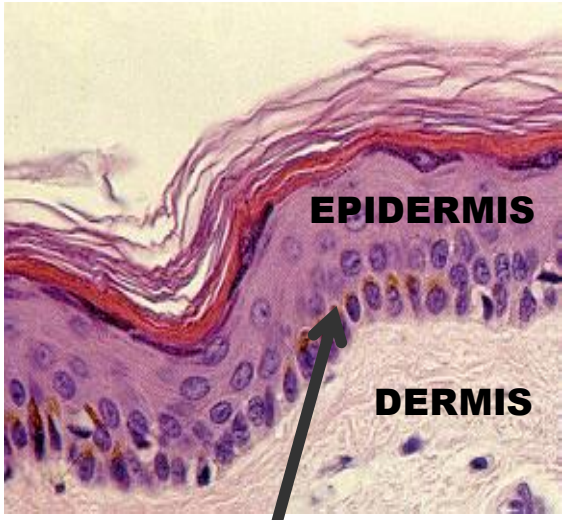
Categorization of dose

  - < 1 Gy: LOW DOSE
  - 1-10 Gy: MODERATE DOSE
  - > 10 Gy: HIGH DOSE

- Regeneration means replacement by the original tissue while Repair means replacement by connective tissue.

Skin effects

Histologic view of the skin



From "Atlas de Histología...". J. Boya

Basal stratum cells, highly mitotic, some of them with melanin, responsible of pigmentation.

- Following the RS laws (Bergonie and Tribondeau), the most RS cells are those from the basal stratum of the epidermis.
- Effects are:
  - Erythema: 1 to 24 hours after irradiation **of about 3-5 Gy**
  - Alopecia: 5 Gy is reversible; **20 Gy is irreversible**.
  - Pigmentation: Reversible, appears 8 days after irradiation.
  - Dry or moist desquamation: traduces epidermal hypoplasia (dose ≅ 20 Gy).
  - Delayed effects: teleangiectasia, fibrosis.

Skin reactions

Injury	Threshold Dose to Skin (Sv)	Weeks to Onset
Early transient erythema	2	<<1
Temporary epilation	3	3
Main erythema	6	1.5
Permanent epilation	7	3
Dry desquamation	10	4
Invasive fibrosis	10	
Dermal atrophy	11	>14
Telangiectasis	12	>52
Moist desquamation	15	4
Late erythema	15	6-10
Dermal necrosis	18	>10
Secondary ulceration	20	>6

Skin damage from prolonged fluoroscopic exposure

Skin Effects

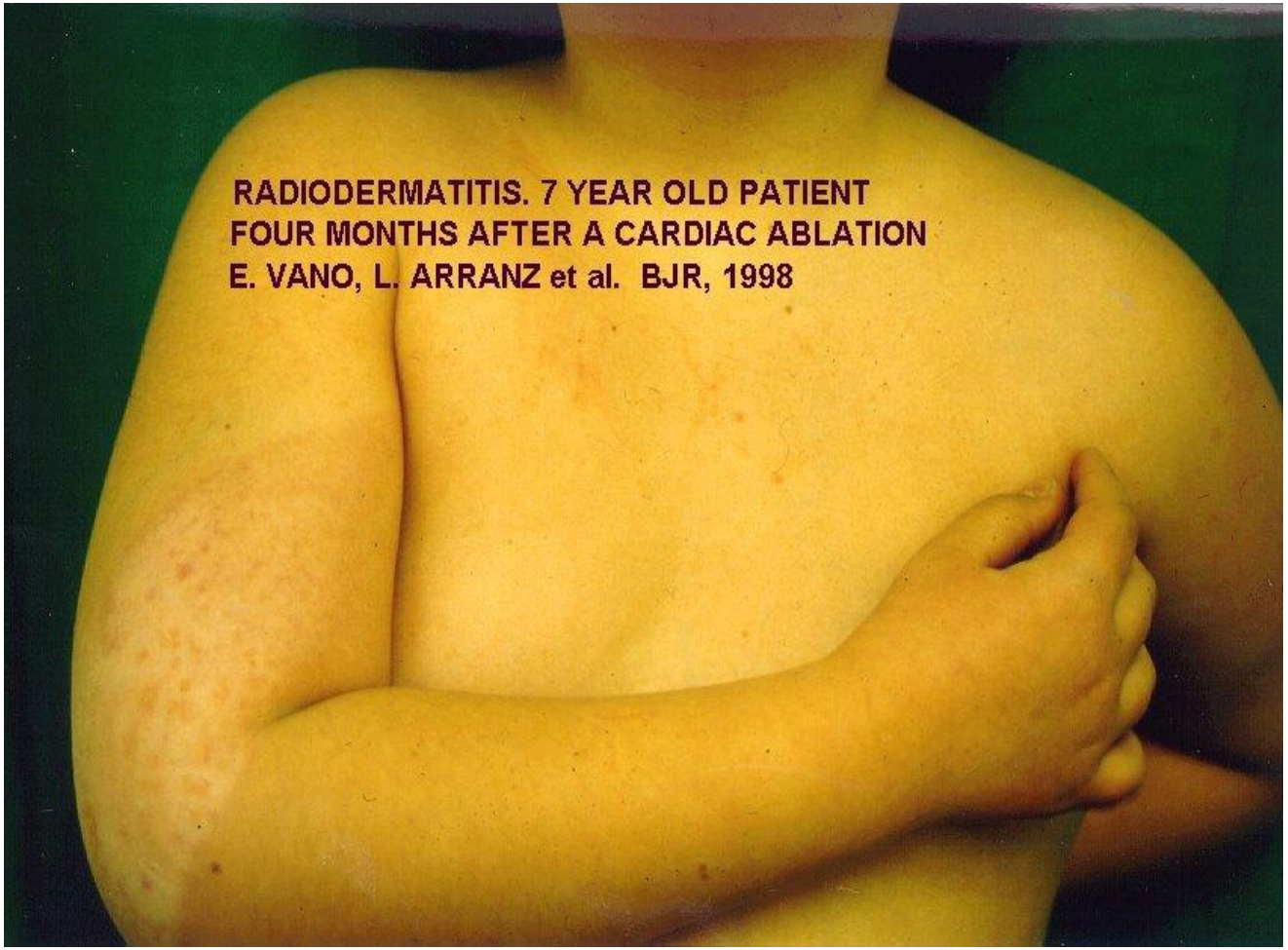
By handling unshielded syringes and vials containing radioactive material the threshold dose of skin erythema will be reached in a short time.

e.g.

1 . The dose rate at the surface of a vial containing 30 GBq Tc-99m is of the order of 2 Gy/h meaning that the threshold dose will be reached after 2 h of exposure. This corresponds to 36 s per working day in a year.

2. After an extravascular injection of 500 MBq of a Tc-99m radiopharmaceutical, the locally absorbed dose at the injection site might be as high as 5-20 Gy!

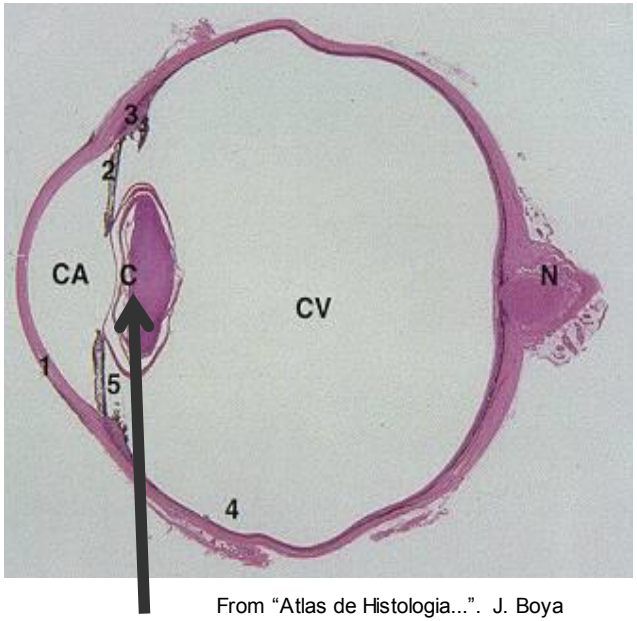
Skin injuries



Skin injuries

Effects in eye

Histologic view of eye:



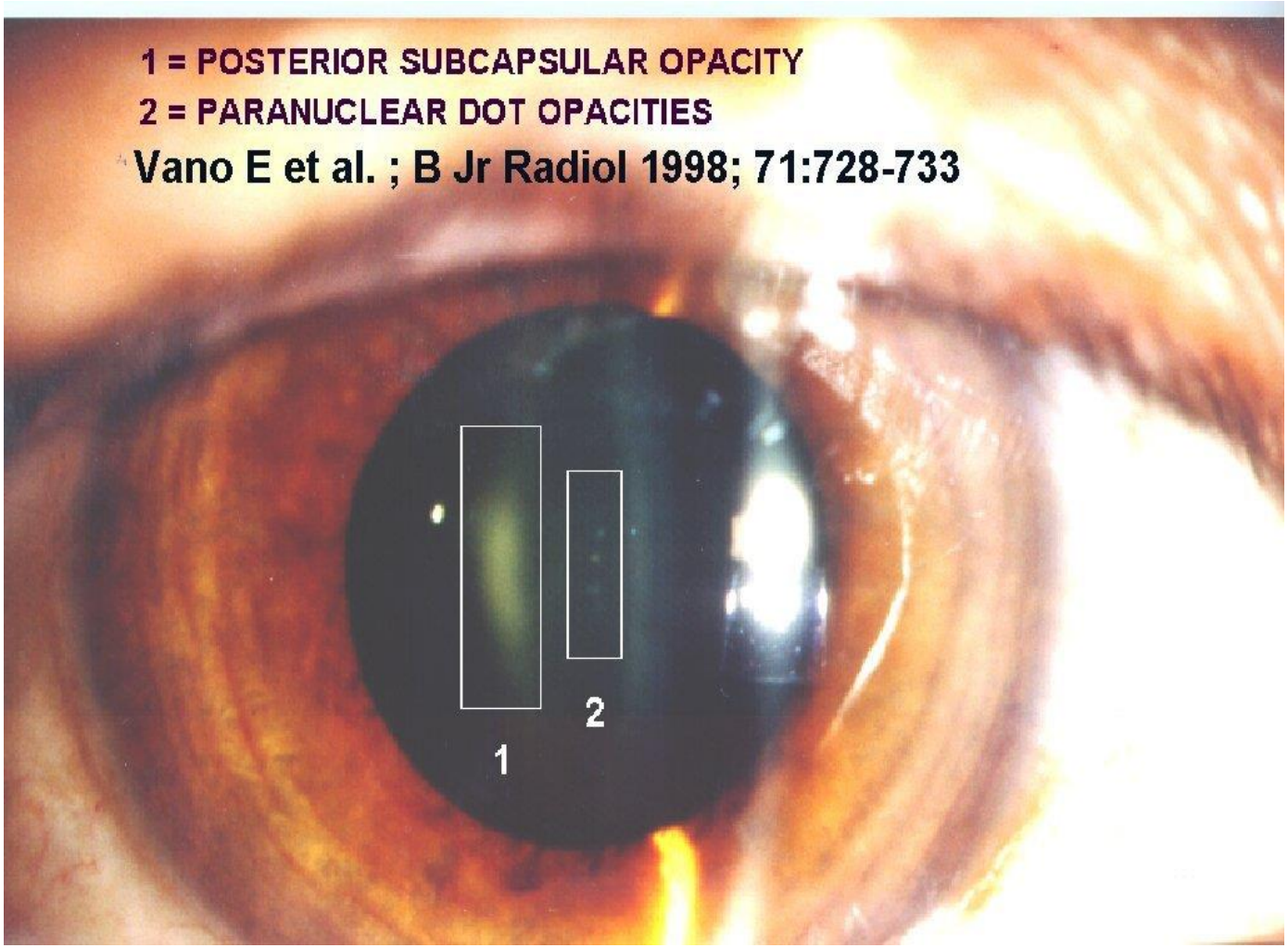
From "Atlas de Histologia...". J. Boya

Eye lens is highly RS, moreover, it is surrounded by highly RS cuboid cells.

- Eye lens is highly RS.
- Coagulation of proteins occur with doses greater than 2 Gy.
- There are 2 basic effects:

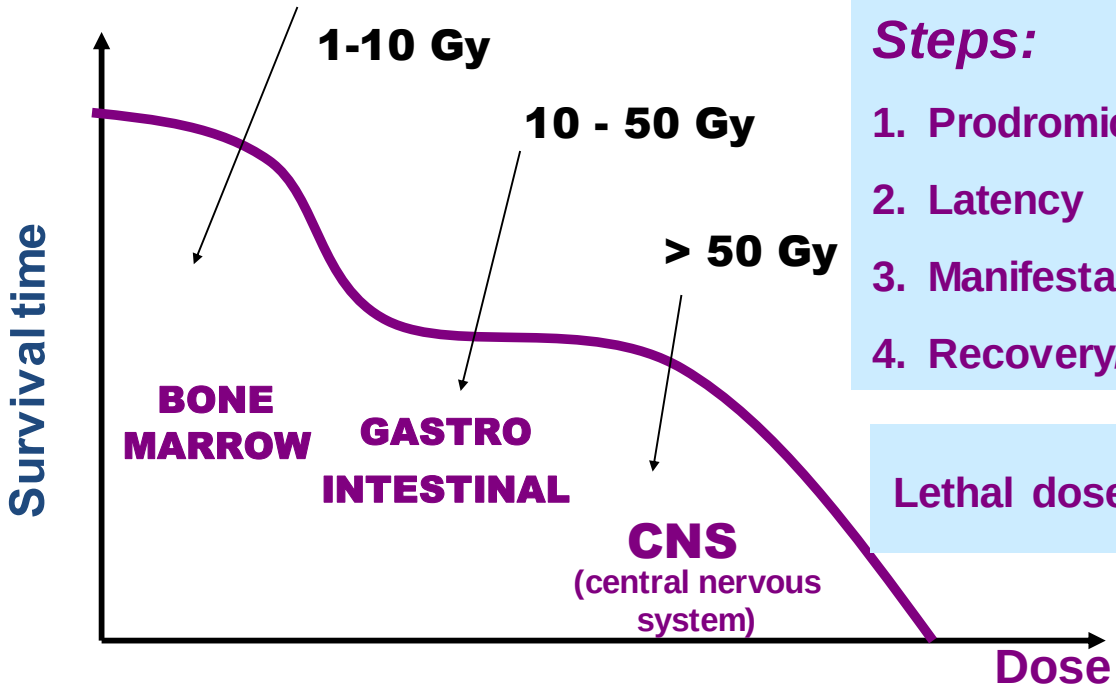
Effect	Sv single brief exposure	Sv/year for many years
Detectable opacities	0.5-2.0	> 0.1
Visual impairment (cataract)	5.0	> 0.15

Eye injuries



Whole body response: adult

Acute irradiation syndrome



Steps:

1. **Prodromic**
2. **Latency**
3. **Manifestation**
4. **Recovery/Death**

Lethal dose 50 / 30

Chronic irradiation syndrome

- Mechanism: Neurovegetative disorder
- Similar to a sick feeling
- Quite frequent in fractionated radiotherapy

LD 50/30 – Radiation dose which would cause death to 50% of the population in 30 days. 2-3 Gy for humans for **whole body irradiation**.

Acute Effects of Total Body Irradiation

Hemopoietic

- Appear at a total body dose of 250– 500 rad (2.5–5 Gy)

↓RBC↓WBC↓PLT: Immunosupression, Infection, Hemorrhage

- death in 10–21 days

Gastrointestinal

- Total body dose of 500–1000 rad (5–10 Gy)

nausea, vomiting, and diarrhea

intestinal crypt cells/ mucosal lining (villi) are destroyed

- death in 3–10 days after radiation exposure

Cerebrovascular

- Minutes after radiation exposure at a total body dose of more than 10,000 rad (100 Gy)

malfunction of the neuron motor pump giving rise to motor incoordination, intermittent stupor, coma, and ultimately

- death in two to three days

Long-Term Effects of Radiation

- SOMATIC: they affect the health of the irradiated person. They are mainly different kinds of cancer (leukemia is the most common, with a delay period of 2-5 years, but also colon, lung, stomach cancer…)
- GENETIC: they affect the health of the offspring of the irradiated person. They are mutations that cause malformation of any kind (such as mongolism)

Somatic Effects

- Establishment of dose-response relationships for carcinogenesis

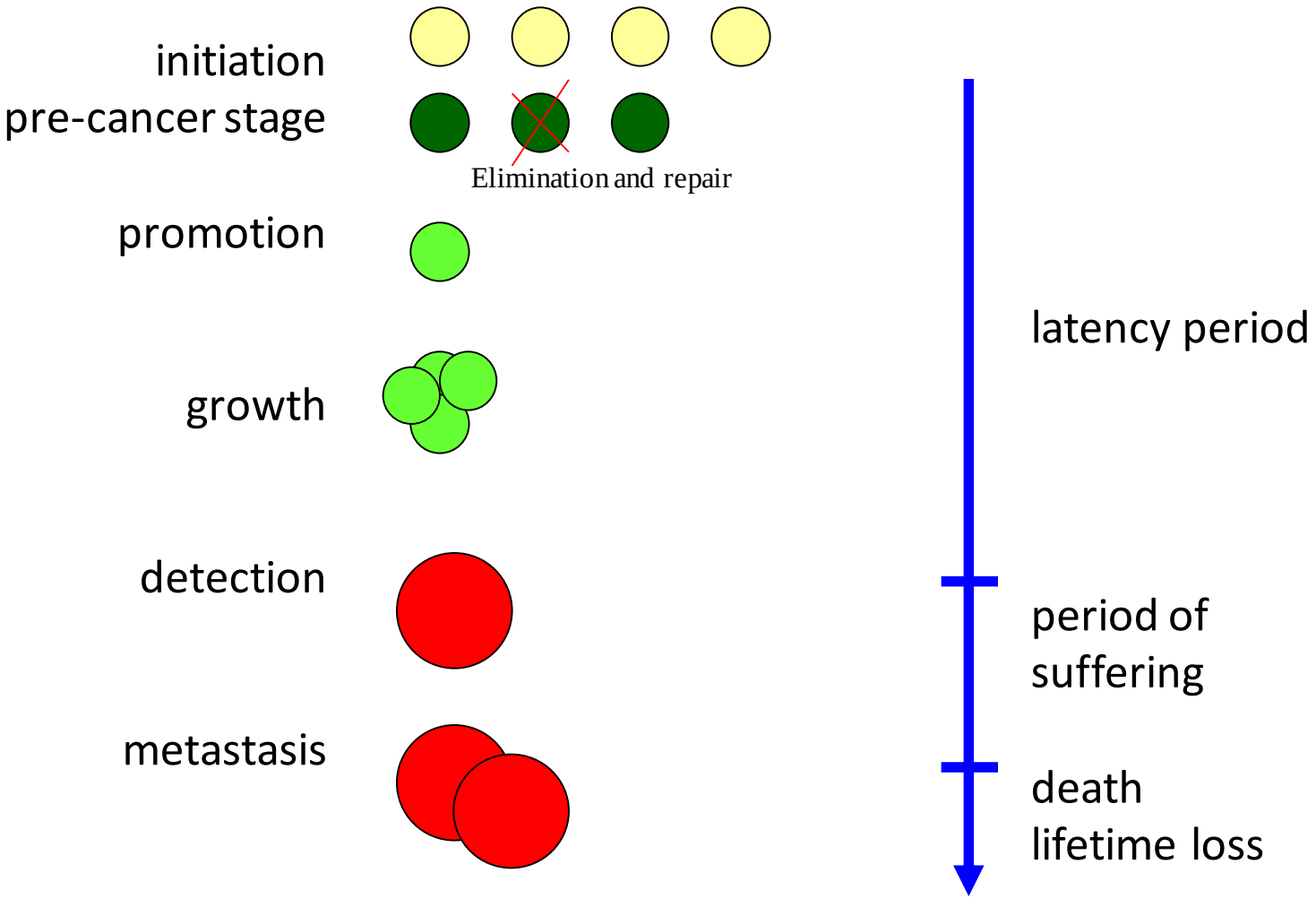
✓ risks at low doses are primarily estimated by extrapolation of the data from high-dose experiments

- Scientific Committee of the Effects of Atomic Radiations (UNSCEAR)
- Committee on the Biological Effects of Ionizing Radiations (BEIR)
- International Commission on Radiological Protection (ICRP)

Somatic Effects

- Carcinogenesis
  - Leukemia
  - Breast cancer
  - Other cancers
- Radiation damage to skin
- Radiation damage to reproductive organs
- Nonspecific life-shortening
- Cataractogenesis
- Radiation damage to embryo and fetus

Carcinogenesis
initiation → promotion → progression



Carcinogenic Effects

An assessment of the atomic bomb survivors showed:

- the leukaemia risk peaked at 10 years after exposure
- thyroid cancer was the first solid cancer reported
- the incidence of breast cancer was higher in young women than older women
- other cancer, with a latent period of up to 30 years, included lung, stomach, colon, bladder and oesophagus

Shimizu et al JAMA 1990, 264:601-604

Radiation Damage to Embryo and Fetus

- Fetus/embryo is more sensitive to ionizing radiation than the adult human
- Increased incidence of spontaneous abortion a few days after conception
- Increased incidence
  - Mental retardation
  - Microcephaly (small head size) especially 8-15 weeks after conception
  - Malformations: skeletal, stunted growth, genital
- Higher risk of cancer (esp. leukemia)
  - Both in childhood and later life

TYPES OF EFFECTS FOLLOWING IRRADIATION *IN UTERO*

Time after conception	Effect	Normal incidence in live-born
First three weeks	No deterministic or stochastic effects in live-born child	-
3rd through 8th weeks	Potential for malformation of organs[a]	0.06 (1 in 17)
8th through 25th weeks	Potential for severe mental retardation[b]	5×10^{-3} (1 in 200)
4th week throughout pregnancy	Cancer in childhood or in adult life[c]	1×10^{-3} (1 in 1000)

[a] Deterministic effect. Threshold ~ 0.1 Gy

[b] 30 IQ units shift: 8-15th week; <30 IQ units shift: 16 - 25th week

[c] Risk in utero ~ risk $\leq$ 10 years of age

Approximate fetal whole body dose (mGy) from common nuclear medicine procedures done in early and late pregnancy

Procedure	Activity (MBq)	Early	9 months
Tc-99m			
Bone scan	750	4.7	1.8
Lung V/Q scan	240	0.9	0.9
Liver colloid	300	0.6	1.1
Thyroid scan	400	4.4	3.7
Renal DTPA	750	9.0	3.5
Red Cell	930	6.0	2.5
I-123 Thyroid uptake	30	0.6	0.3
I-131 Thyroid uptake	0.55	0.04	0.15

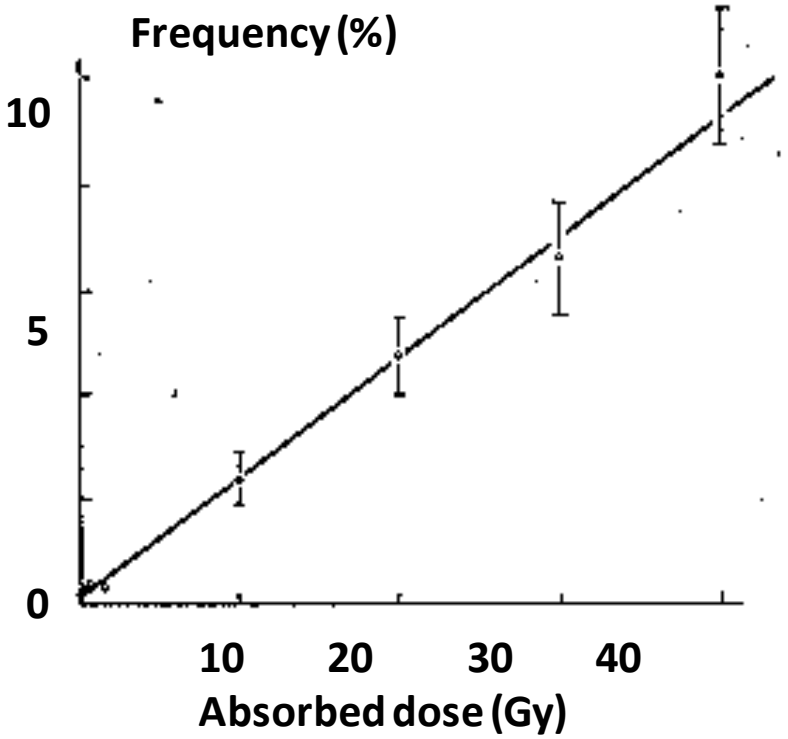
Genetic Effects

- **Spontaneous mutations** (chance of spontaneous mutation is 1 in 100,000): radiation does not produce any new mutations and simply increases the frequency of spontaneous mutations

- **Doubling dose**: the amount of radiation dose that doubles the spontaneous mutations in one generation in a species (in humans, it is considered to be of the order of 100 rad (100 cGy)

- **Genetically significant dose**: the dose that, if received by everyone of the entire population, would cause the same genetic damage as the gonadal dose (now being received by a limited number of individuals of the population through medical procedures, natural radiations, TV viewing, flying at high altitudes, etc)

Genetic Effects



Hormesis

- Bimodal effect of radiation
- below a certain threshold level radiation is protective, and harmful effects are seen only when this threshold is exceeded.

Rationale - radiation at low levels induces protective cellular mechanisms which prevent DNA damage occurring spontaneously or due to other stresses

- ➢ stimulatory response at low doses and an inhibitory response at higher doses.

Acknowledgement and further reading

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