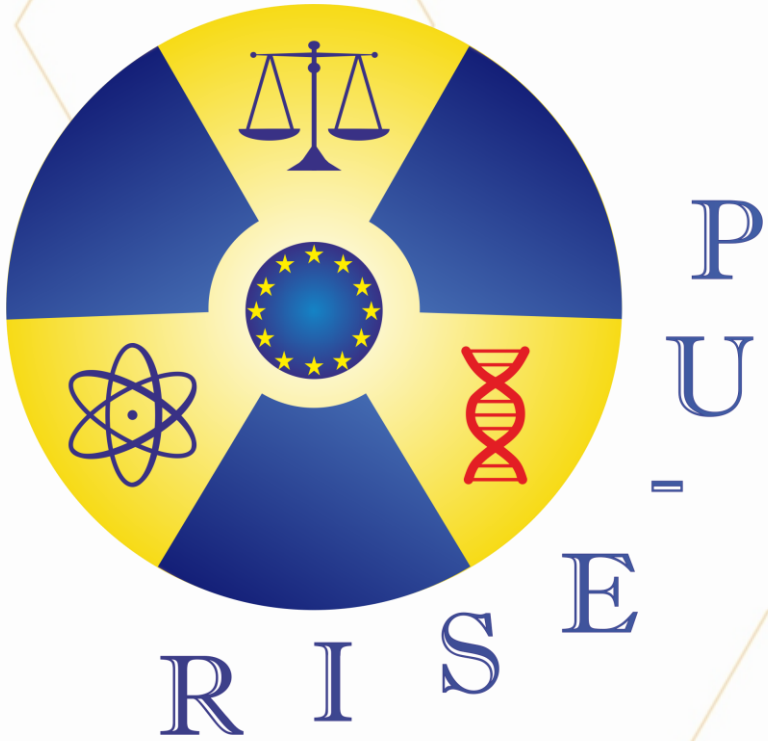


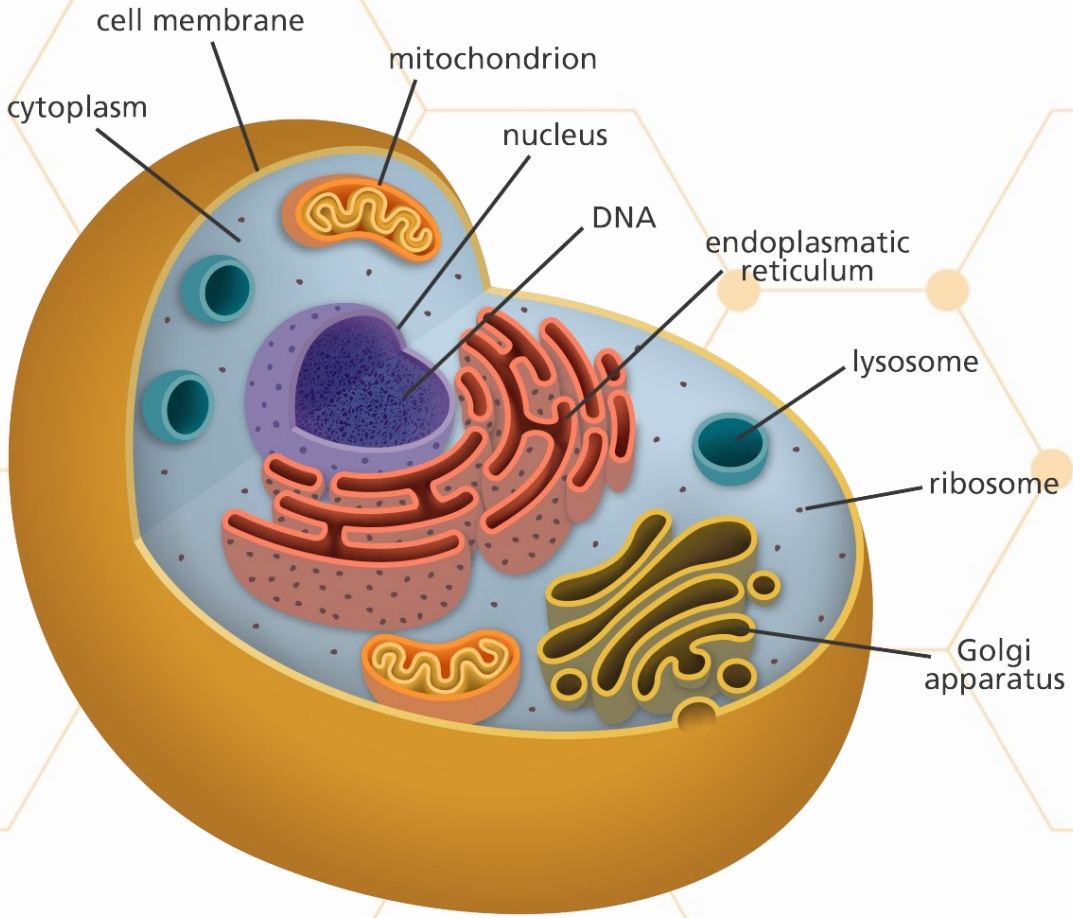
Part 2

Radiation Safety:
Medical and Biological Aspect

1. Fundamentals of radiation biochemistry. Breaking of chemical bonds through excitation ionization; direct and indirect influence of radiation: formation of free radicals, interaction with DNA; interaction with proteins and lipids.
2. Effects of radiation on cells, chromosomes, DNA. Point mutations, chromosome breaks, mitosis; mitotic dysfunction, cell death; consequences of cell death; consequences of cell damage; DNA repair; cell sensitivity. Radiosensitizers and protective factors. Chromosomal aberrations as a biological indicator of dosage.
3. Effects of total body irradiation. Overall dose-response curve; threshold; heaviness; acute radiation syndrome (ARS); hematopoietic system; gastrointestinal tract; central nervous system. Effects of partial irradiation of the body. Skin; thyroid gland, lungs, lens of the eye; gonads. Threshold doses; fractionation and dose rate effects.
4. Elementary genetics; natural mutations; gamete formation and chromosome damage (examples); gene mutations; data sources: human and animals; double dose concept; the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) and the approach of the International Commission on Radiological Protection (ICRP); ICRS risk tolerances: impact on next generations.
5. Radiation effects. Sensitivity at different stages of development; brain development and developmental delay; induction of leukemia and cancer. Epidemiological studies. Statistical requirements; modern types of research; association and mixing coefficients; power and accuracy; prospects and pitfalls. Radiation damage. Necessity for cumulative damage. Effective dose; dose limits; the concept of collective dose; approach adopted by the ICRP; comparison of risks from different types of activities.

Radiation-physical and **radiation-chemical** processes occurring in any living cells are similar to each other, since the material composition of cells of different organisms does not differ significantly. Therefore, under the influence of ionizing radiation, transformations of similar nature are observed:

- transition of molecules to the free radical
- state breaks of macromolecules
- chemical modification of molecules of various substances
- anaplasia - destruction of the cell structure

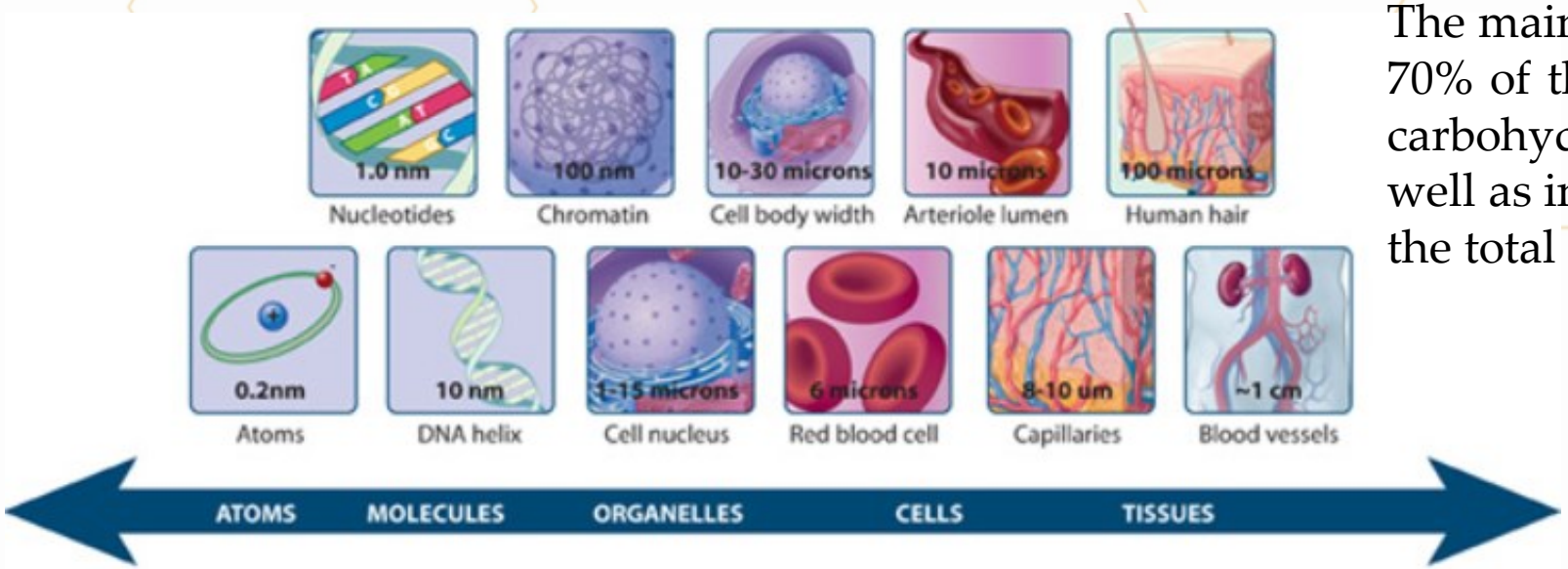


A cell is an elementary, expedient structural and functional unit of a living organism. Cells are prokaryotic - which do not have a formed cell nucleus and eukaryotic - with a clearly formed cell nucleus. Cells differ in shape, size, structure. They are characterized by different forms of reproduction.

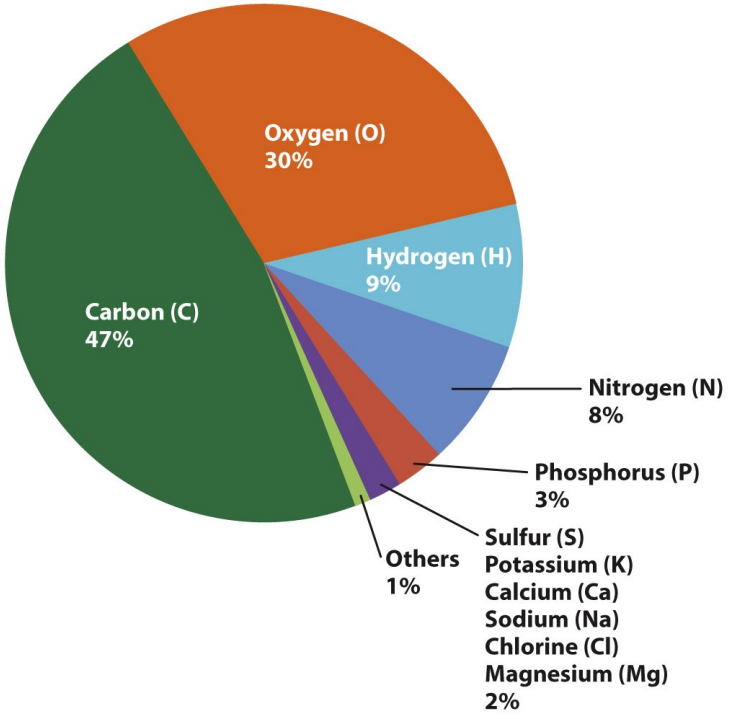
Cell is an elementary biological system that underlies the structure, development and reproduction of animal and plant organisms. A cell is a complex, expedient formation that can include up to a billion molecules. In a unicellular organism (bacteria, infusoria), the cell functions as a single unit. In multicellular organisms of plants and animals, each cell represents only a part of the organism, individual organs, tissues.

https://www.labxchange.org/library/pathway/lx-pathway:087f7cb8-09cf-406e-bc60-5193fee3512e/items/lx-pb:087f7cb8-09cf-406e-bc60-5193fee3512e:html:6725c47f

The shape of cells is very diverse (round, oval, star-shaped, spindle-shaped, filamentous, square, etc.). Cell sizes range from a few microns (most cells) to several centimeters, the largest cells being the eggs of birds and reptiles.
In physical and chemical terms, cells are a complex heterogeneous system, which is characterized by constant self-healing, self-regulation, self-defense, self-adaptation, self-improvement, etc.



The main constituents of the cell are proteins (50-70% of the dry weight of the cell), nucleic acids, carbohydrates, fats and fat-like substances, as well as inorganic ions and water (up to 80-85% of the total weight of the living cell).



Cells include trace elements (up to 98%), microelements (0.01%), in particular, zinc, copper, fluorine, iodine, cobalt, molybdenum; ultra-elements, for example, uranium, radium, gold (approximately 0.00001%).

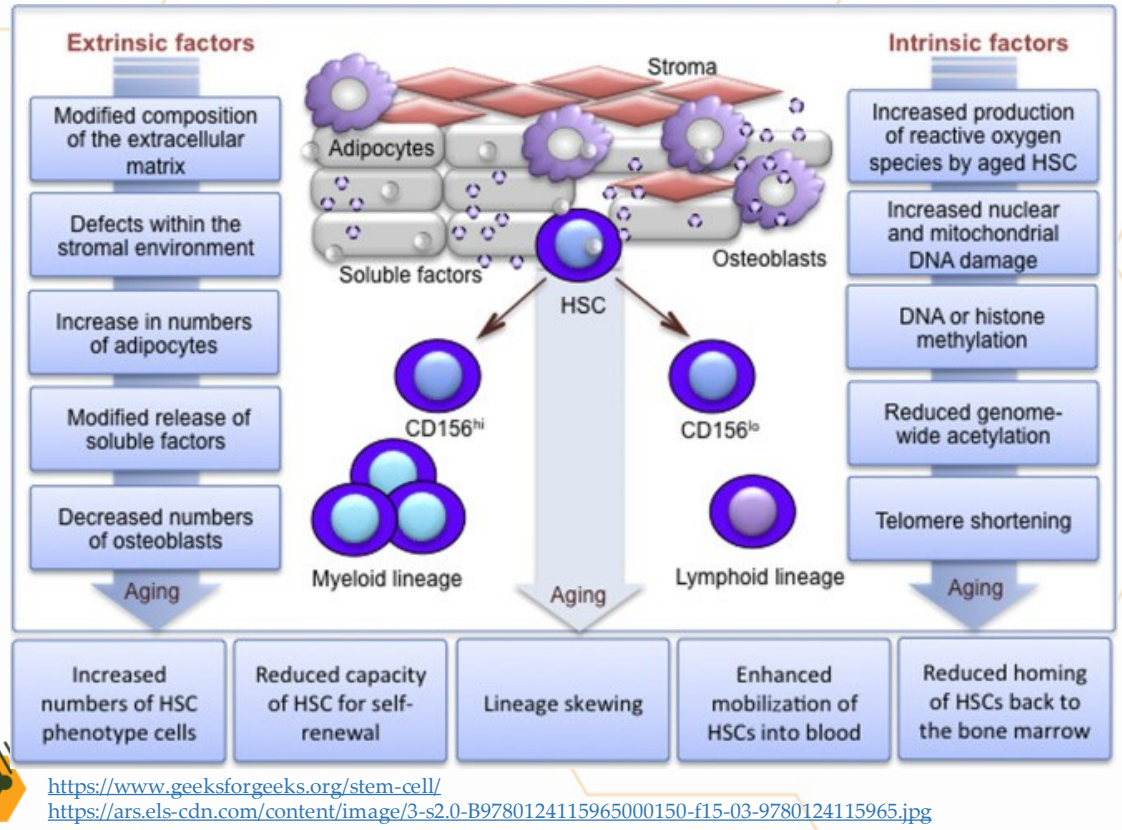
https://www.nature.com/scitable/content/the-relative-scale-of-biological-molecules-and-14704956/
https://www.macmillanhighered.com/BrainHoney/Resource/6716/digital_first_content/trunk/test/morris2e/morris2e_ch2_16.html

Cells reproduce by division, which is based on the ability of DNA to exact self-repair (autoreproduction by matrix replication). The bacterial cell divides within 30 minutes. Cells of higher organisms, and including plants, divide within 22-24 hours.

It is believed that the nerve cells are not capable of reproduction.

Special attention should be paid to **stem** (cambial) cells. They belong to a special hierarchy of cells of a living organism, each of which is able to change (differentiate) in a special way. They divide asymmetrically, so the division produces one daughter cell similar to the mother and the second one, which is able to differentiate.

Cell aging is accompanied by a decrease in the activity of metabolic processes.



https://www.geeksforgeeks.org/stem-cell/
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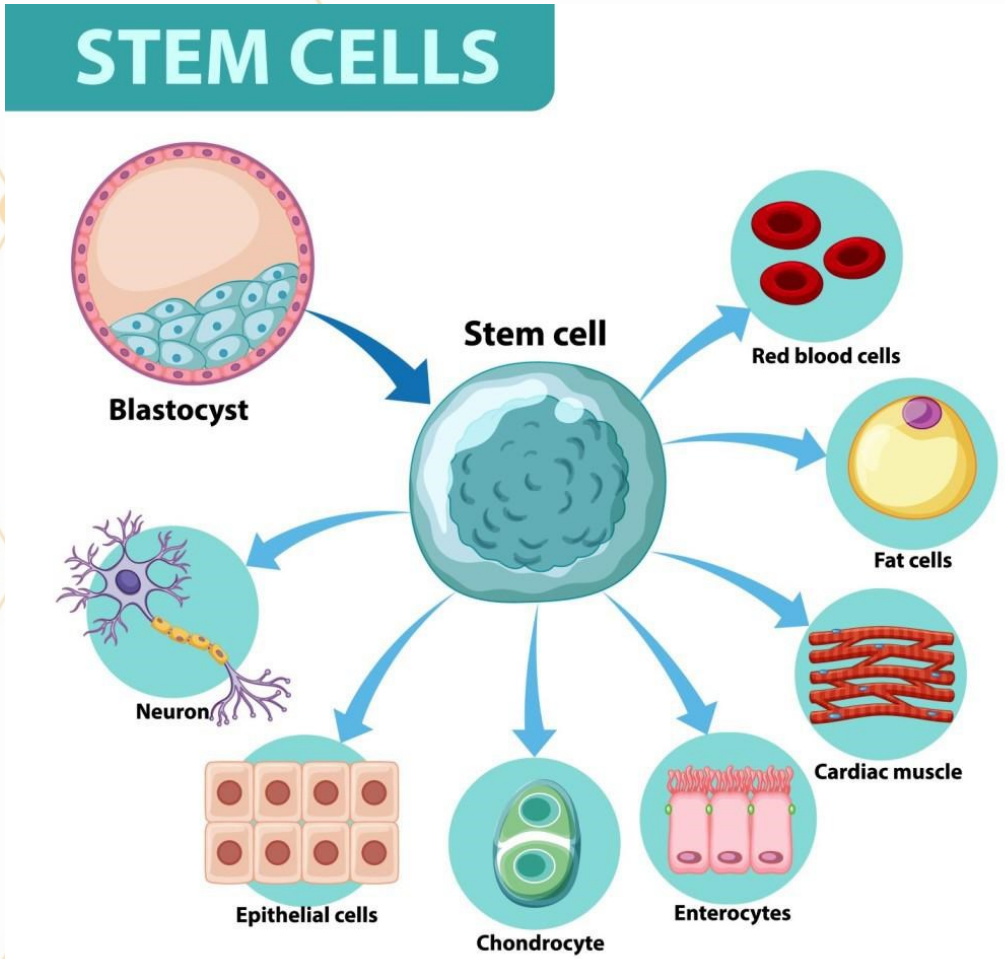
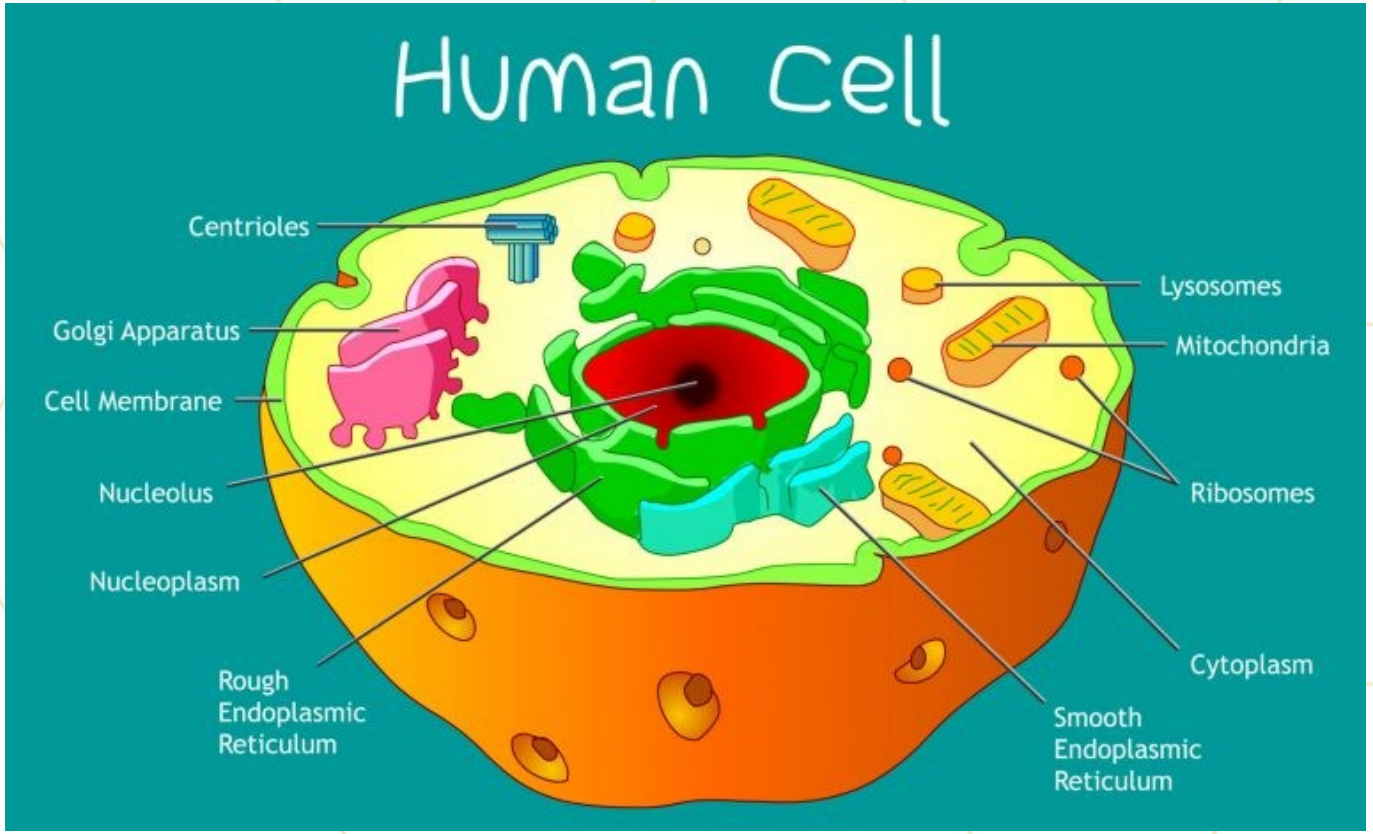


Cell membrane is a non-living surface part of the cell.

Mitochondria are elongated or rounded bodies scattered in the cytoplasm, their length is up to 5 μm. Mitochondria are very important centers of intracellular enzymatic activity. They are sometimes called the "power stations" of the cell, because they convert substances coming from the food into energy-rich compounds that are used by the cell to carry out all processes that require energy.

Centrosome is a small body that looks like a dot or two dots, from which rays diverge to the surrounding cytoplasm. Centrosomes function during cell division.

The Golgi apparatus (GA) consists of several irregularly shaped bodies and is located near the centrosome. Its function is to accumulate and subsequently secrete the secreted product.



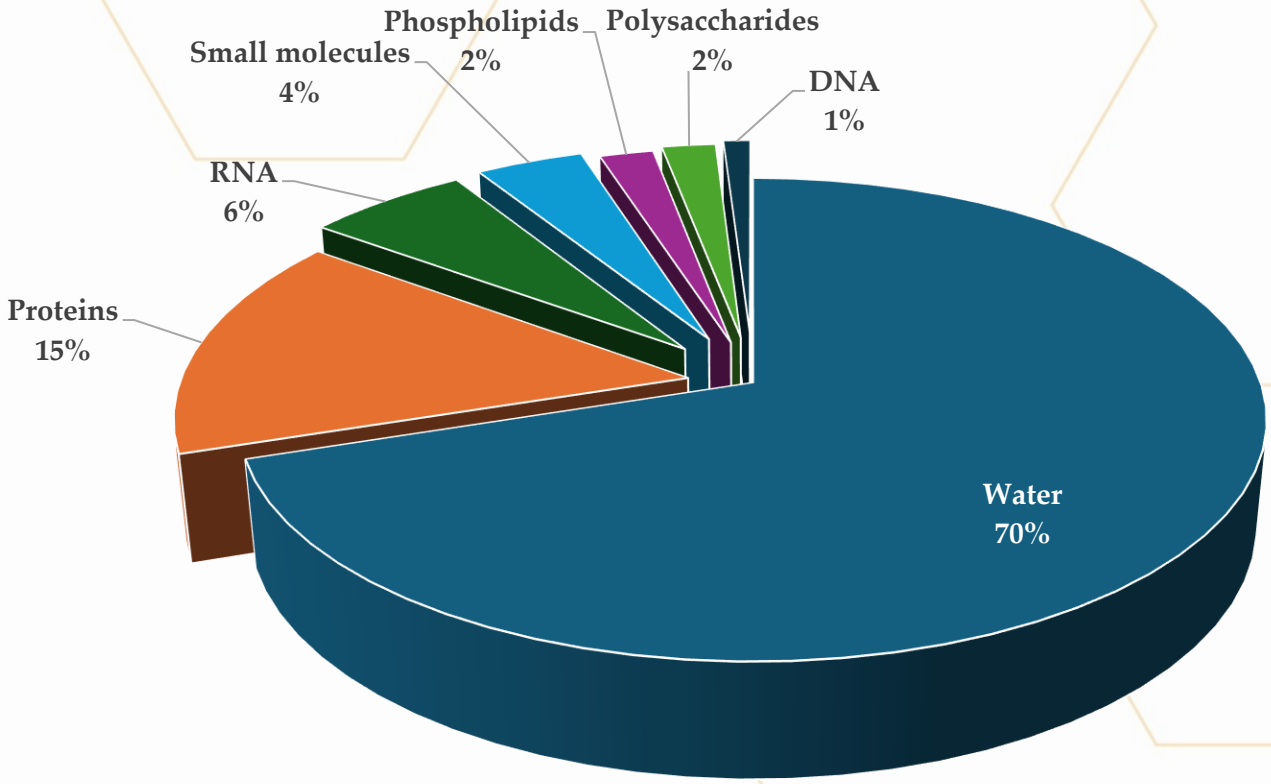
Vacuoles are transparent, spherical formations. They can not be considered a living part of the cell, because they contain excess water, salts and other substances and no own protoplasm.

The nucleus is surrounded by a nuclear membrane, which is similar to the cytoplasmic membrane, but the nuclear membrane is more porous, and whole protein molecules can penetrate through it.
The nucleus is filled with transparent nucleoplasm, which is immersed in long thin threads - **chromosomes**.

The nucleus, mitochondria, and membranes are the most sensitive to radiation in a cell.

The average cell has a volume of about 1000 cubic microns.

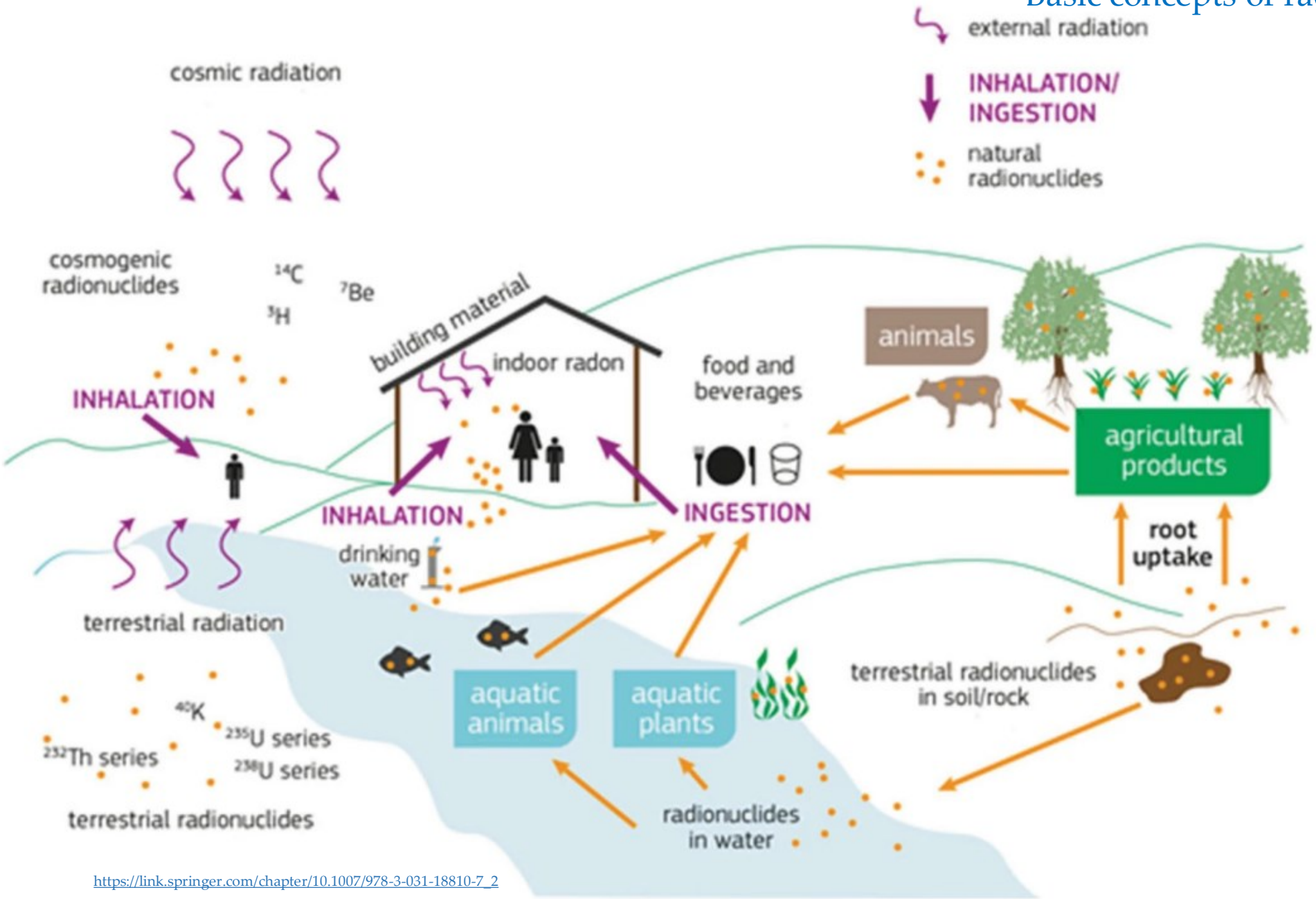
Almost all cells are 70% water and 30% dry matter substance.



The composition of dry matter includes approximately 50-60% of proteins, up to 15-25% RNA, the DNA content varies significantly from 1% to 4%, and in fungal cells - up to 0,1%.

The content of polysaccharides (starch, glycogen, cellulose, etc.) is often about 10%, and lipids - a few percent (except for some specialized cells of plants, animals, and microorganisms that store fat).

Low molecular weight compounds such as sugars, amino acids, vitamins, inorganic salts, make up no more than a few percent of the cell.



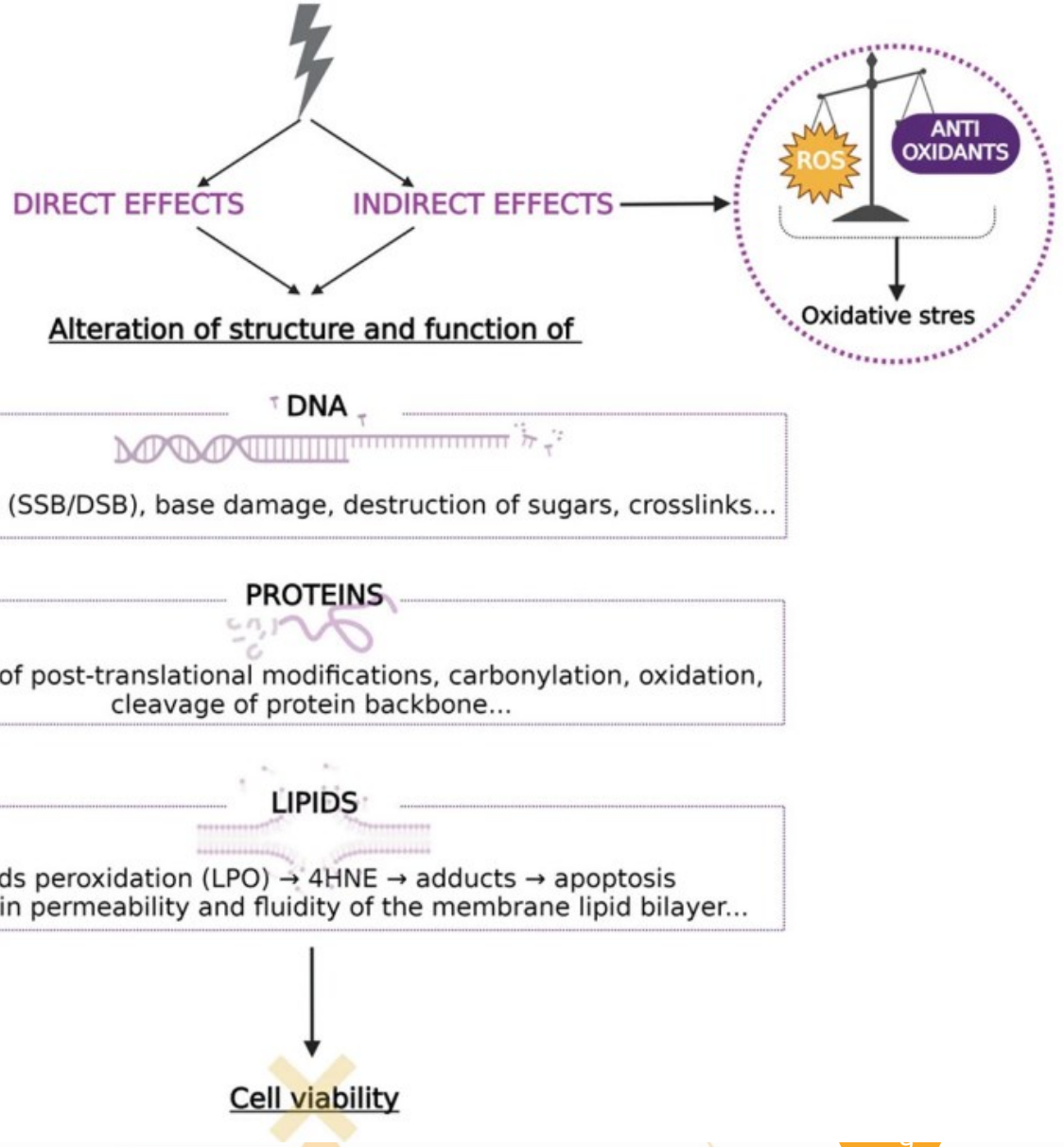
https://link.springer.com/chapter/10.1007/978-3-031-18810-7_2

The interaction of ionizing radiation (IR) with matter leads to biological damage that can impair cell viability. Biological damage induced by IR arises from either direct or indirect action of radiation.

Direct effects occur when IR interacts with critical target molecules such as DNA, lipids, and proteins, leading to ionization or excitation, which causes a chain of events that ultimately leads to the alteration of biomolecules.

Indirect effects occur when IR interacts with water molecules, the major constituent of the cell.

This reaction, called water radiolysis, generates high-energy species known as reactive oxygen species (ROS) that are highly reactive toward critical targets (cell macromolecules) and, when associated with reactive nitrogen species (RNS), lead to damage to the cell structure.



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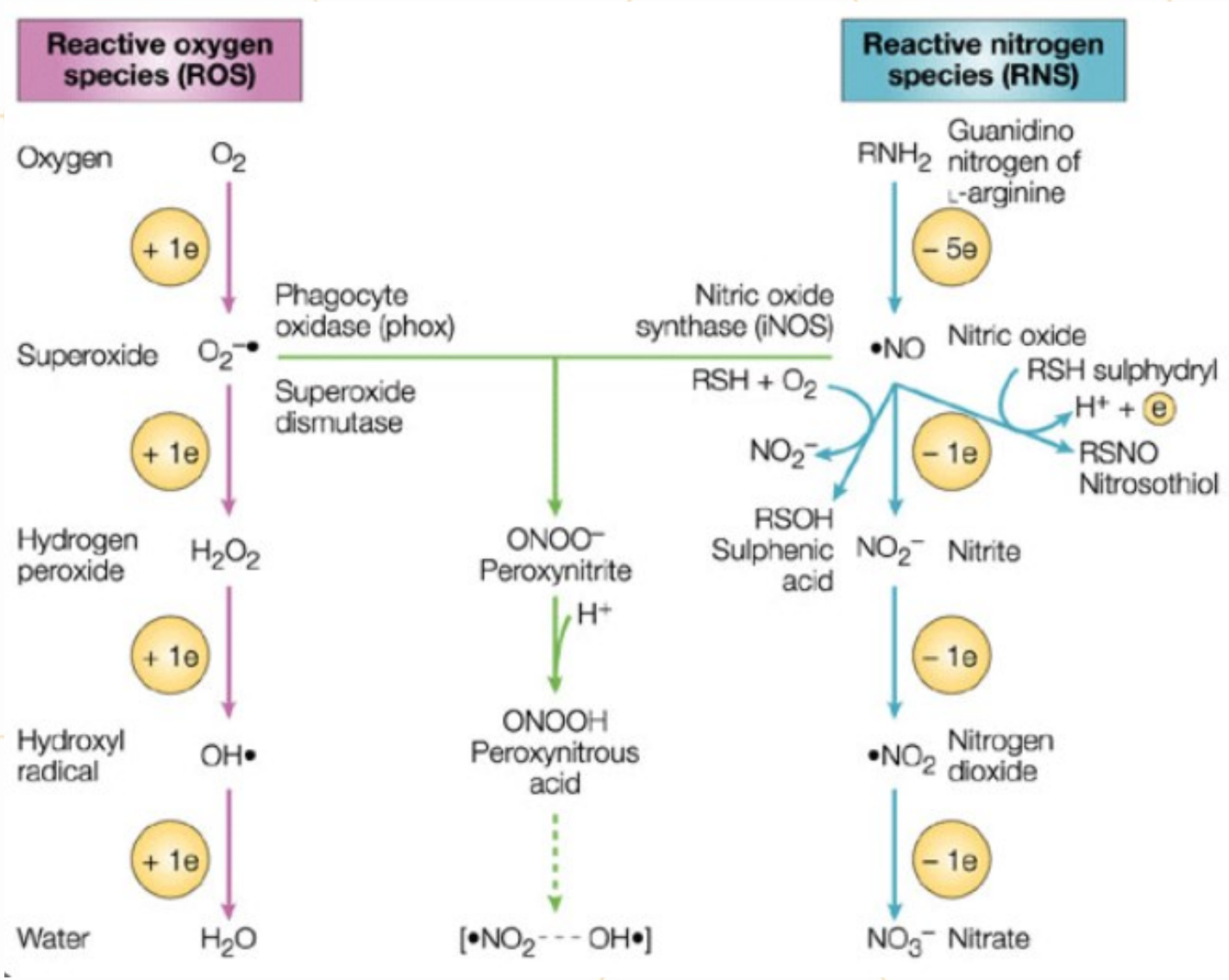
Reactive nitrogen species (RNS) are a family of antimicrobial molecules derived from nitric oxide ($^{\bullet}NO$) and superoxide ($O_2^{\bullet -}$) produced via the enzymatic activity of inducible nitric oxide synthase 2(NOS_2) and nicotinamide adenine dinucleotide phosphate NADPH oxidase, respectively. NOS_2 is expressed primarily in macrophages after induction by cytokines and microbial products, notably interferon-gamma (IFN-γ) and lipopolysaccharide (LPS).

Reactive nitrogen species act together with **reactive oxygen species (ROS)** to damage cells, causing nitrosative stress. Therefore, these two species are often collectively referred to as ROS/RNS.

Reactive nitrogen species are also continuously produced in plants as by-products of aerobic metabolism or in response to stress.



https://www.nature.com/articles/nrmicro1004

Ionizing radiation (IR) can act on biological molecules (RH, representative of hydrocarbons) causing ionization and excitation. One or more chemical bonds may be broken giving atoms or molecules with unpaired electrons, which are very reactive and have a short life. The formation of these radicals occurs in the picosecond time range after the passage of the photons. *The bond may be repaired, or cross-linking may occur due to radical-radical reactions.* These free radicals may also react with oxygen, and in the case of lipids may initiate chain reactions.

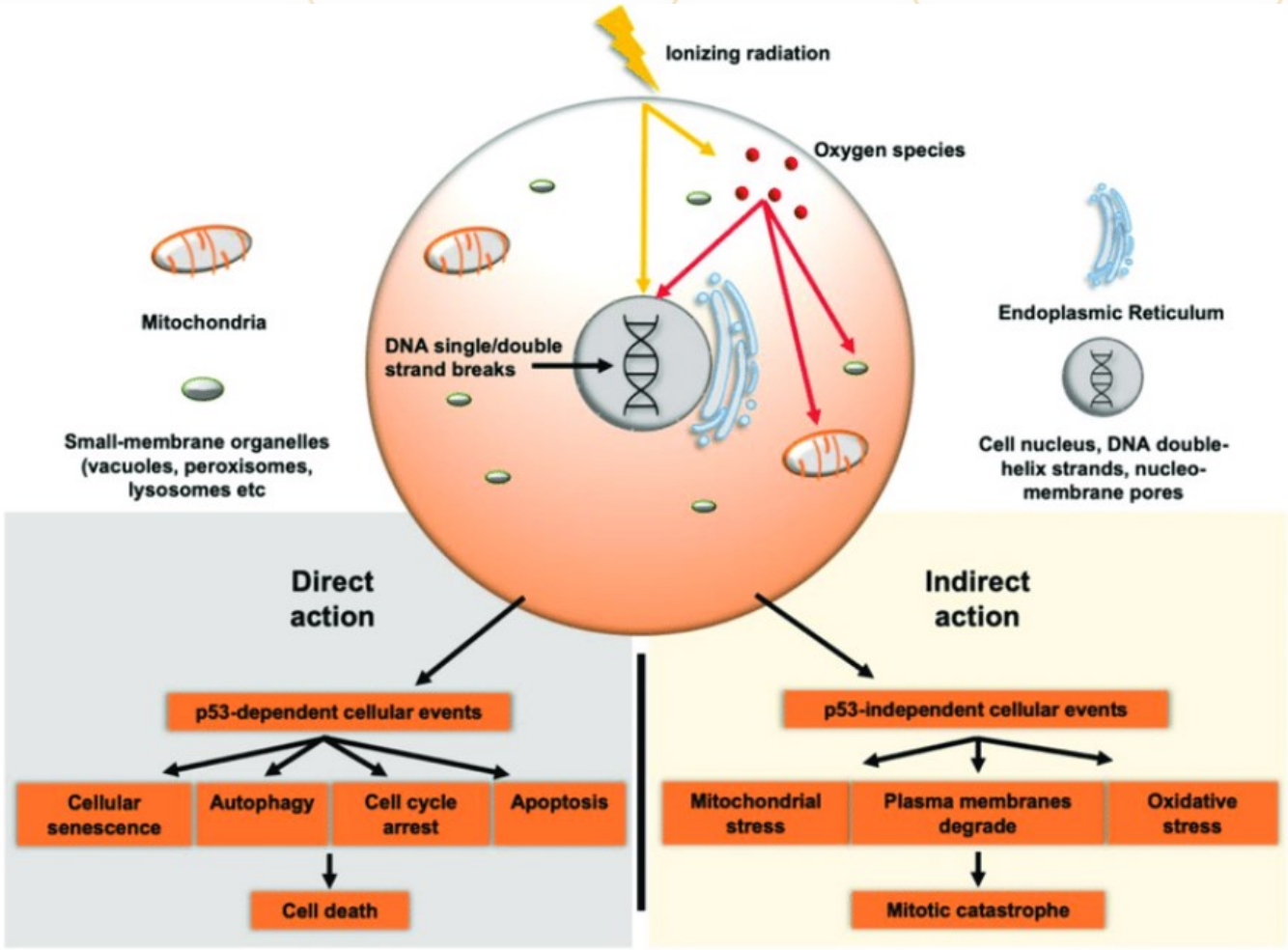
$$IR + RH \rightarrow R^{\bullet} + H^{\bullet}$$

Both $H^{\bullet}$ and $R^{\bullet}$ radicals can react with another molecule, e.g. DNA, lipids, proteins.

$$R^{\bullet} + R'H \rightarrow R'^{\bullet} + RH$$

Radicals can produce cross linking reactions.

$$R^{\bullet} + R^{\cdot} \rightarrow R^{\bullet} - R^{\cdot}$$



It is estimated that about one third of biological damage by γ-radiation is caused by direct effects. This process becomes more dominant with high LET radiation, such as neutrons or α-particles.

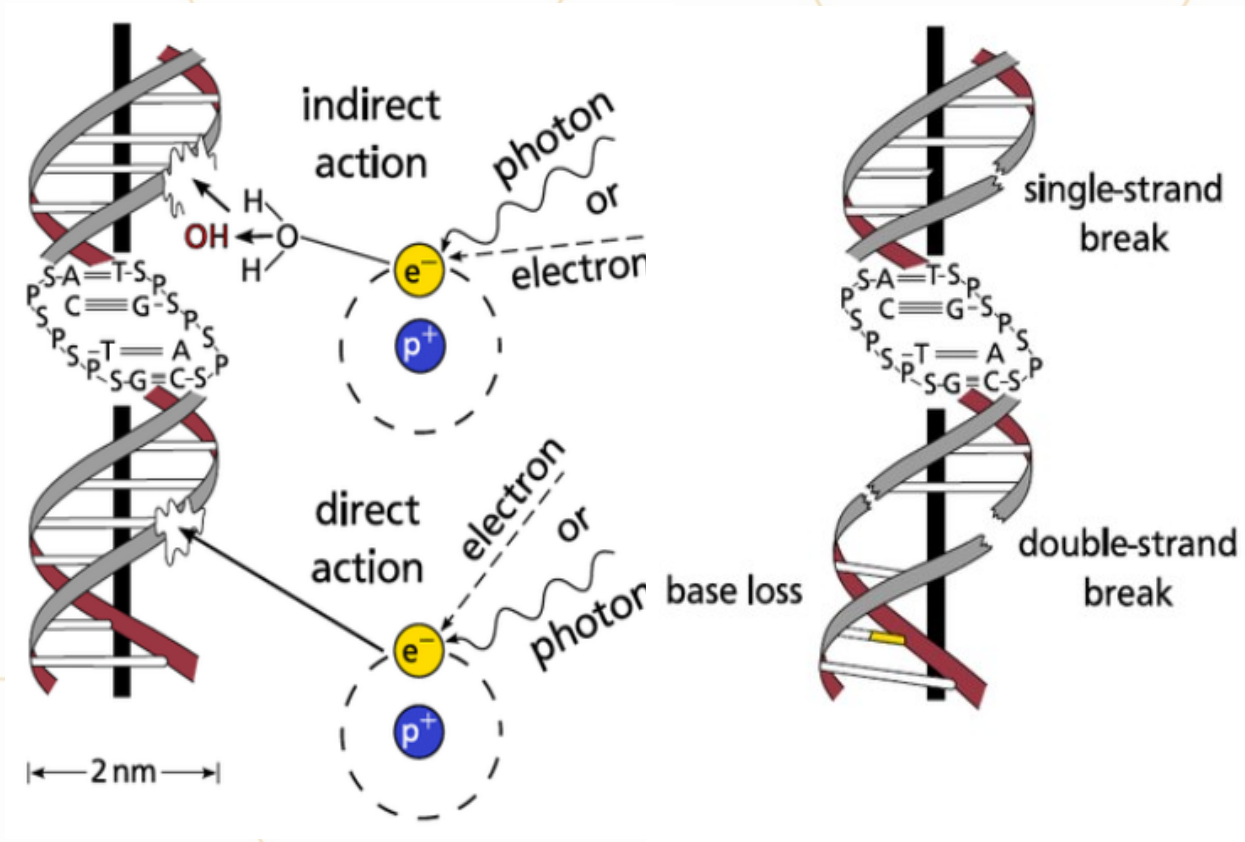
https://link.springer.com/chapter/10.1007/978-3-031-18810-7_2/
http://dx.doi.org/10.3390/cancers13225714

Indirect damages produced by IR in the cell macromolecules are mediated by ROS (resulting from water radiolysis) and by RNS (formed following the reaction of O_2 with endogenous nitric oxide).

The indirect effects contribute to about two-thirds of the damages induced by low linear energy transfer (LET) radiation (X-rays, gamma-rays, beta particles), which is explained by the fact that they are more sparsely ionizing compared to high LET radiation.

When radiation deposits energy in a biological tissue, it takes time to perceive that an effect has occurred.

The succession of the generation of events determines the **four sequential stages** that translate into the biological effects.



Stages

- *Physical*
- *Physicochemical*
- *Chemical*
- *Biological*

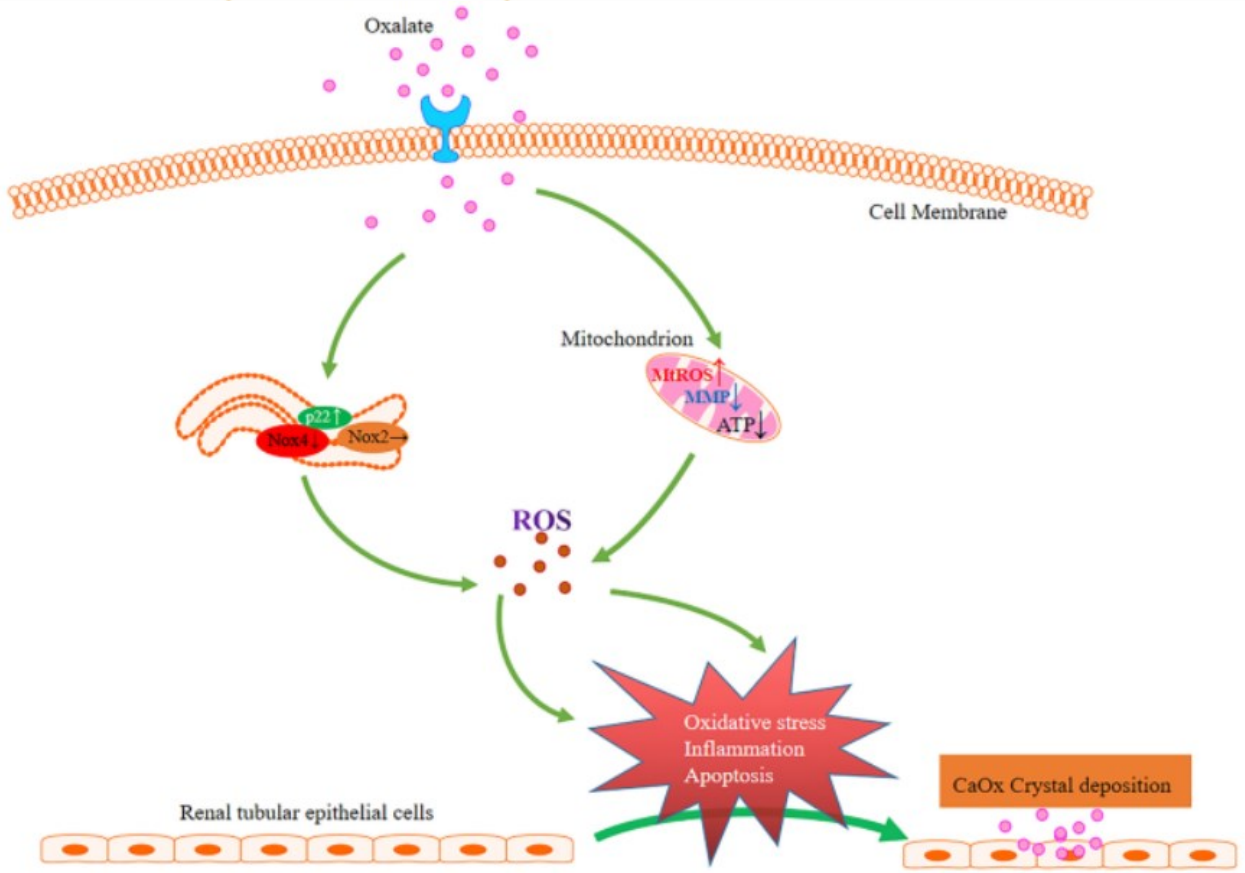
https://link.springer.com/chapter/10.1007/978-3-031-18810-7_2/
http://dx.doi.org/10.13140/2.1.1665.7606

The physical stage is very transient, lasting less than 10^{-16}–10^{-15} s, during which energy (kinetic if particles, or electromagnetic if waves) is transferred to the electrons of atoms or molecules, determining the occurrence of ionization and/or excitation. It is at this stage that ions are formed, which will initiate a sequence of chemical reactions that end up in a biological effect. In the case of water radiolysis (decomposition of water molecules due to IR), the ions H_2O^+ and e^- are formed, as well as the excited water molecule (H_2O^*).

Very soon (10^{-12} s) after the formation of these ions, **the physicochemical stage** begins, with their diffusion in the medium and consequent intermediate formation of oxygen and nitrogen radical species, i.e., atoms, molecules, or ions that have at least one unrepaired valence electron and hence are very reactive chemically.

Following the example of water radiolysis, it is at this stage that **$H^{\cdot}$ + $HO^{\cdot}$, H_2 + 2HO, $HO^{\cdot}$ + H_3O^+, $HO^{\cdot}$ + H_2 + OH^-**, and e^-_{aq} are formed, but also superoxide anion ($O_2^{\cdot -}$) and hydrogen peroxide (H_2O_2).

Peroxynitrite anion ($ONOO^-$) is also formed following the reaction of $O_2^{\cdot -}$ with endogenous nitric oxide (NO). Together with peroxynitrous acid (ONOOH), nitrogen dioxide ($NO_2^{\cdot}$), dinitrogen trioxide (N_2O_3), and others, they are referred to as RNS. The activation of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, the mitochondrial electron transport chain (ETC), or the nitric oxide synthase by IR can also contribute to ROS/RNS generation.



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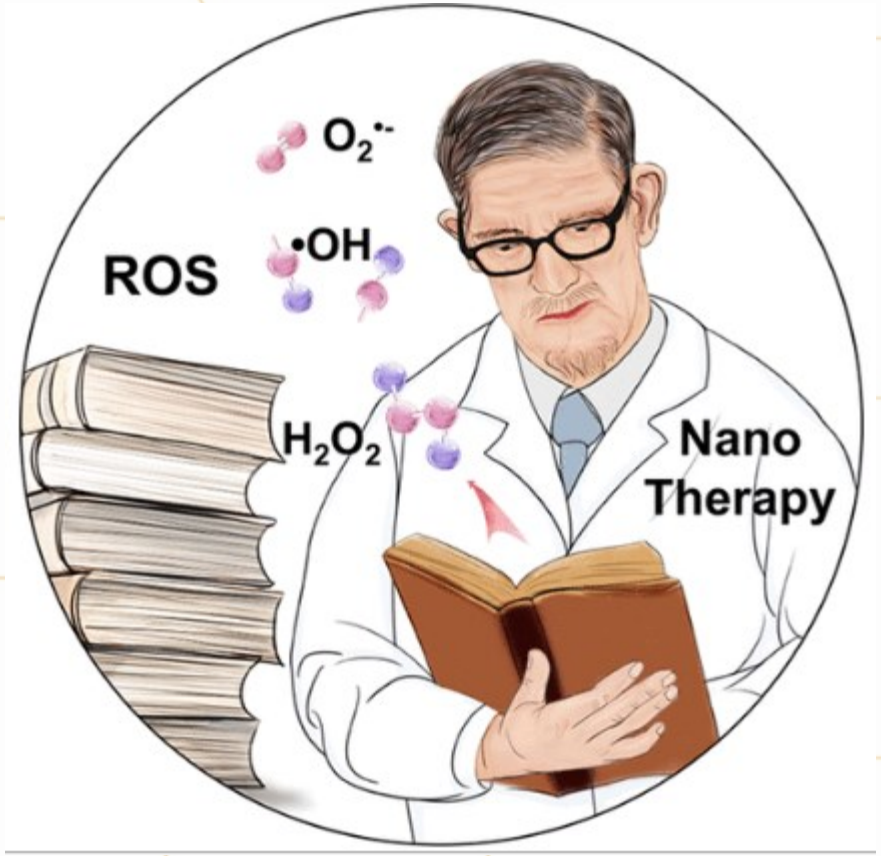
https://www.x-mol.net/paper/article/1490738504087515136

In the next **chemical stage**, the formed radicals and ions recombine and interact with critical cellular organic molecules (DNA, lipids, proteins), inducing structural damages that will translate into disruption of the function of these molecules. Within the DNA molecule, possible chemical reactions with nitrogenous bases, deoxyribose, or phosphate groups may result in breaks and recombinations with the consequent formation of abnormal molecules. Among ROS, OH, which has a strong oxidative potential, is a main contributor to cell damages. The chemical stage can last from 10^{-12} s to a few seconds. ROS and RNS have also been largely implicated in the so-called non-targeted effects of IR.

The **biological phase** occurs, as a consequence of the spreading of chemical reactions involving various biological processes. The existence of more or less effective cellular damage repair mechanisms is responsible for the more or less belated appearance of biological effects and explains the possible long duration of this stage: from a few minutes to decades, depending on the type of radiation, the dose and dose rate, and the radiosensitivity of the irradiated tissue.

Differences in tissue radiosensitivity can be partially explained by the cellular antioxidant capacity, which may vary between cell types. Indeed, to counteract oxidative insults, cells have evolved several defense mechanisms that consist of enzymatic and nonenzymatic systems.

When the amount of ROS/RNS exceeds the antioxidant capacity of the cells, a state of oxidative stress arises, characterized by a decreased pool of antioxidants and modifications in nucleic acids, lipids, and proteins. Oxidative stress can persist for much longer and extend far beyond the primary targets as well as can be transmitted to progeny of the inflicted cells. Responsible for this seems to be the continuous production of ROS and RNS, which can last for months.



https://link.springer.com/chapter/10.1007/978-3-031-18810-7_2/
https://pubs.acs.org/doi/10.1021/acs.chemrev.8b00626

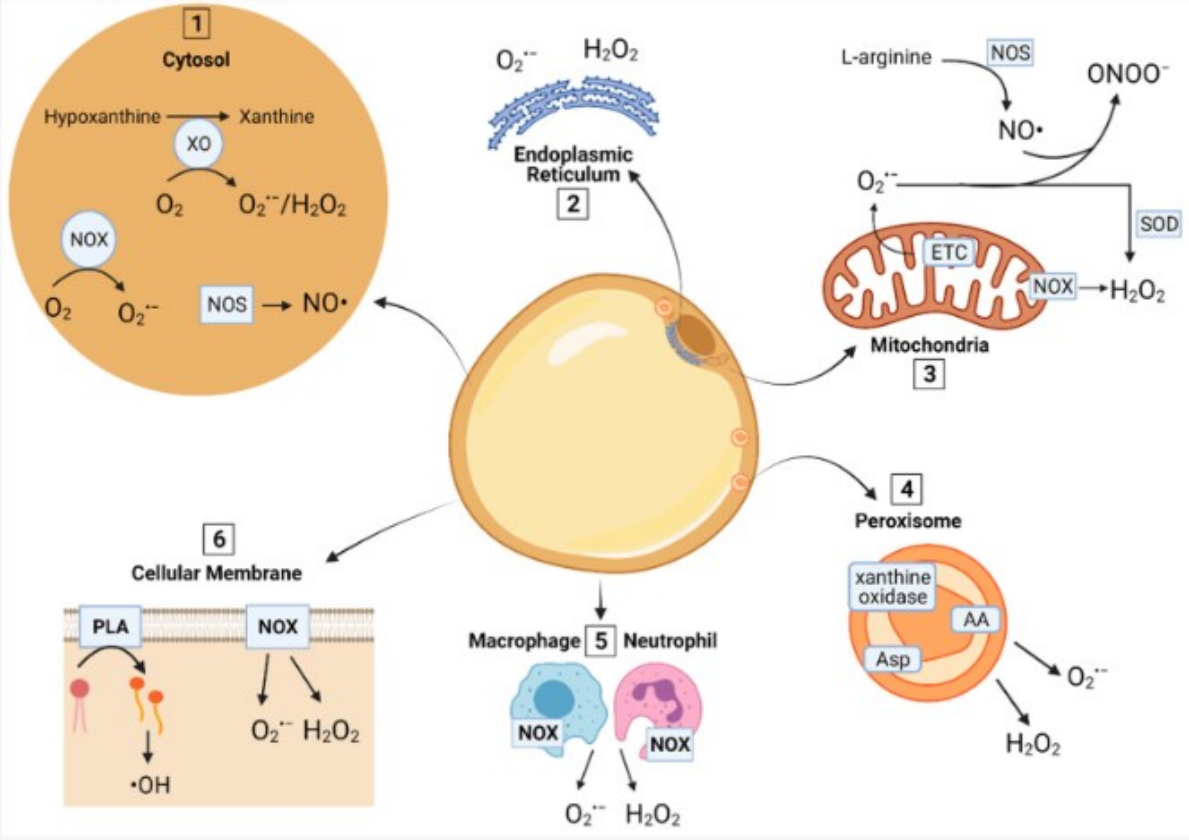
Virtually all cell molecules and organelles may be damaged by IR, with consequences for the cell function depending on the impact of the damage inflicted.

A nucleus is regarded as the main target of IR due to the genetic information contained in the DNA. Therefore, damages to this molecule are considered the most critical ones for cell survival. While efficient repair mechanisms exist to preserve genome integrity, IR may break bonds in purine and pyrimidine nitrogenous bases in the DNA (which may lead to mutations).

Mitochondria can also be subject to radiation damage, both directly and indirectly. These organelles may represent more than 30% of the total cell volume, and the mitochondrial circular DNA can suffer strand breaks, base mismatches, or even deletions of variable length. In this context, mitochondria constitute a major target of IR.

Irradiation may also cause morpho-functional changes in the **endoplasmic reticulum** (ER).

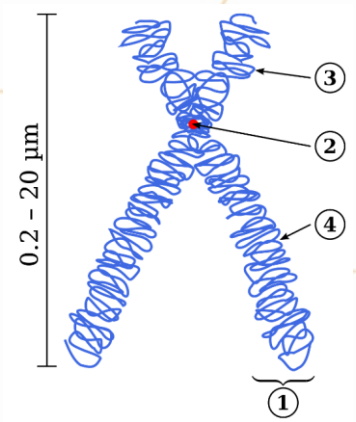
Irradiation may also disorganize the structure of the **Golgi apparatus** due to the induced fragmentation and rearrangement of its cisterns. Given the effects of IR on the endoplasmic reticulum-Golgi apparatus complex, the ensuing alterations in the synthesis and maturation of proteins in the irradiated cells come as no surprise. Lysosomes may also increase in number and volume in the irradiated cells, which is accompanied by upregulation of the enzymatic activity in these organelles.



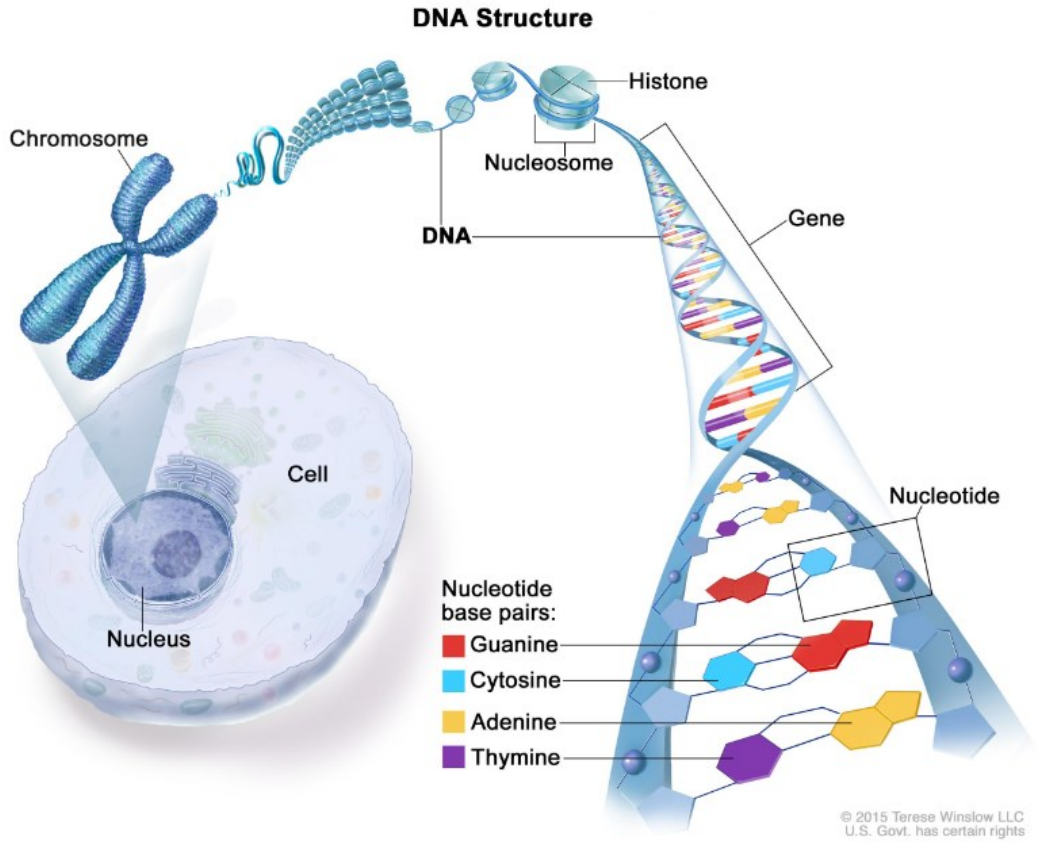
https://doi.org/10.3390/antiox10071090

Chromosomes are thread-like structures present in the nucleus. These are nothing but DNA tightly coiled around a protein called **histone** (just like a thread wound around a cardboard tube).

- Chromosomes exist in pairs.
- Human cells contain 23 such pairs or 46 chromosomes.
- Each chromosome is comprised of one super-long DNA molecule.
- The DNA is coiled around histone and then many such histones are packed together to form a chromosome.



(1) Chromatid – one of the two identical parts of the chromosome after S phase.
(2) Centromere – the point where the two chromatids are joined together.
(3) Short arm is termed p.
(4) Long arm is termed q.



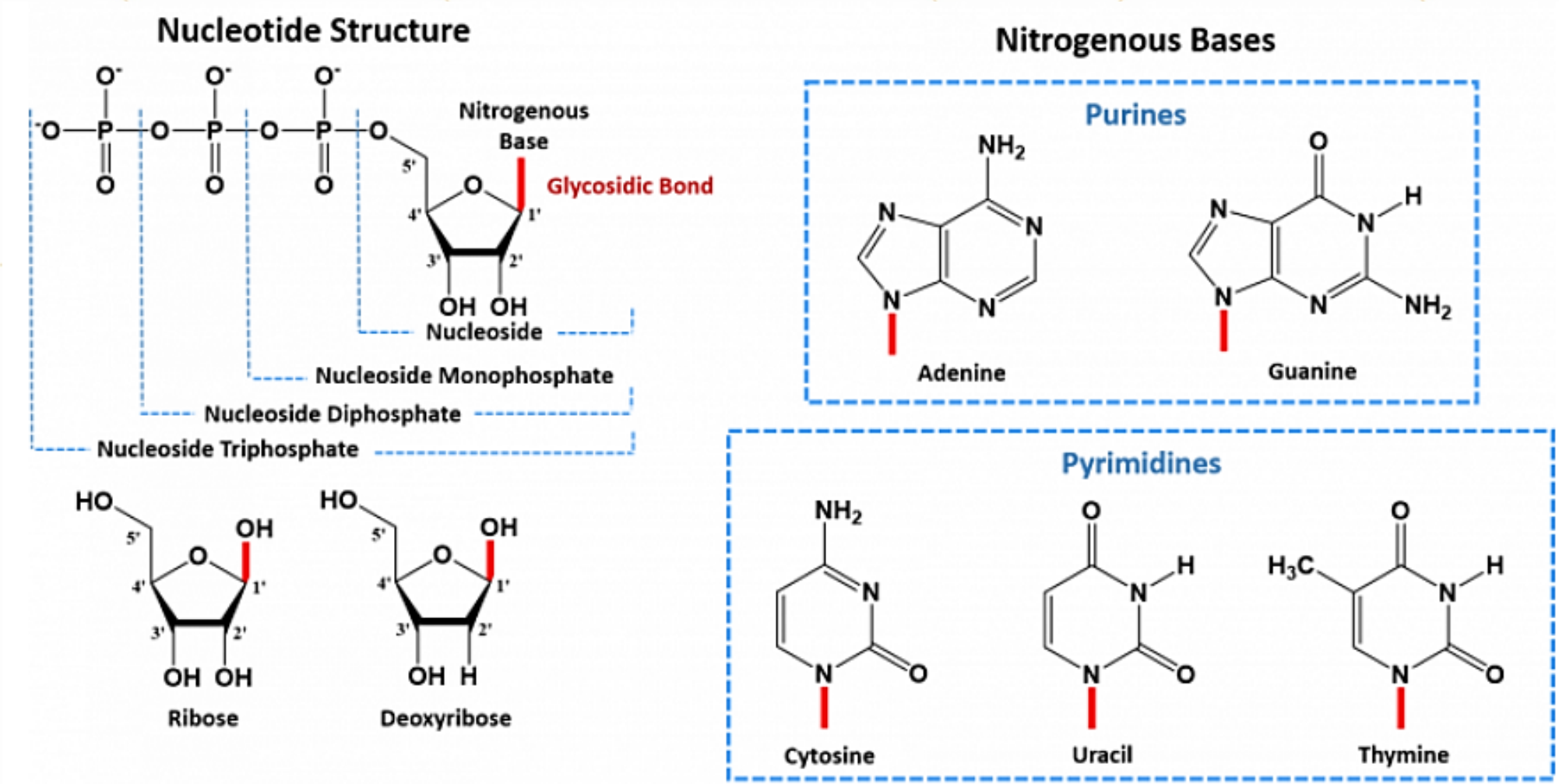
Deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) carry the genetic instructions for the development, functioning, growth, and reproduction of all known organisms and viruses.

The DNA macromolecule is composed of two polynucleotide chains that coil around each other to form a double helix.

The RNA macromolecule usually exists as a single polynucleotide chain that is much shorter than the comparative DNA molecule.

https://www.civilsdaily.com/biotechnology-basics-of-cell-nucleus-chromosomes-dna-genes-etc/

The monomer building blocks of nucleic acids



https://wou.edu/chemistry/courses/online-chemistry-textbooks/ch450-and-ch451-biochemistry-defining-life-at-the-molecular-level/chapter-4-dna-rna-and-the-human-genome/

For the DNA molecule, four nitrogenous bases are incorporated into the standard **DNA** structure. These include the Purines: **Adenine (A) and Guanine (G),** and the Pyrimidines: **Cytosine (C) and Thymine (T). RNA** uses the same nitrogenous bases as DNA, except for Thymine. Thymine is replaced with **Uracil (U)** in the RNA structure.

DNA is called the blueprint of life because it contains the genetic code which are instructions needed for an organism to grow, develop, survive, and reproduce. ***DNA does this by controlling protein synthesis. Proteins are the most important material in our body.***

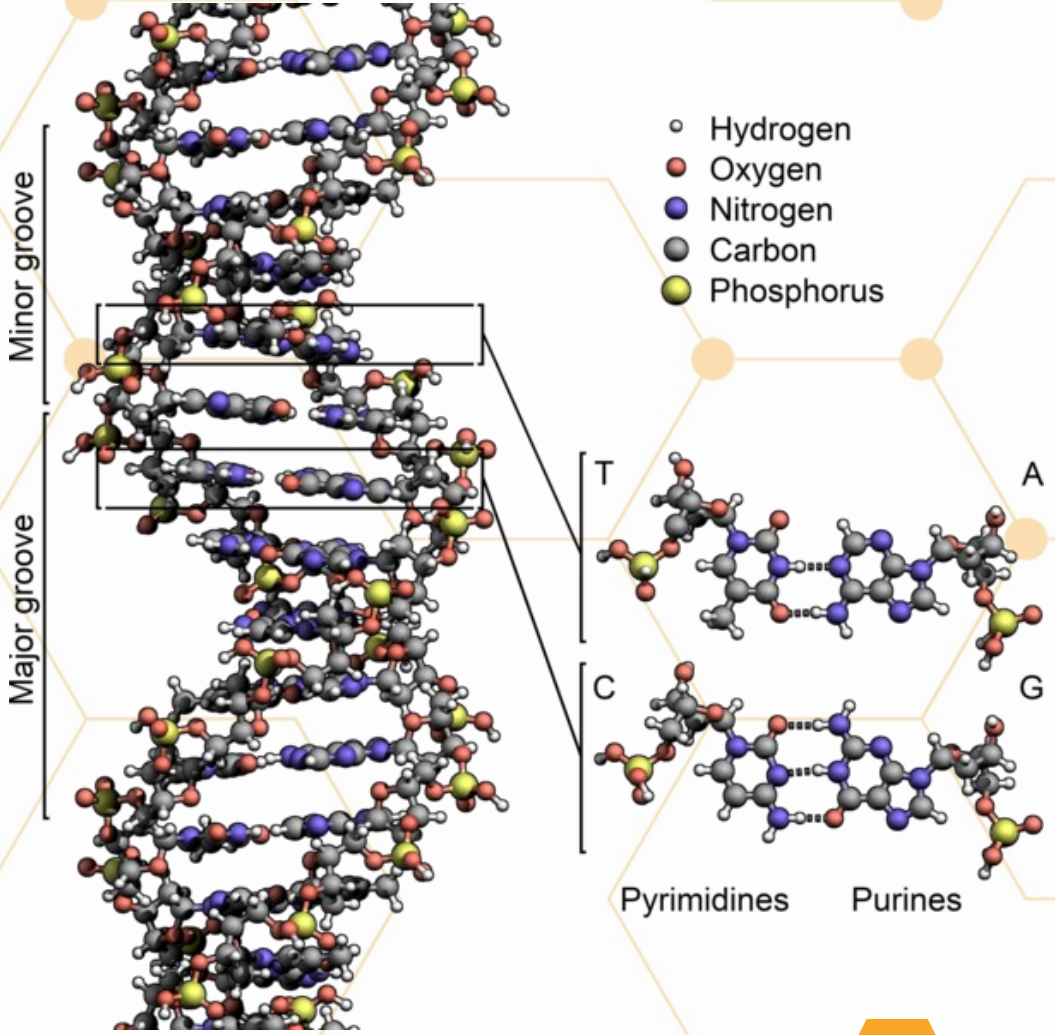
Many would associate them with muscles, but they also aid the production of enzymes which are responsible for conducting all chemical processes and reactions within the body. So, it could be derived that protein synthesis is responsible for all activities carried on by the body and it is controlled by the genes.

In 1953, Francis Crick and James Watson discovered the structure of DNA.

The famous Double Helix model for the structure of DNA is one of the most well-known models

The salient features

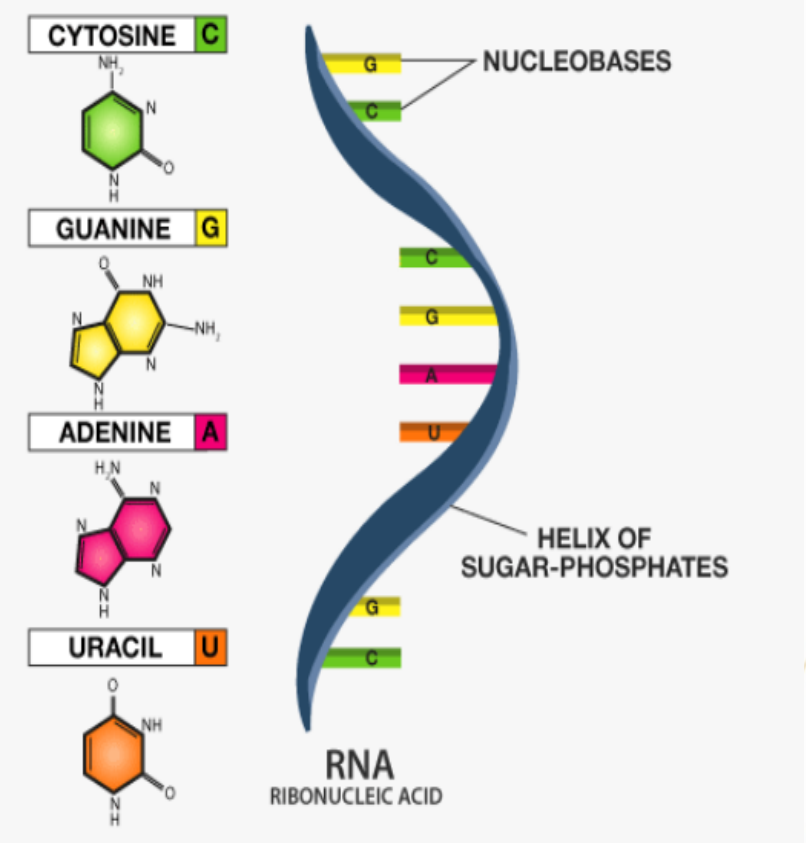
- It is a twisting structure made up of 2 polymer chains.
- The 'backbone' of each chain is constituted by sugar-phosphate and connecting ladders of nitrogenous bases projected inside.
- The polymer chain comprises smaller monomers called nucleotides.
- Each nucleotide has 3 parts – a sugar(ribose), a phosphate molecule and a nitrogenous base.
- There are 4 kinds of Nitrogenous Bases – Adenine(A), Thymine(T), Guanine(G) and Cytosine(C). These bases are complementary.
- A attaches with T and C attaches with G to form complementary pairs that make up the connecting attachments of the double helix model.



https://wou.edu/chemistry/courses/online-chemistry-textbooks/ch450-and-ch451-biochemistry-defining-life-at-the-molecular-level/chapter-4-dna-rna-and-the-human-genome/

In contrast to DNA, **RNA** is single-stranded, and the nitrogenous bases are not necessarily paired with their complements (U takes the place of T in RNA, bonding with A.) The bases are, however, reactive. If there are stretches of complementary base pairs elsewhere on the RNA molecule or on another RNA molecule, those segments will form hydrogen bonds, tying the two complementary parts together. When sections of RNA bind with each other, the RNA strand(s) folds into specific shapes, which affect how they catalyze reactions.

The patterns of RNA base pairs determine how the strands fold, allowing them to perform different functions for the cells.



Management of DNA and RNA is critical for organisms to live and reproduce

Three main types of RNA:

- messenger RNA (mRNA),
- ribosomal RNA (rRNA),
- and transfer RNA (tRNA).

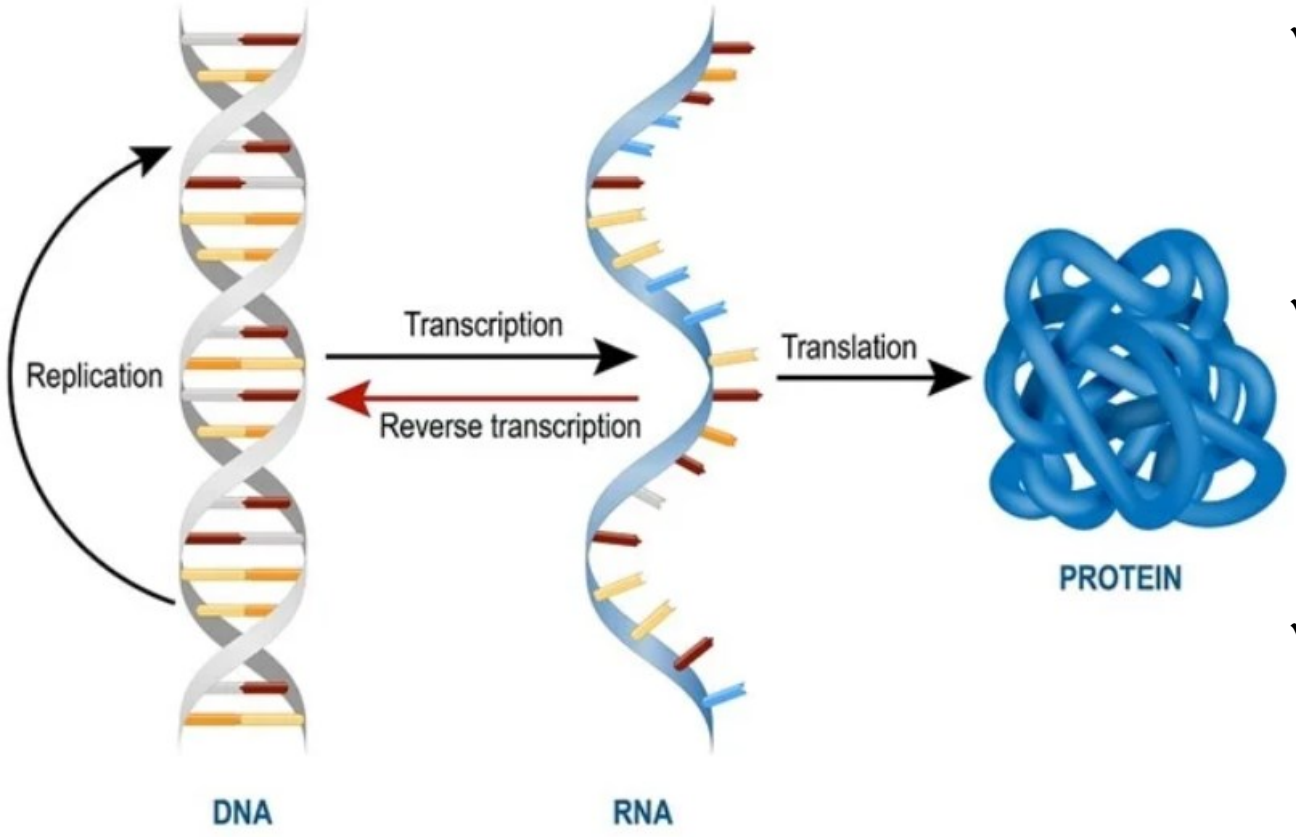
mRNA accounts for just 5% of the total RNA in the cell. mRNA is the most heterogeneous of the 3 types of RNA in terms of both base sequence and size. It carries complementary genetic code copied, from DNA during transcription, in the form of triplets of nucleotides called codons.

rRNAs are found in the ribosomes and account for 80% of the total RNA present in the cell. Ribosomes are composed of a large subunit called the 50S and a small subunit called the 30S, each of which is made up of its own specific rRNA molecules. Different rRNAs present in the ribosomes include small rRNAs and large rRNAs, which belong to the small and large subunits of the ribosome, respectively.

tRNA is the smallest of the 3 types of RNA, possessing around 75-95 nucleotides. tRNAs are an essential component of translation, where their main function is the transfer of amino acids during protein synthesis. Therefore, they are called transfer RNAs.

https://byjus.com/biology/structure-of-rna
https://www.news-medical.net/life-sciences/-Types-of-RNA-mRNA-rRNA-and-tRNA.aspx

RNA, like DNA, is made up of chains of bases. For RNA, these are adenine, guanine, cytosine, and uracil. Unlike DNA, RNA has one chain of bases (called a single strand). RNA is involved in the protein-making process, which has **three key steps**:



- ✓ The first key step in making a protein is called **transcription**. During transcription, a section of DNA that makes up a gene is copied into a matching chemical called 'pre-messenger ribonucleic acid' or 'pre-mRNA' for short.
- ✓ In the next step called **splicing**, sections called exons are joined together by cutting out the areas in between (called introns) to make mRNA. It is a bit like just leaving the ingredients in a recipe by cutting out the introduction and other extra information. This is because not all the information in the pre-mRNA is needed to make a protein.
- ✓ In the last step, called **translation**, a protein-making machine called a ribosome binds to the mRNA recipe and attaches amino acids (the ingredients) according to this recipe. The amino acids join together into a long chain that folds into the protein.

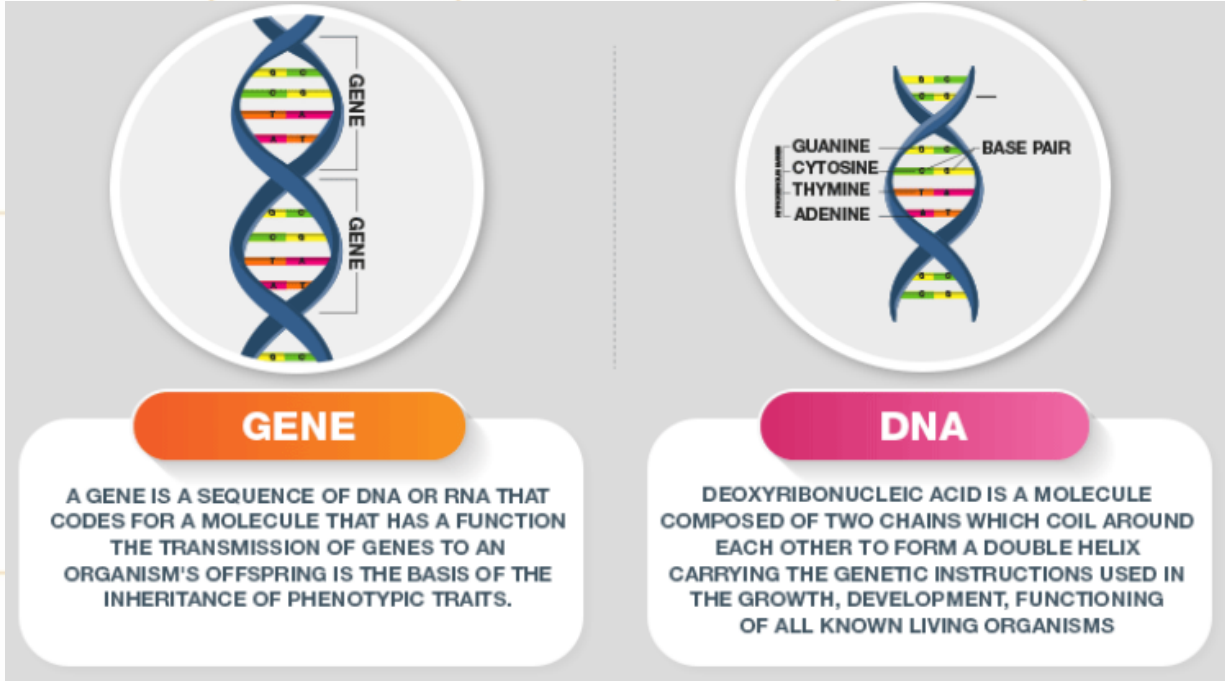
https://www.news-medical.net/life-sciences/-Types-of-RNA-mRNA-rRNA-and-tRNA.aspx
https://www.genetics.edu.au/SitePages/DNA-RNA-Genes-and-Chromosomes.aspx

Genes, as we know, are hereditary markers from which we derive various characteristics like skin color, height, etc. More technically, each DNA molecule consists of sequences of **Genes**. Each gene is a particular set of instructions for specific functions. E.g., the globin gene would aid the production of hemoglobin, another gene would do so for insulin, and so on and so forth. Each gene naturally consists of a sequence of nucleotides and base pairs.

Alleles are alternate-form genes that correspond to the same characteristic but provide for variations in that characteristic. A very crude example is as follows: assume a hen. A particular gene would be responsible for the color of its feathers, say black and white.

Hence, we say the same gene has 2 variants known as alleles. Naturally, the nucleotide sequence in them will differ.

Difference between gene and DNA	
Gene	**DNA - deoxyribonucleic acid**
Genes are the DNA stretches that encode for specific proteins.	DNA is a biomolecule, which contains genetic information
Regulates the traits of an organism.	Regulates gene regulation.
Gene is a specific sequence present on a short stretch of DNA.	DNA made up of two long chains of polynucleotides wound together
Genes are made up of either DNA or RNA.	DNA is a polymer of nucleotides
A gene is located on a chromosome.	DNA is located within the nucleus of the cell.
Are coded with heredity information.	Encodes the genetic instructions.



https://byjus.com/biology/difference-between-gene-and-dna/
https://www.genetics.edu.au/SitePages/DNA-RNA-Genes-and-Chromosomes.aspx

Linear energy transfer (LET) is the average (radiation) energy deposited per unit path length along the track of an ionizing particle. Its units are **keV/µm**.

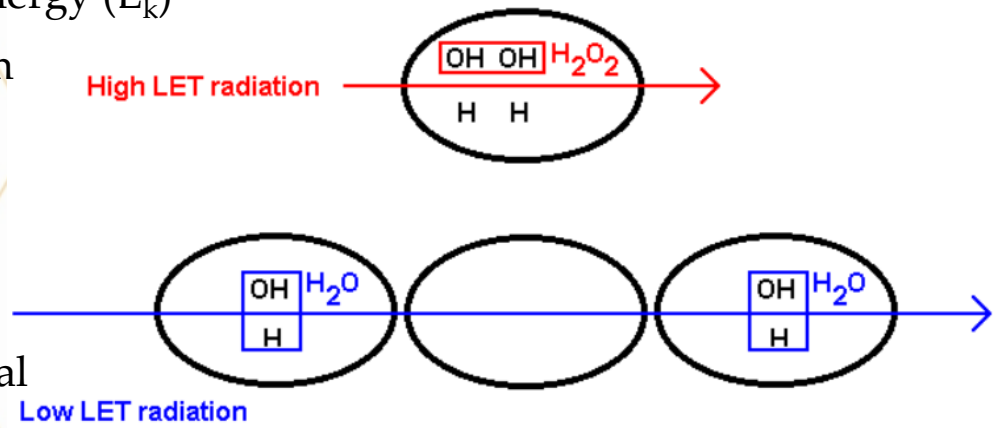
Linear energy transfer describes the energy deposition density of a particular type of radiation, which largely determines the biological consequence of radiation exposure.

The linear energy transfer of a charged particle [2] is $\propto Q^2/E_k$

- linear energy transfer is proportional to the square of the charge of the particle (Q^2)
- linear energy transfer is inversely proportional to the particle's kinetic energy (E_k)

High linear energy transfer radiations: linear energy transfer 3-200 keV/µm

- commonly mediated by:
  - α-particles
  - protons
  - neutrons
- greater density of interactions at the cellular level
- more likely, than low linear energy transfer, to produce biological damage in a given volume of tissue



Low linear energy transfer radiations: linear energy transfer 0.2-3 keV/µm

- commonly mediated by:
  - electrons
  - positrons
  - gamma rays
  - X-rays
- less likely than high linear energy transfer to produce tissue damage in the same volume of tissue

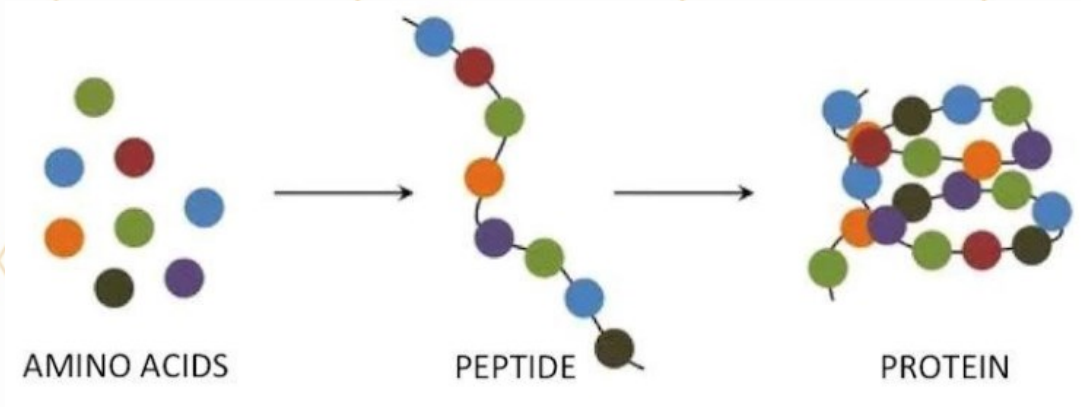
https://radiopaedia.org/articles/linear-energy-transfer

Each gene can be represented as a sequence of codons where codons are a sequence of base triplets – meaning 3 bases combine together to form a **codon**. Each codon corresponds to a specific **amino acid**.

E.g., AUG codon corresponds to the amino acid methionine.

Amino acids combine to form a particular **peptide** chain.

The peptide chains undergo a structural transformation to form 3-dimensional molecules called **proteins**.



Types of proteins in a human body

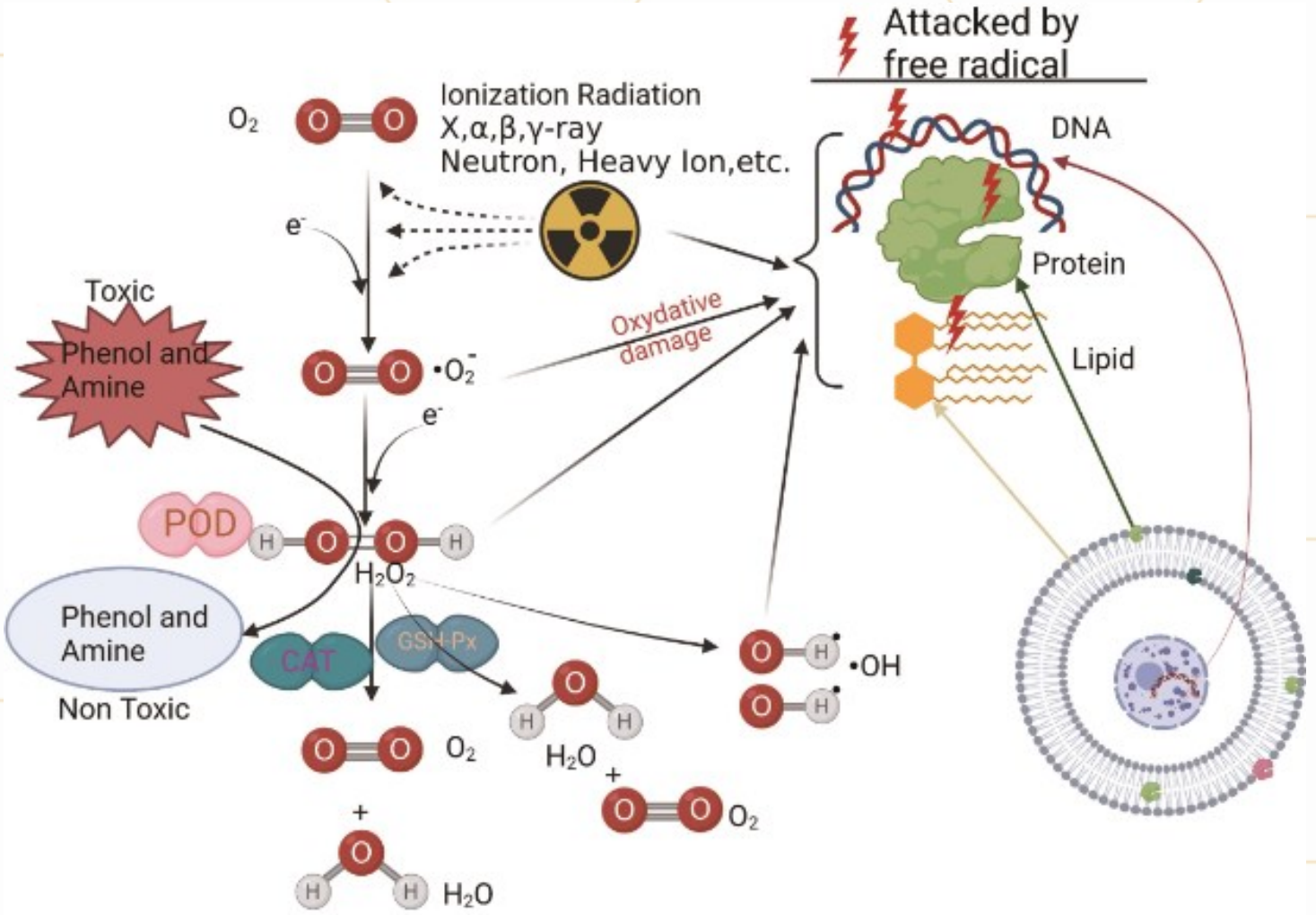
Protein	Function	Examples
Enzymes	Facilitate biochemical reactions	Lactase, Pepsin
Hormonal	Messenger proteins that help to coordinate bodily activities	Insulin, Oxytocin
Structural	Provide support	Keratin, Collagen
Contractile	Responsible for movement	Actin, Myosin
Transport	Move molecules from one place to another	Haemoglobin, Cytochromes

https://www.civilsdaily.com/biotechnology-basics-of-cell-nucleus-chromosomes-dna-genes-etc/

With low LET radiation, the damage tends to be spatially isolated along the DNA molecule. With high LET radiation, clusters of damage occur on a given chromosome.

Such clustered damage is more complex and difficult to repair than the isolated damage caused by low LET radiation. Repair may require enzymes from multiple repair pathways.

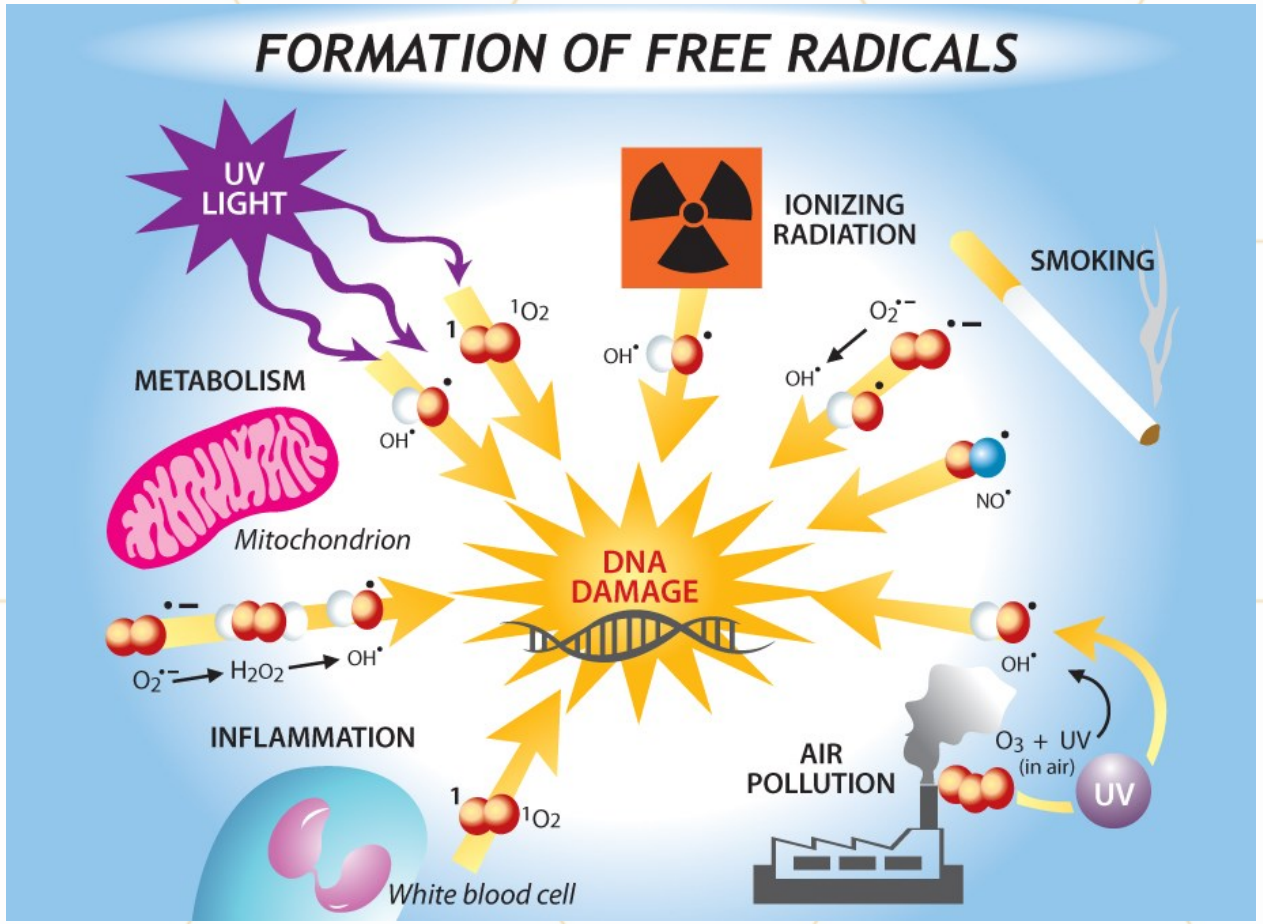
Clustered damage rarely occurs in the absence of radiation, i.e., it is somewhat "unique" to radiation.



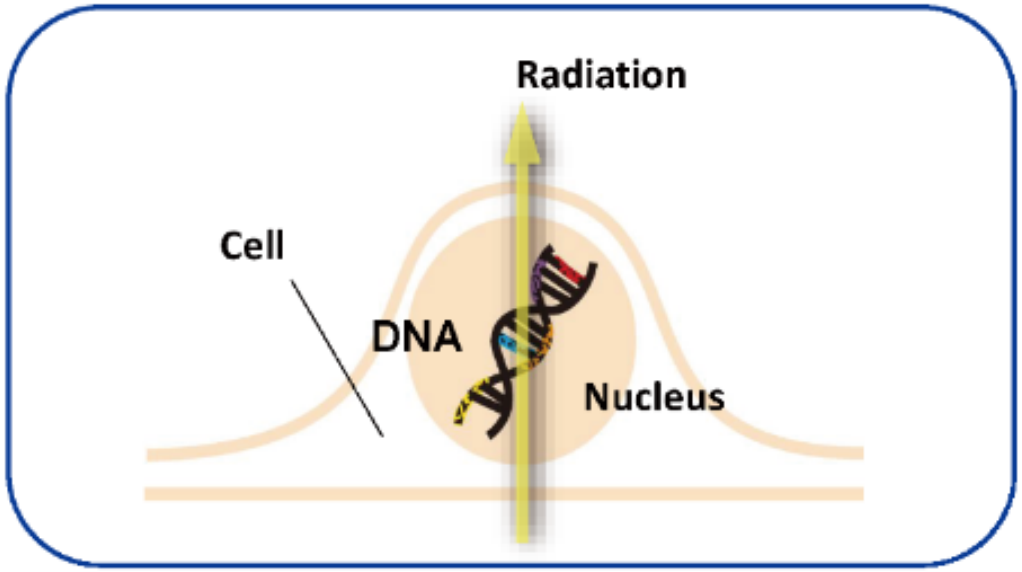
The following table (UNSCEAR 2000) indicates the estimated DNA damage per gray (100 rads)

DNA-protein crosslinks	150 per cell
Base damage	500 per cell
Single strand breaks	1,000 per cell
Double strand breaks	40 per cell

This involves alterations to individual nitrogenous bases. These alterations are primarily due to the formation of free radicals in the water that are closely bound to the chromosomes. As an example of such damage, the free radicals might induce the deamination of the nitrogenous base cytosine and convert it to uracil. It is even possible that the base might be completely removed. DNA base damage is often (although not always) what is meant by the term **mutation**. It is sometimes referred to as a genetic (vs. chromosomal) mutation.



https://www.nrc.gov/docs/ML1122/ML11229A692.pdf

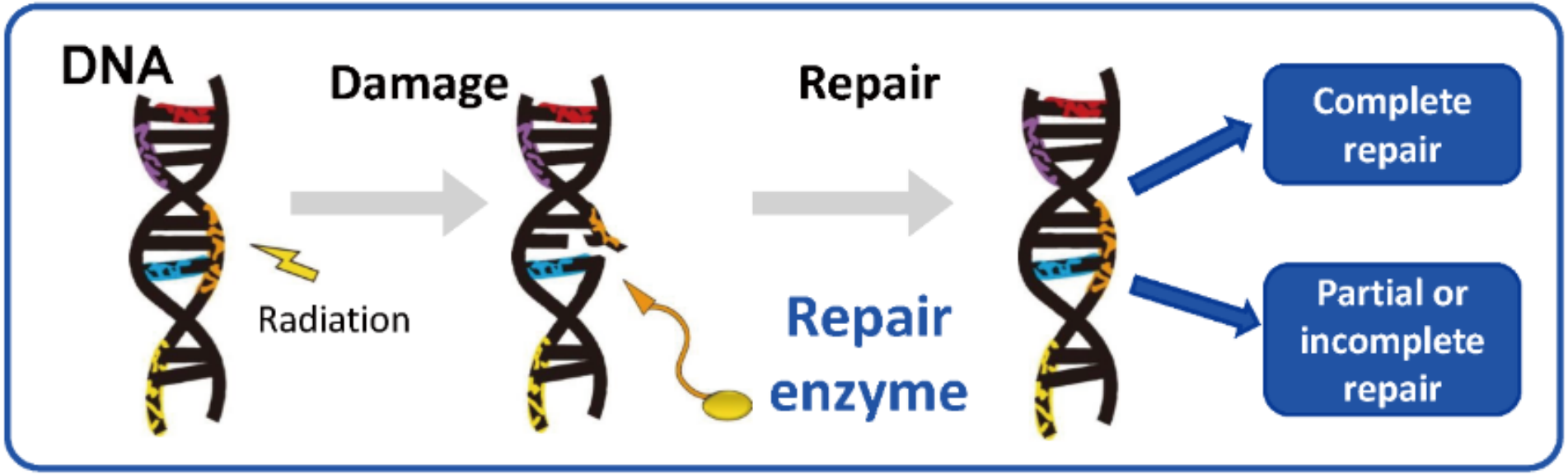


Damage per 1 mGy of X-rays (per cell)

Base damage: 2.5 locations

Single-strand break: 1 location

Double-strand breaks: 0.04 locations



https://www.env.go.jp/en/chemi/rhm/basic-info/1st/03-02-02.html

Ionizing radiation (IR) directly damages DNA or indirectly affects it through the generation of highly reactive hydroxyl radicals (•OH) from water molecules. IR can cause different types of damage to the DNA such as base lesions, and single-strand and double-strand breaks.

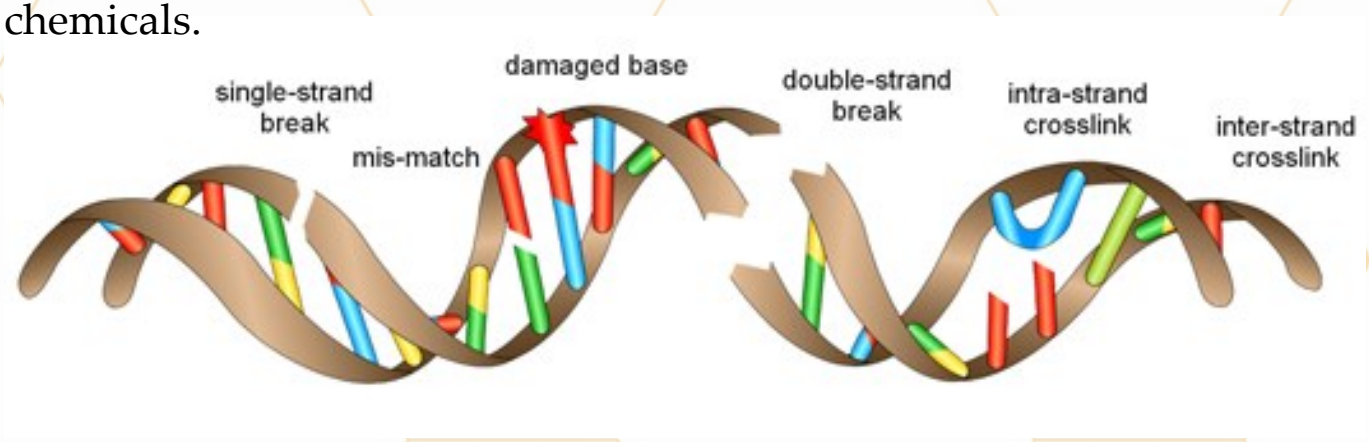
Types of DNA Damage and Mechanisms:

1. DNA Strand Breaks

DNA strand breaks occur when one or both strands of DNA are interrupted. There are two types: single-strand breaks (SSBs) where one strand is cut, and double-strand breaks (DSBs) where both strands are cut. These breaks can be caused by ionizing radiation like X-rays and gamma rays, as well as certain chemicals.

2. Oxidative Damage

Oxidative damage can occur due to the action of reactive oxygen species (ROS) which leads to the formation of lesions. The highly reactive ROS, such as hydroxyl radicals (•OH), can cause oxidative damage to DNA bases.



3. Alkylation of Bases

Alkylating agents, both endogenous and exogenous, can modify DNA bases by introducing alkyl groups. These modifications can be cytotoxic, mutagenic, or have neutral effects on the cell.

4. Base Loss

Base loss occurs when the nitrogenous bases in DNA are removed, leaving behind apurinic/apyrimidinic (AP) sites or abasic sites. AP sites are chemically unstable and can lead to DNA strand breaks or mutagenic events if left unrepaired.

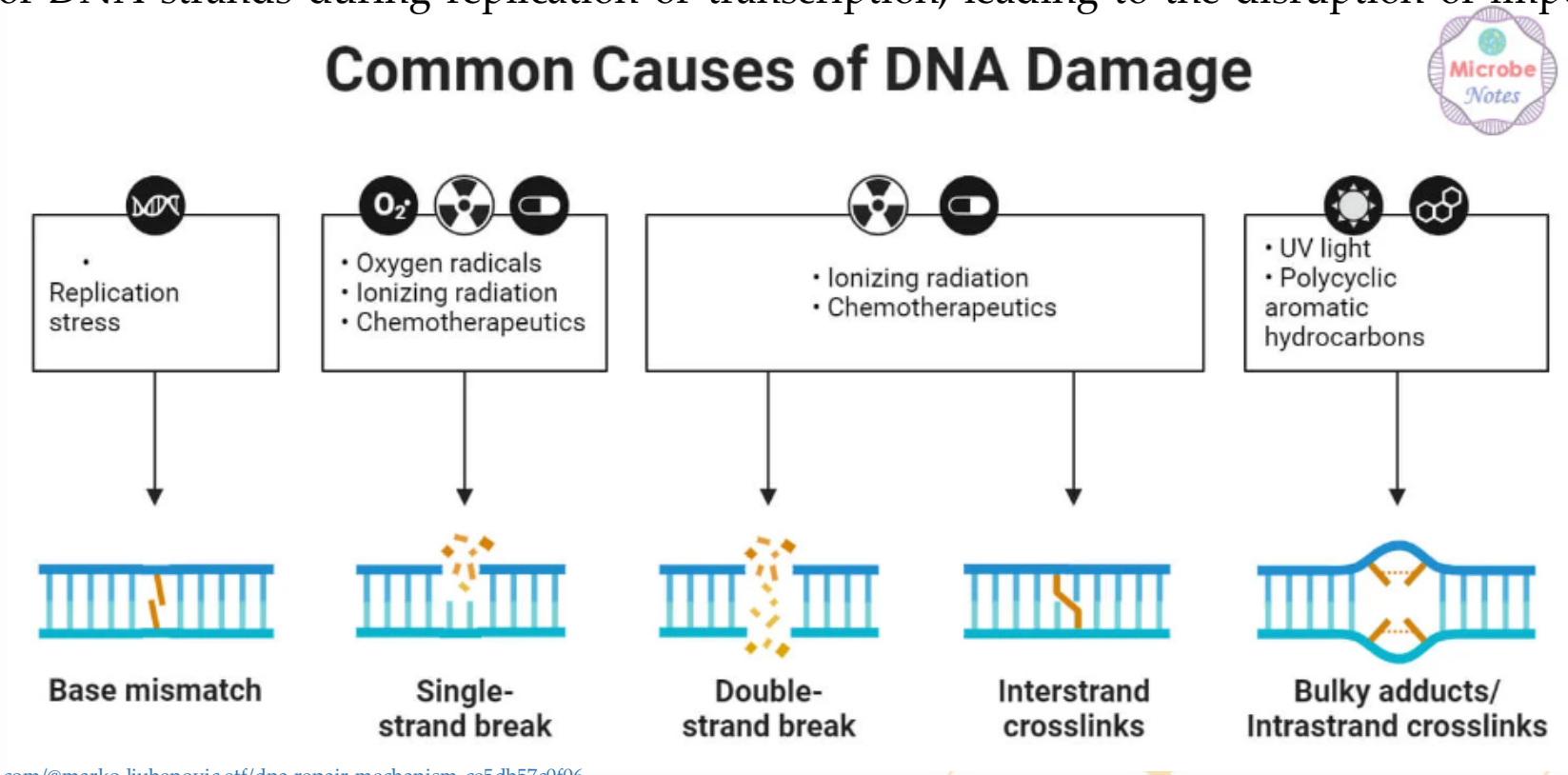
https://medium.com/@marko.ljubenovic.etf/dna-repair-mechanism-ce5db57c0f06

5. Bulky Adduct Formation

Bulky adducts are formed when certain chemicals, such as polycyclic aromatic hydrocarbons (PAHs), covalently bind to DNA bases. These adducts create bulky modifications that stick out from the DNA and disrupt its structure. They can interfere with DNA replication, transcription, and repair processes, potentially leading to mutations.

6. DNA Crosslinking

DNA crosslinking occurs when two nucleotides in DNA become covalently linked together. Crosslinks can form within the same DNA strand (intrastrand crosslinks) or between opposite DNA strands (interstrand crosslinks). DNA crosslinks prevent the separation of DNA strands during replication or transcription, leading to the disruption of important cellular processes.



https://medium.com/@marko.ljubenovic.etf/dna-repair-mechanism-ce5db57c0f06

Although causes of DNA damage are vastly diverse, so are the ways the cell has to deal with them.

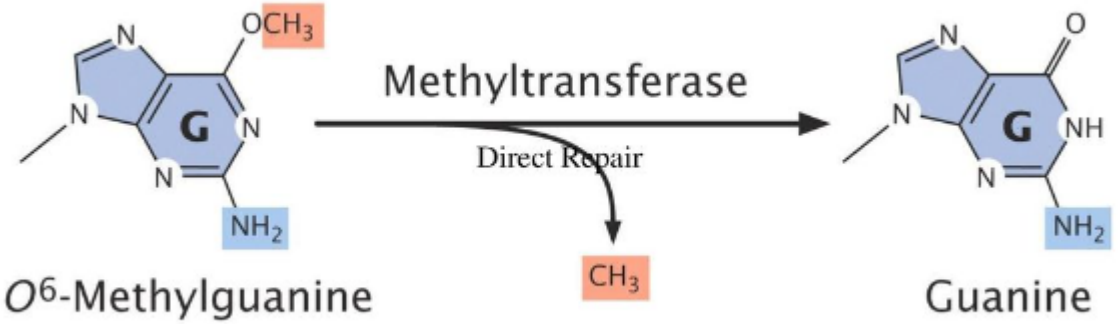
DNA repair mechanisms:

Direct repair is what we call a few highly specialized systems that are capable of restoring the chemistry and structure of the damaged DNA back to its original state. These mechanisms do not require a template — the type of damage they reverse can occur in only one of four bases.

Photolyase are enzymes that repair damage caused by UV light, by converting photoproducts into their original bases. These enzymes require visible light (precisely, a wavelength of 300–500 nm, which is the blue/violet end of the spectrum) to work. The process is known as photoreactivation. These enzymes occur in almost all living organisms (including bacteria, fungi, plants, and most animals) except placental mammals, i.e. humans.

Methyl guanine methyl transferase (MGMT) is a protein that reverses alkylation, specifically methylation of guanine bases. They do so by transferring the alkyl group from the base to their own polypeptide chain. MGMT inactivates itself after doing this, making it a suicide protein. Therefore, each MGMT molecule can be used only once, making this a very expensive process. Methylation of cytosine and adenine can also be reversed by the cell.

Mismatch repair. DNA mismatch loops arise by deamination, or by incorporation of inappropriate nucleotides during DNA replication or recombination. DNA mismatch repair (MMR) is a highly conserved biological pathway. It is a rather complicated process that has been extensively studied and well-characterized in E. coli. In humans, several MMR proteins have been identified: MutS, MutL, EXO1, RPA, PCNA, DNA polymerase, and DNA ligase. MMR prevents mutations from becoming permanent in dividing cells by correcting mismatches, and it does so by determining the template and non-template strand, and then replacing the wrong base with the correct one (but the removal process involves more nucleotides — several base pairs of the newly synthesized DNA strand can be removed at once).



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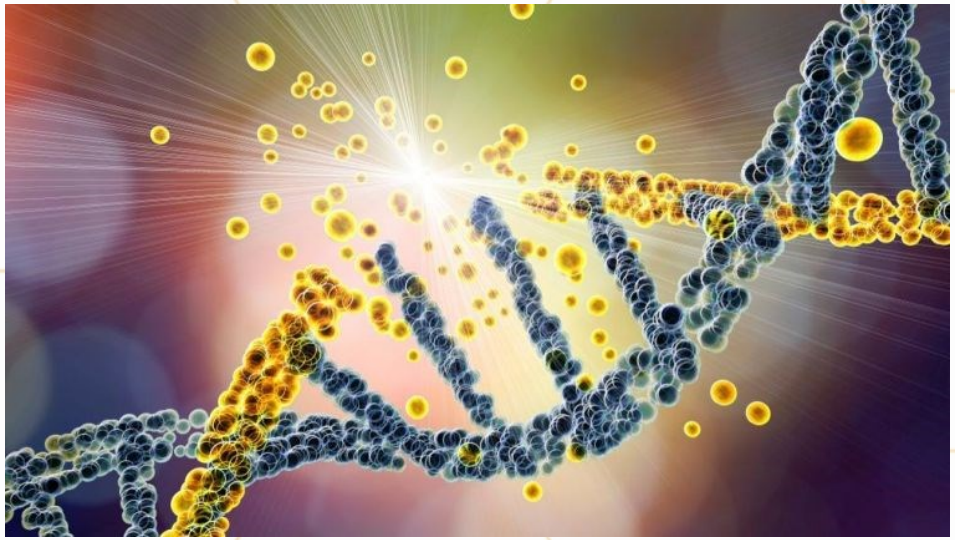
https://medium.com/@marko.ljubenovic.etf/dna-repair-mechanism-ce5db57c0f06

DNA repair mechanisms. Single-strand damage

When only one strand of a double helix is damaged, the other one can be used as a template to correct the damaged stand. There are several excision repair mechanisms that do so.

Base excision repair (BER) repairs lesions that are mostly caused by spontaneous hydrolytic deaminations of bases, reactive oxygen or methylating agents. First, damaged bases are removed from the DNA by lesion-specific glycosylases (enzymes) that hydrolyze the base sugar bond, resulting in an AP site (a gap in the DNA that has neither purine nor a pyrimidine base). Second, the AP site is processed by the enzyme endonuclease, which cuts the sugar-phosphate backbone, creating a single-stranded break. Finally, polymerase removes the damaged region, correctly synthesizing the new strand from the template (another strand). This is called "short-patch" BER, and also a "long-patch" BER exists which replaces 6–13 nucleotides. It is worth noting that single-stranded breaks in DNA caused by damage, such as those caused by ionizing radiation, are following the same processing, so they end up being repaired by the BER pathway.

Nucleotide excision repair (NER) is a versatile repair pathway that can eliminate a broad variety of structurally unrelated DNA lesions. However, it is not the actual lesion that is recognized by the NER-system, but rather the damage-induced change in DNA — bulky, helix-distorting damage, such as pyrimidine dimerization caused by UV light. The basic mechanism of NER consists of several successive steps: the recognition of damage, the local opening of the double helix around the injury (both upstream and downstream), and the incision of the damage-containing DNA strand (usually a 12–24 nucleotide long strand). Afterward, enzymes can fill the gap by synthesizing new strands. In humans (and eukaryotes in general), this is a very complex process involving many different proteins.



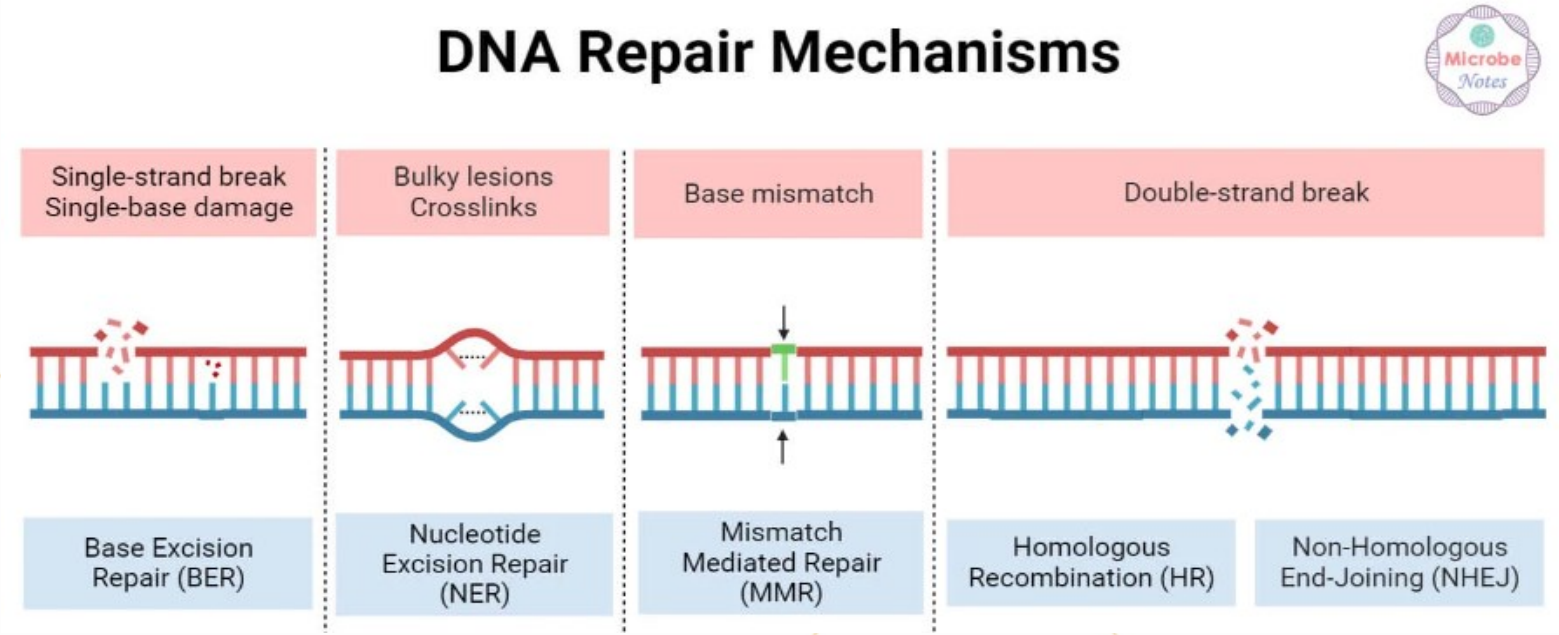
https://www.rdm.ox.ac.uk/news/study-reveals-stop-eating-response-to-dna-damage/responsive_image?ratio=r16x9&scale=w760
https://medium.com/@marko.ljubenovic.etf/dna-repair-mechanism-ce5db57c0f06

DNA repair mechanisms. Double-strand damage

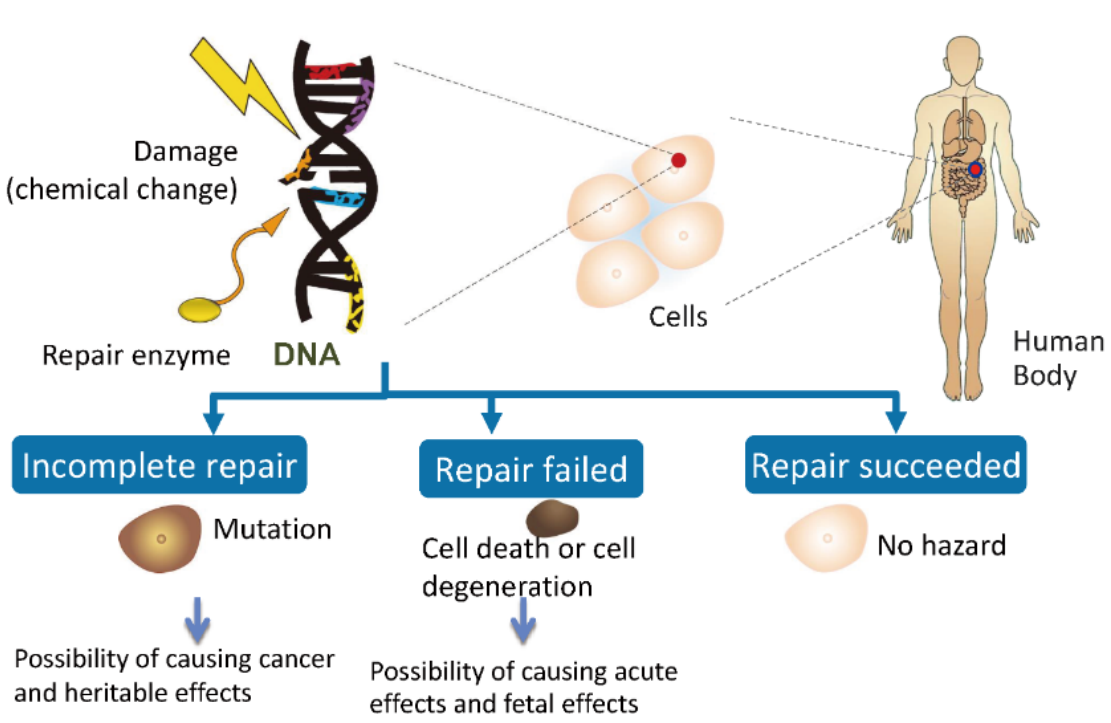
Double-strand breaks (DSB) are frequently formed by factors such as radiation, oxidation, mechanical stress, cellular metabolism and through DNA replication. Efficient repair of DSBs is necessary since replication and transcription are blocked at the site of a double-strand break (DSB), and the exposed ends are susceptible to degradation, which may result in loss of genetic information and/or genome rearrangement..

Homologous recombination (HR) is a process in which genetic information from a highly homologous DNA molecule is used as a template for repair. The broken strands are kept together while single-stranded regions are created with overhanding ends coated in recombinase that can invade a homologous DNA molecule. The enzymes responsible for HR repair are nearly identical to those for chromosomal crossover.

Non-homologous end joining (NHEJ) is a process in which DNA Ligase IV, a specialized form of DNA ligase enzyme, directly joins the two ends. For accurate repair, NHEJ relies on short homologous sequences called microhomologies, which are present on the tails of the DNA ends. If these are compatible, the repair is usually accurate, but this process frequently leads to loss of generic information and can also introduce mutations during repair.



https://medium.com/@marko.ljubenovic.etf/dna-repair-mechanism-ce5db57c0f06



Looking closely into the irradiated portion, radiation may directly or indirectly damage the DNA sequences of a gene. These damaged DNA sequences are repaired by a pre-existing system in the body. Minor damage is successfully repaired and restored. However, when many parts are damaged, they cannot be fully repaired and the cells themselves die. Even when some cells die, if other cells can replace them, dysfunction does not occur in organs and tissues. However, when a large number of cells die or degenerate, there is the possibility that deterministic effects (tissue reactions) will appear, such as hair loss, cataracts, skin injury, or other acute disorders, as well as fetal disorders.

When a cell, in which DNA was not completely repaired, survives, the cell gene may mutate and cause a stochastic effect such as cancer or heritable effect.

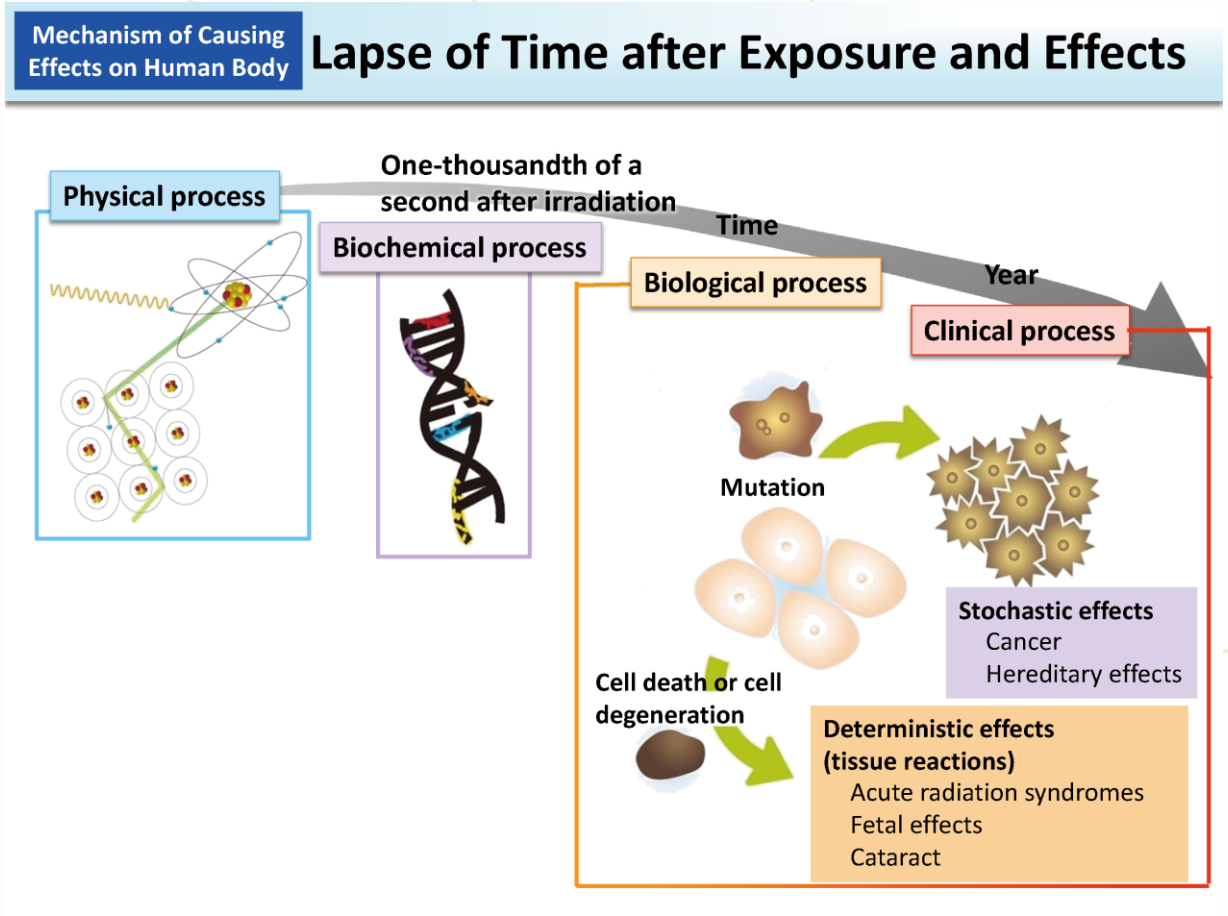
DNA is damaged not only by radiation but also by carcinogens in foods, tobacco, chemical substances in the environment, reactive oxygen, etc.

It is said that DNA is damaged at 10,000 to 1,000,000 locations per cell every day.

Damage due to low-dose exposures is significantly rare compared with metabolic DNA damage. However, radiation provides energy locally and causes complicated damage affecting multiple parts of DNA strands.

Approx. 85% of radiation effects are caused by reactive oxygen, etc. created by radiation, and approx. 15% is direct damage by radiation.

https://www.env.go.jp/en/chemi/rhm/basic-info/1st/03-02-03.html



In as short a time as one-thousandth of a second after irradiation, DNA breaks and base damage occur.

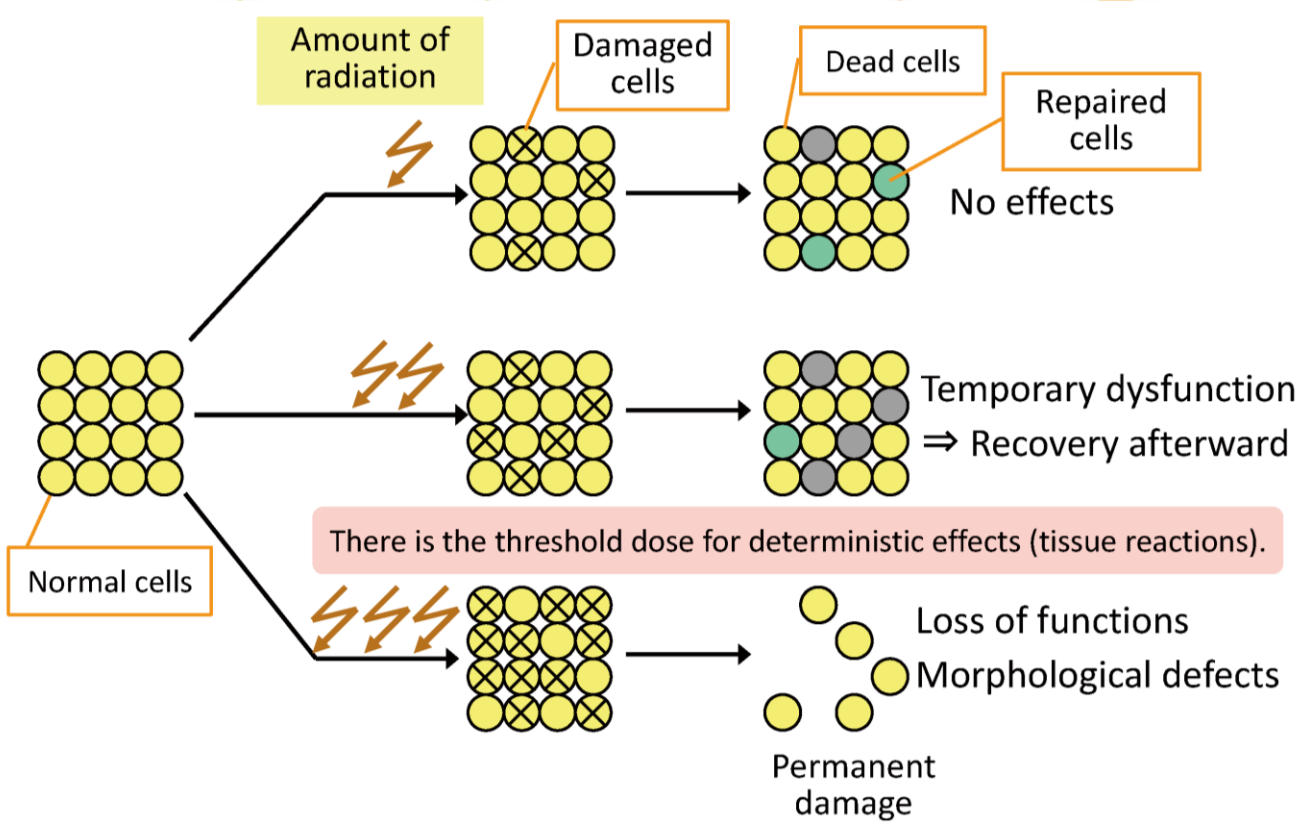
In a second after irradiation, DNA repair starts, and if repair fails, cell deaths and mutation occur within an hour to one day. It takes some time until such a reaction at the cell level develops into clinical symptoms at an individual level.

This period is called the incubation period.

Effects due to which symptoms appear within several weeks are called **acute (early) effects**, while effects that develop symptoms after a relatively long period are called **late effects**.

In particular, it takes several years to decades until a person develops cancer.

https://www.env.go.jp/en/chemi/rhm/basic-info/1st/03-02-04.html



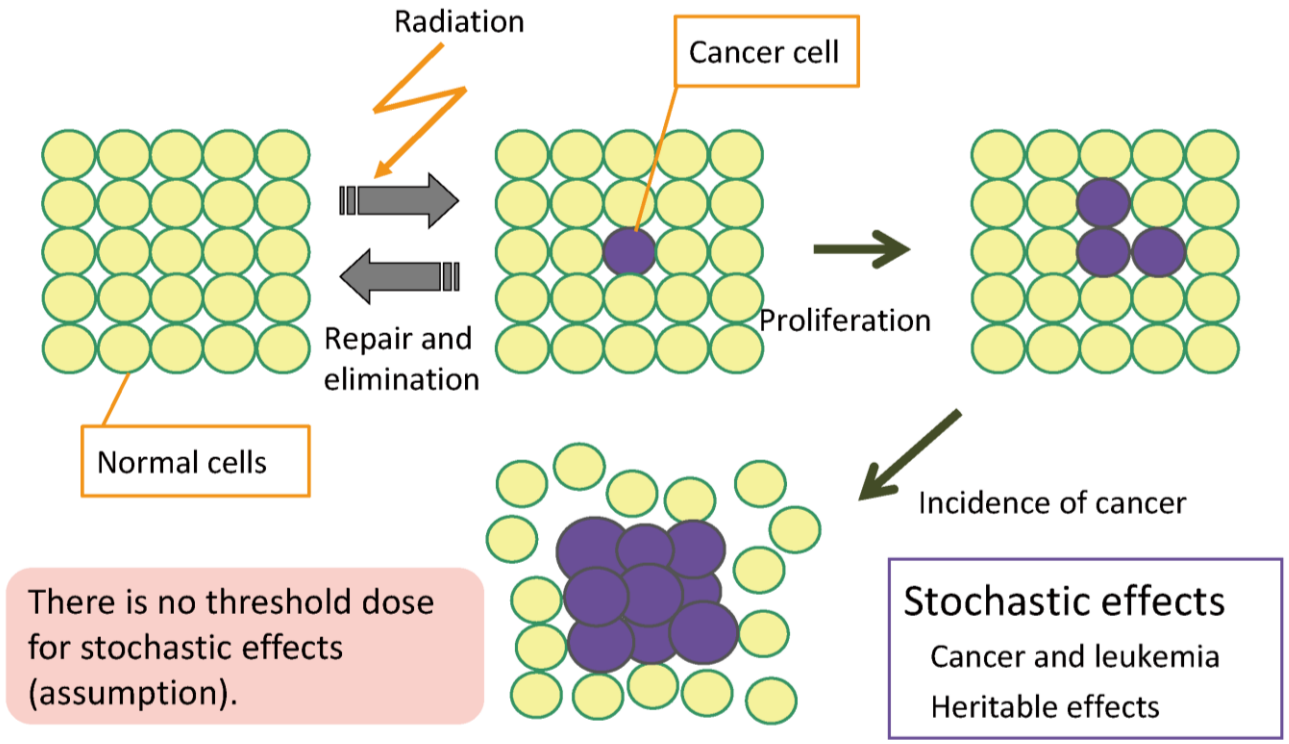
Even if some cells die due to exposure to a small amount of radiation, if tissues and organs can fully function with the remaining cells, clinical symptoms do not appear.

When the amount of radiation increases and a larger number of cells die, relevant tissues and organs suffer temporary dysfunction, and some clinical symptoms may appear. However, such symptoms improve when normal cells proliferate and increase in number.

When cells in tissues or organs are damaged severely due to a large amount of radiation, this may lead to permanent cell damage or morphological defects.

In this manner, for deterministic effects (tissue reactions) due to cell deaths, there is a certain exposure dose above which symptoms appear and under which no symptoms appear. Such a dose is called the **threshold dose**.

https://www.env.go.jp/en/chemi/rhm/basic-info/1st/03-02-05.html



Risks of the effects of cellular mutation are considered to increase even if a mutation occurs in a single cell.

Mutated cells are mostly repaired or eliminated but some survive and if their descendant cells are additionally mutated or the level of gene expression changes, the possibility of developing cancer cells increases.

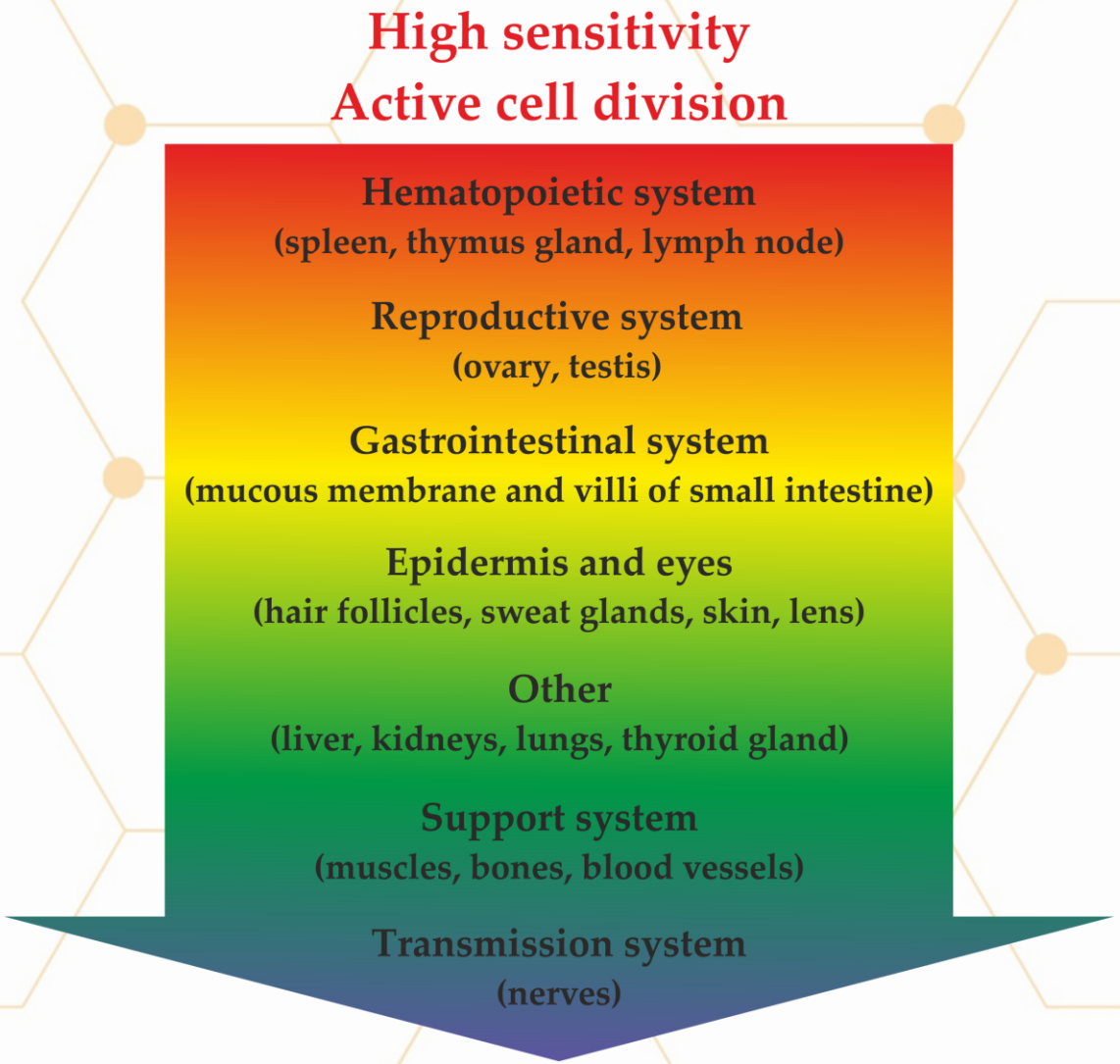
The proliferation of cancer cells leads to clinically diagnosed cancer (diagnosed by a doctor based on physical symptoms). Cells become cancerous as multiple mutated genes have accumulated without being repaired. Therefore, when assessing cancer-promoting effects, all doses that a person has received so far need to be taken into account.

https://www.env.go.jp/en/chemi/rhm/basic-info/1st/03-02-07.html

Actively dividing less differentiated cells tend to show higher **radiosensitivity**. For example, hematopoietic stem cells in bone marrow are differentiated into various blood cells, while dividing actively. Immature (undifferentiated) hematopoietic cells that have divided (proliferated) from stem cells are highly sensitive to radiation and die due to a small amount of radiation more easily than differentiated cells.

As a result, the supply of blood cells is suspended and the number of various types of cells in blood decreases. In addition, the epithelium of the digestive tract is constantly metabolized and is also highly sensitive to radiation.

On the other hand, nerve tissues and muscle tissues, which no longer undergo cell division at the adult stage, are known to be resistant to radiation.



Prodromal phase and exposure dose

Symptom	Mild (1-2 Gy)	Moderate (2-4 Gy)	Severe (4-6 Gy)	Very severe (6-8 Gy)	Lethal (> 8 Gy)
Vomiting	2 hours or later after exposure (Rate of incidence) Up to 50%	1 to 2 hours 70 to 90%	Within 1 hour 100%	Within 30 minutes 100%	Within 10 minutes 100%
Diarrhea	None	None	Moderate	Severe	Severe
Headache	Very mild	Mild	Moderate	Severe	Severe
Consciousness	Unaffected	Unaffected	Unaffected	Affected	Loss of consciousness
Body temperature	Normal	Slight fever	Fever	High fever	High fever

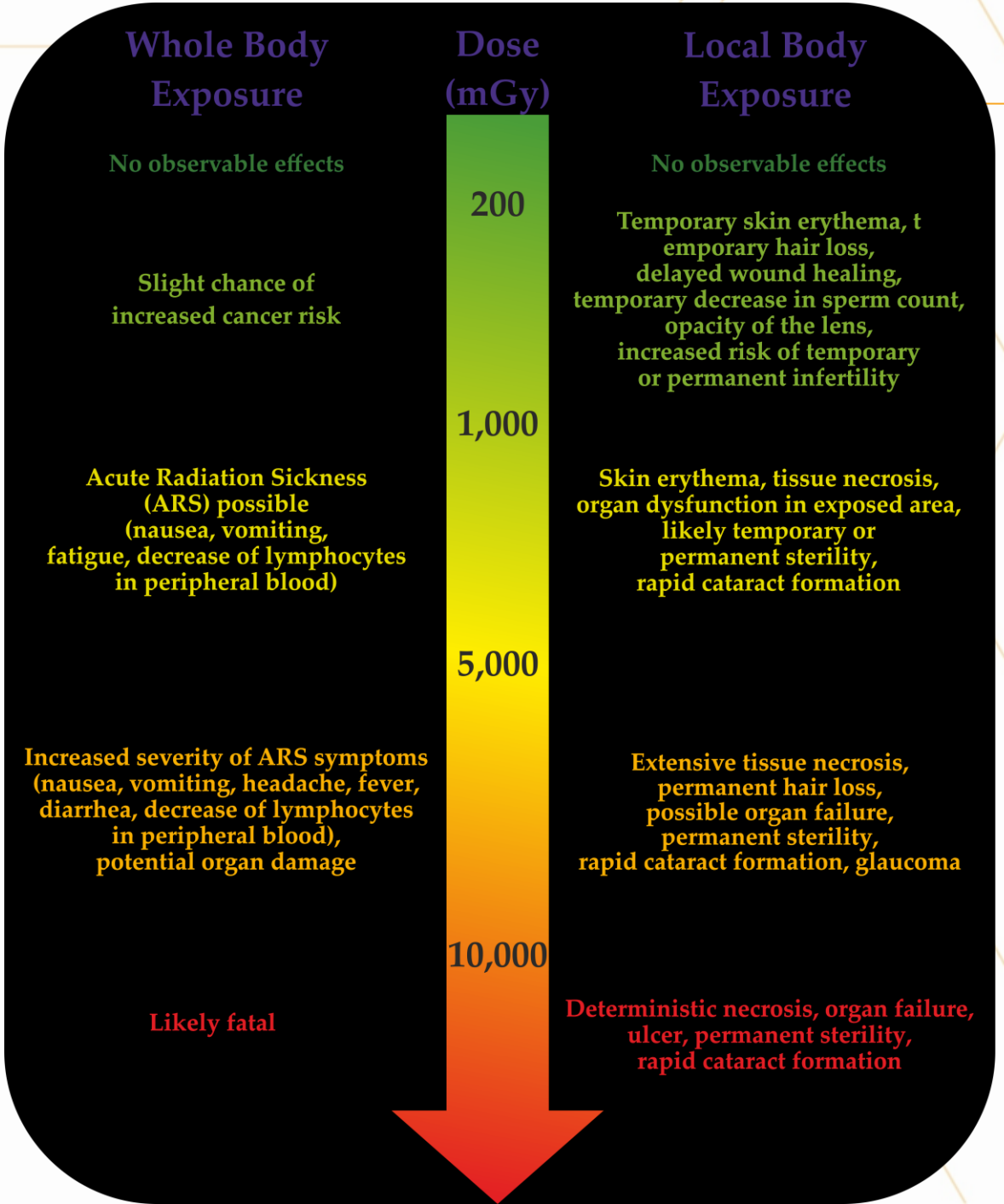
Gy: Grays

Source: Prepared based on IAEA Safety Reports Series No.2 "Diagnosis and Treatment of Radiation Injuries" (1998)

From prodromal symptoms that appear within 48 hours after the exposure, exposure doses can roughly be estimated in the case of acute exposure. Exposure to radiation of 1 to 2 Gy may cause loss of appetite, nausea, and vomiting. In addition, a very mild headache appears.

Exposure to radiation of 2 to 4 Gy may cause vomiting, mild headache, or slight fever (1 to 3 hours, 10 to 80% incidence). Exposure of 4 to 6 Gy causes a 100% incidence of vomiting within one hour after exposure and also causes moderate diarrhea and headache as well as an 80 to 100% incidence of fever.

Exposure of 6 to 8 Gy causes a 100% incidence of vomiting within 30 minutes and also causes severe diarrhea/headache as well as a 100% incidence of high fever. Furthermore, a disturbance of consciousness may appear. Exposure to radiation exceeding 8 Gy causes a 100% incidence of vomiting within 10 minutes and causes symptoms such as severe diarrhea/headache, high fever, and loss of consciousness.



Whole body exposure and local exposure

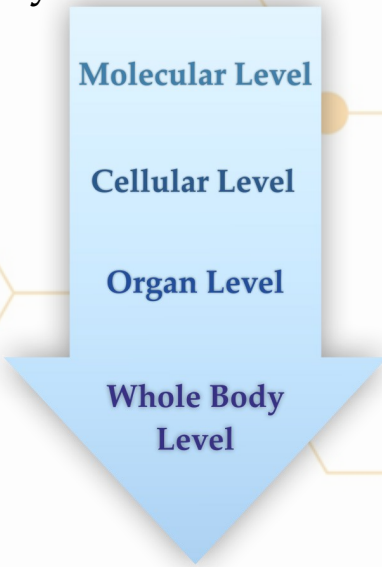
Radiation exposure at levels exceeding **100 mGy** at one time may cause effects on the human body due to cell deaths.

Organs highly sensitive to radiation are more likely to be affected by a small amount of radiation.

As the testes, in which cells are dividing actively, are highly sensitive to radiation, even low doses of radiation at the levels of **100 to 150 mGy** temporarily decrease the number of sperm and cause transient sterility.

Bone marrow is also highly sensitive to radiation and lymphocytes in blood may decrease due to exposure to radiation even less than **1,000 mGy** (1 Gy). However, these effects are naturally subdued.

On the other hand, clinical symptoms may appear that require clinical care after exposure to radiation of more than **2,000 mGy** (2 Gy) at one time.



Acute Responding Tissues
(responses seen during standard therapy)

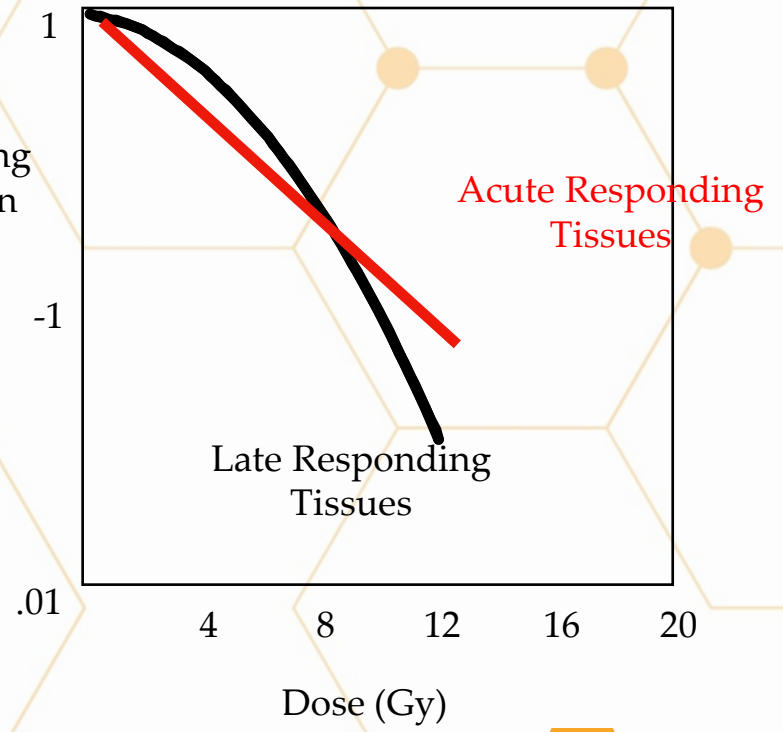
- Gut
- Skin
- Bone Marrow
- Mucosa

Late Responding Tissues
(responses seen after end of therapy)

- Brain
- Spinal Cord
- Kidneys
- Lungs
- Bladder

The biological effect depends on

- Dose size (D) - (alpha and beta)
- Dose rate per fraction (d) - (alpha and beta)
- Time during which irradiation is performed (T) - (alpha and beta)
- Time between fractions (t)
- Radiation volume (V)
- Radiation quality (Q) – RBE
- Presence/absence of oxygen – OER
- Efficiency and completeness of DNA repair
- Cell cycle phase and level of gene activation
- Type of tissue



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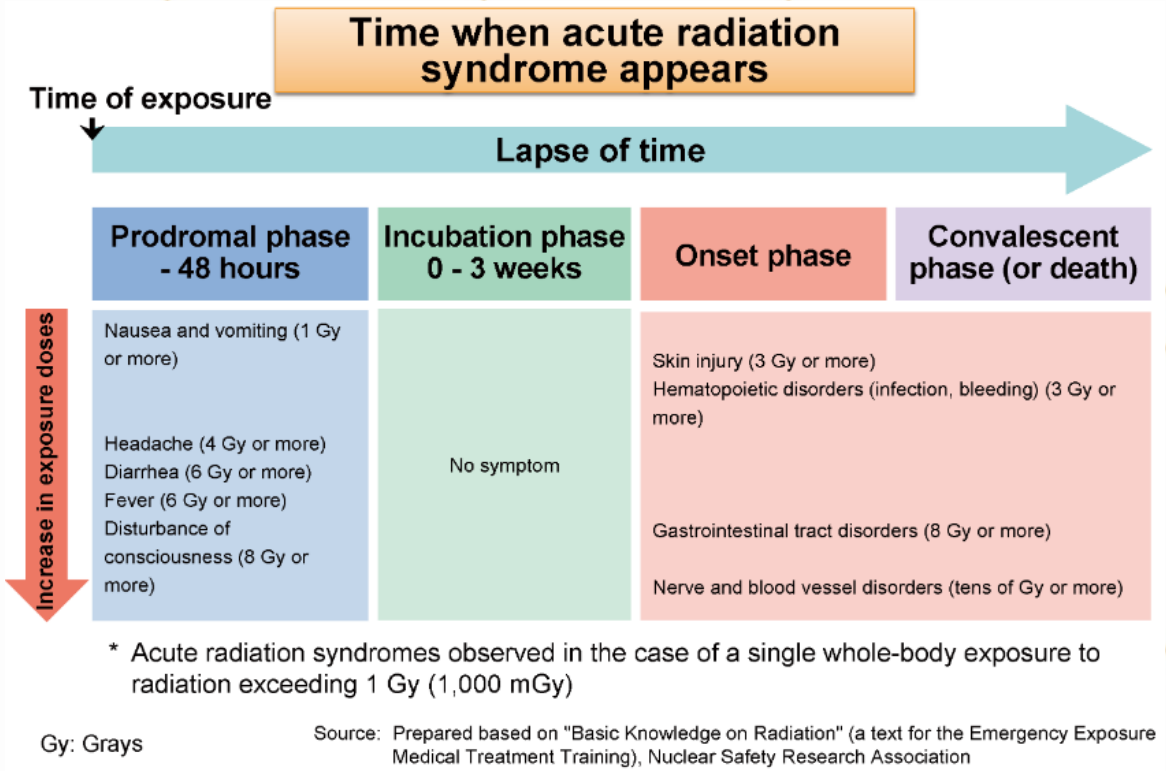


A single whole-body exposure to radiation exceeding 1 Gy (1,000 mGy) causes disorders in various organs and tissues, leading to complicated clinical developments. This series of disorders in organs is called **acute radiation syndrome,** which typically follows a course from the prodromal phase to the incubation phase, the onset phase, and finally to the convalescent phase or to death in the worst case.

From prodromal symptoms that appear within 48 hours after the exposure, exposure doses can roughly be estimated.

In the onset phase after the incubation phase, disorders appear in the order of hematopoietic organ, gastrointestinal tract, skin, and nerves and blood vessels, as doses increase. Disorders mainly appear in organs and tissues highly sensitive to radiation. In general, the larger the exposure dose, the shorter the incubation phase.

Skin covers a large area of 1.3 to 1.8 m^2 of the whole body of adults. Epidermis, which is the result of gradual differentiation of basal cells that are created at the basal stratum, finally becomes a stratum corneum and is separated from the body surface as scurf. It is said to take approx. 20 to 40 days until basal cells move from the basal stratum to the skin surface, which means that two to more than four weeks is required for exposed subcutaneous cells existing in the stratum corneum to the basal stratum to come up to the skin surface. Therefore, skin erythema may appear immediately after exposure depending on radiation intensity, but skin injury generally appears after the lapse of a few weeks or more

p.96 of Vol. 1, "Prodromal Phase of Acute Radiation Syndrome and Exposure Doses"
https://www.env.go.jp/en/chemi/rhm/basic-info/1st/03-03-02.html

Three classic ARS Syndromes are:

Bone marrow syndrome (sometimes referred to as hematopoietic syndrome) the full syndrome will usually occur with a dose between 0.7 and 10 Gy (70 – 1000 rads) though mild symptoms may occur as low as 0.3 Gy or 30 rads.

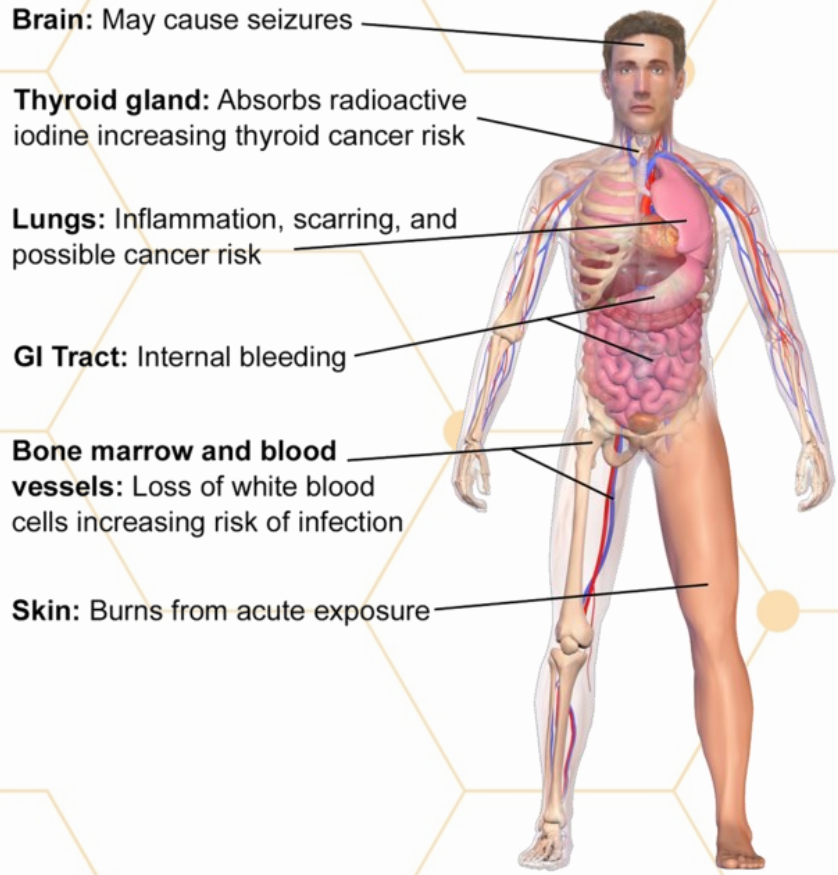
- The survival rate of patients with this syndrome decreases with increasing dose. The primary cause of death is the destruction of the bone marrow, resulting in infection and hemorrhage.

Gastrointestinal (GI) syndrome: the full syndrome will usually occur with a dose greater than approximately 10 Gy (1000 rads) although some symptoms may occur as low as 6 Gy or 600 rads.

- Survival is extremely unlikely with this syndrome. Destructive and irreparable changes in the GI tract and bone marrow usually cause infection, dehydration, and electrolyte imbalance. Death usually occurs within 2 weeks.

Cardiovascular (CV) / Central Nervous System (CNS) syndrome: the full syndrome will usually occur with a dose greater than approximately 50 Gy (5000 rads) although some symptoms may occur as low as 20 Gy or 2000 rads.

- Death occurs within 3 days. Death likely is due to collapse of the circulatory system as well as increased pressure in the confining cranial vault as the result of increased fluid content caused by edema, vasculitis, and meningitis.



Selected Risks from Radiation Sickness

Although the dose ranges provided apply to most healthy adult members of the public, a great deal of variability of radiosensitivity among individuals exists, depending upon the age and condition of health of the individual at the time of exposure. Children and infants are especially sensitive.

https://www.cdc.gov/nceh/radiation/emergencies/arsphysicianfactsheet.htm
https://www.wikiwand.com/en/Acute_radiation_syndrome

Four stages of ARS are:

Prodromal stage (N-V-D stage): The classic symptoms for this stage are nausea, vomiting, as well as anorexia and possibly diarrhea (depending on dose), which occur from minutes to days following exposure. The symptoms may last (episodically) for minutes up to several days.

Latent stage: In this stage, the patient looks and feels generally healthy for a few hours or even up to a few weeks.

Manifest illness stage: In this stage the symptoms depend on the specific syndrome and last from hours up to several months.

Recovery or death: Most patients who do not recover will die within several months of exposure. The recovery process lasts from several weeks up to two years.

These stages are described in more detail in the table on the following slides

https://www.cdc.gov/nceh/radiation/emergencies/arsphysicianfactsheet.htm

Syndrome	Dose	Prodromal Stage	Latent Stage	Manifest Illness Stage	Recovery
Hematopoietic (Bone Marrow)	> 0.7 Gy (> 70 rads) (mild symptoms may occur as low as 0.3 Gy or 30 rads)	Symptoms are anorexia, nausea and vomiting. Onset occurs 1 hour to 2 days after exposure. Stage lasts for minutes to days.	Stem cells in bone marrow are dying, although patient may appear and feel well. Stage lasts 1 to 6 weeks.	Symptoms are anorexia, fever, and malaise. Drop in all blood cell counts occurs for several weeks. Primary cause of death is infection and hemorrhage. Survival decreases with increasing dose. Most deaths occur within a few months after exposure.	In most cases, bone marrow cells will begin to repopulate the marrow. There should be full recovery for a large percentage of individuals from a few weeks up to two years after exposure. Death may occur in some individuals at 1.2 Gy (120 rads). The $LD_{50/60}$ is about 2.5 to 5 Gy (250 to 500 rads)

The absorbed doses quoted here are "gamma equivalent" values. Neutrons or protons generally produce the same effects as gamma, beta, or X-rays but at lower doses. If the patient has been exposed to neutrons or protons, consult radiation experts on how to interpret the dose.

The $LD_{50/60}$ is the dose necessary to kill 50% of the exposed population in 60 days.

https://www.cdc.gov/nceh/radiation/emergencies/arsphysicianfactsheet.htm

Syndrome	Dose	Prodromal Stage	Latent Stage	Manifest Illness Stage	Recovery
Gastrointestinal (GI)	> 10 Gy (> 1000 rads) (some symptoms may occur as low as 6 Gy or 600 rads)	Symptoms are anorexia, severe nausea, vomiting, cramps, and diarrhea. Onset occurs within a few hours after exposure. Stage lasts about 2 days.	Stem cells in bone marrow and cells lining GI tract are dying, although patient may appear and feel well. Stage lasts less than 1 week.	Symptoms are malaise, anorexia, severe diarrhea, fever, dehydration, and electrolyte imbalance. Death is due to infection, dehydration, and electrolyte imbalance. Death occurs within 2 weeks of exposure.	The LD^{100} is about 10 Gy (1000 rads)

The absorbed doses quoted here are "gamma equivalent" values. Neutrons or protons generally produce the same effects as gamma, beta, or X-rays but at lower doses. If the patient has been exposed to neutrons or protons, consult radiation experts on how to interpret the dose.

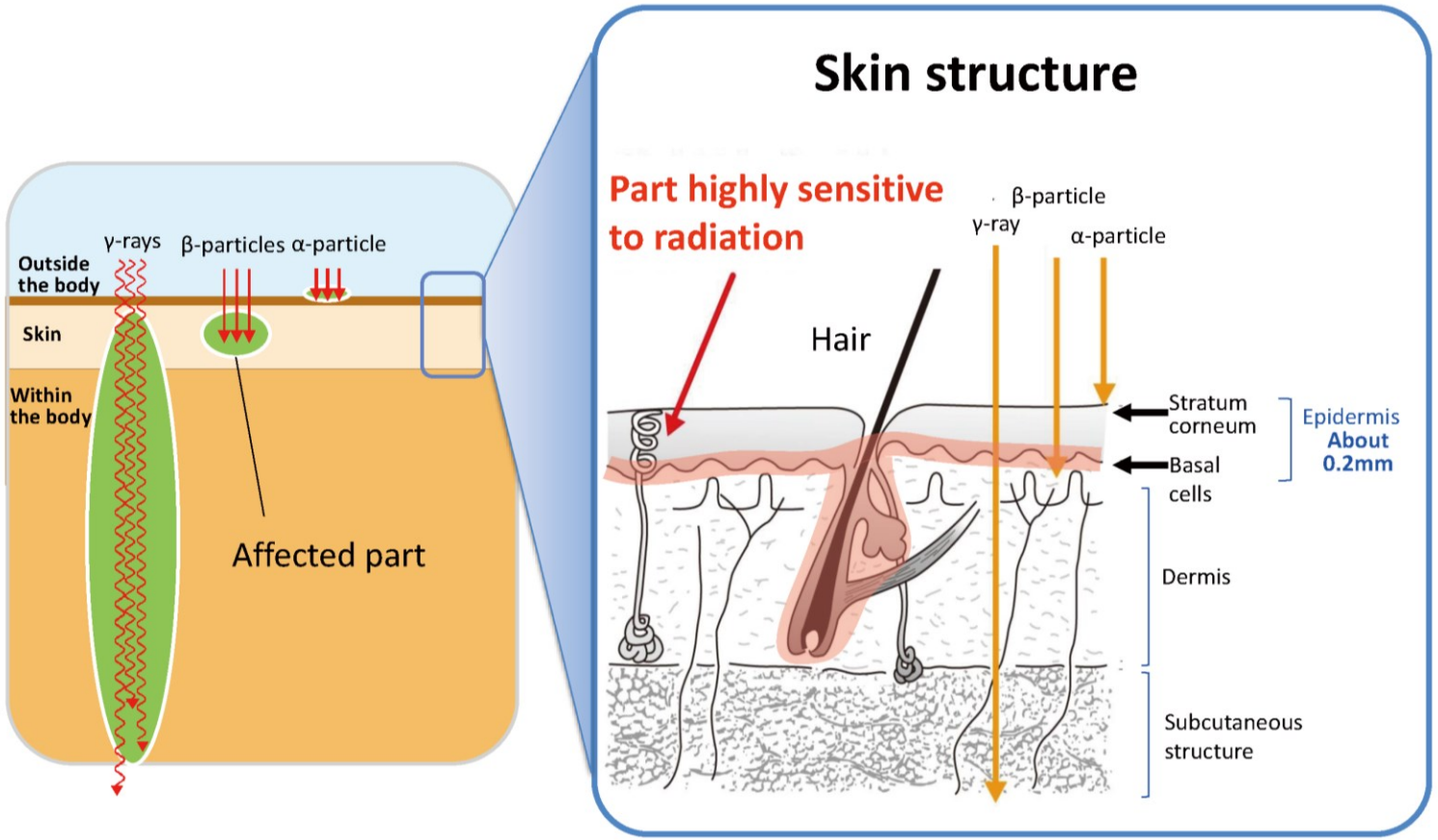
The LD_{100} is the dose necessary to kill 100% of the exposed population

https://www.cdc.gov/nceh/radiation/emergencies/arsphysicianfactsheet.htm

Syndrome	Dose	Prodromal Stage	Latent Stage	Manifest Illness Stage	Recovery
Cardiovascular (CV) / Central Nervous System (CNS)	> 50 Gy (5000 rads) (some symptoms may occur as low as 20 Gy or 2000 rads)	Symptoms are extreme nervousness and confusion; severe nausea, vomiting, and watery diarrhea; loss of consciousness; and burning sensations of the skin. Onset occurs within minutes of exposure. Stage lasts for minutes to hours.	Patient may return to partial functionality. Stage may last for hours but often is less.	Symptoms are return of watery diarrhea, convulsions, and coma. Onset occurs 5 to 6 hours after exposure. Death occurs within 3 days of exposure.	No recovery is expected.

The absorbed doses quoted here are “gamma equivalent” values. Neutrons or protons generally produce the same effects as gamma, beta, or X-rays but at lower doses. If the patient has been exposed to neutrons or protons, consult radiation experts on how to interpret the dose.

https://www.cdc.gov/nceh/radiation/emergencies/arsphysicianfactsheet.htm

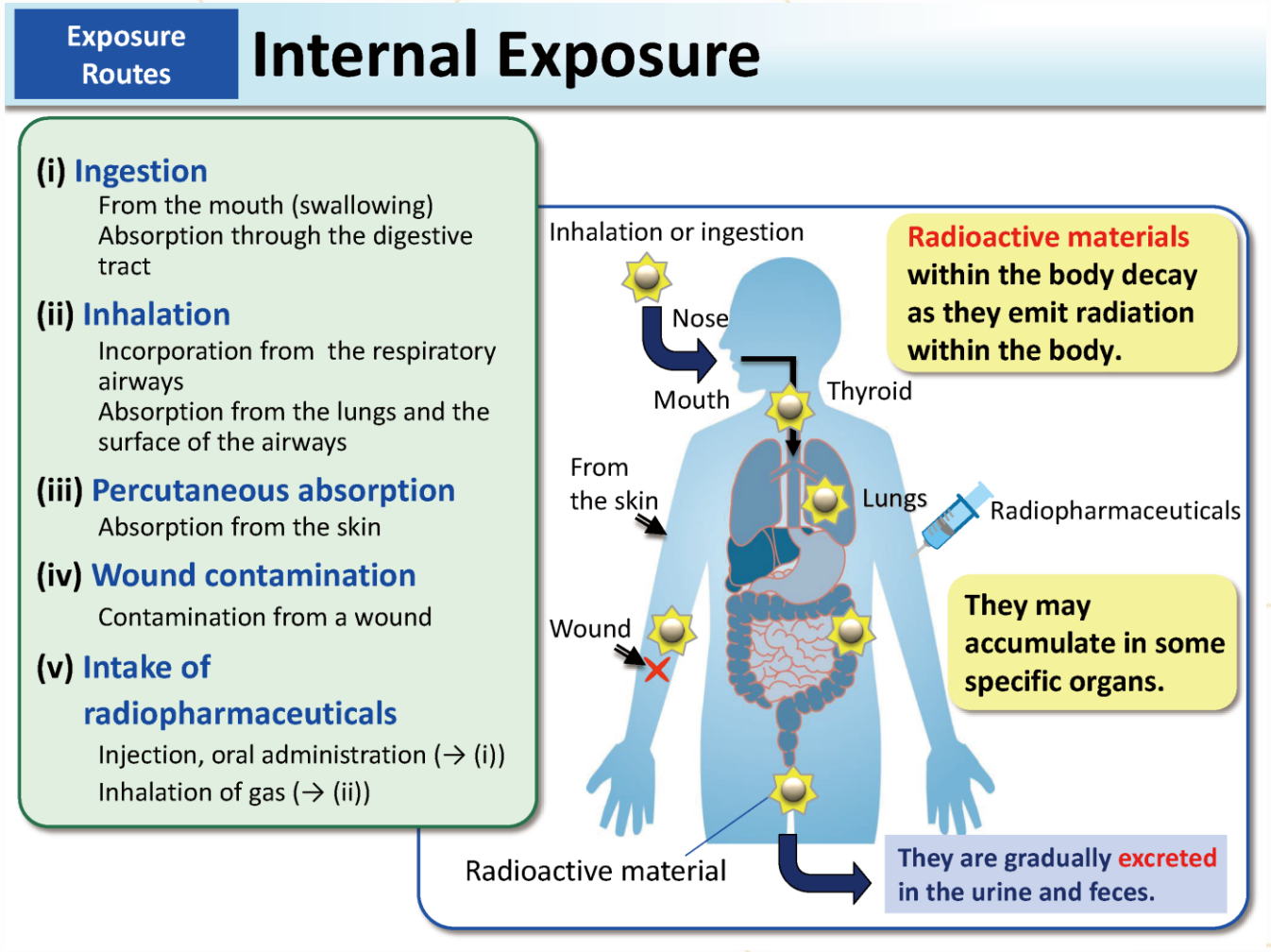


In external exposure, α-particles having weak penetrating power stop at the epidermis and therefore do not produce any effects.

But if a large amount of radioactive material that emit β-particles adheres to the surface of the body for an extended period of time, they will affect the skin's basal cells and hair-root cells that have high sensitivity to radiation, possibly causing skin erythema that is characterized by reddening of the skin, hair loss, etc.

However, such exposure is extremely rare, and the major problems with external exposure are associated with radioactive materials emitting γ-rays that affect the inside of the body.

https://www.env.go.jp/en/chemi/rhm/basic-info/1st/02-01-03.html



https://www.env.go.jp/en/chemi/rhm/basic-info/1st/02-01-04.html

Internal exposure occurs due to radioactive materials being taken in the following routes: ingestion together with food (ingestion); incorporation while breathing (inhalation); absorption from the skin (percutaneous absorption); penetration from a wound (wound contamination), and administration of radiopharmaceuticals through injection, etc.

Radioactive materials incorporated into the body emit radiation within the body. Accumulation in some specific organs may occur depending on the types of radioactive materials.

This is largely due to the physicochemical properties of radioactive materials. For example, strontium, having similar properties to calcium, tends to accumulate in calcium-rich parts, such as bones, once it enters the body; cesium, because of its properties similar to potassium, tends to distribute throughout the body once it enters the body.

Iodine, being a constituent element of thyroid hormones, tends to accumulate in the thyroid, whether it is radioactive iodine or stable iodine

Exposure Routes

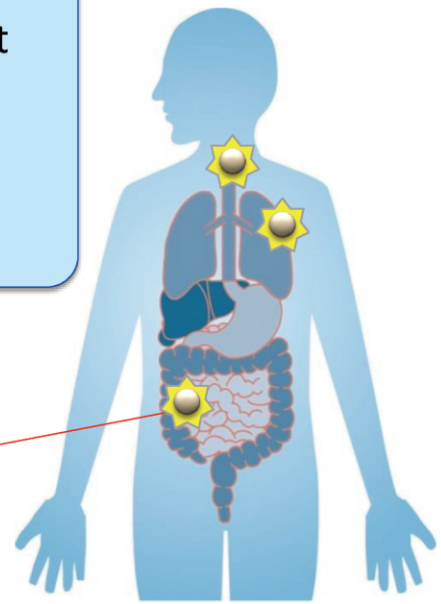
Internal Exposure and Radioactive Materials

The characteristics of radioactive materials that especially cause problems in internal exposure

(i) α-emitters > β-emitters or γ-emitters

(ii) Materials that enter easily but are difficult to excrete

(iii) Materials that are likely to accumulate in specific organs



Radioactive materials within the body disintegrate into other elements and are gradually excreted in the urine and feces through metabolism.

The time required for radioactive materials to reduce to half by disintegration is called *physical half-life* (T_p), and the time required for radioactive materials within the body to reduce to half through metabolism is called *biological half-life* (T_b).

Radioactive materials that enter the body decrease both through their physical half-life and biological half-life.

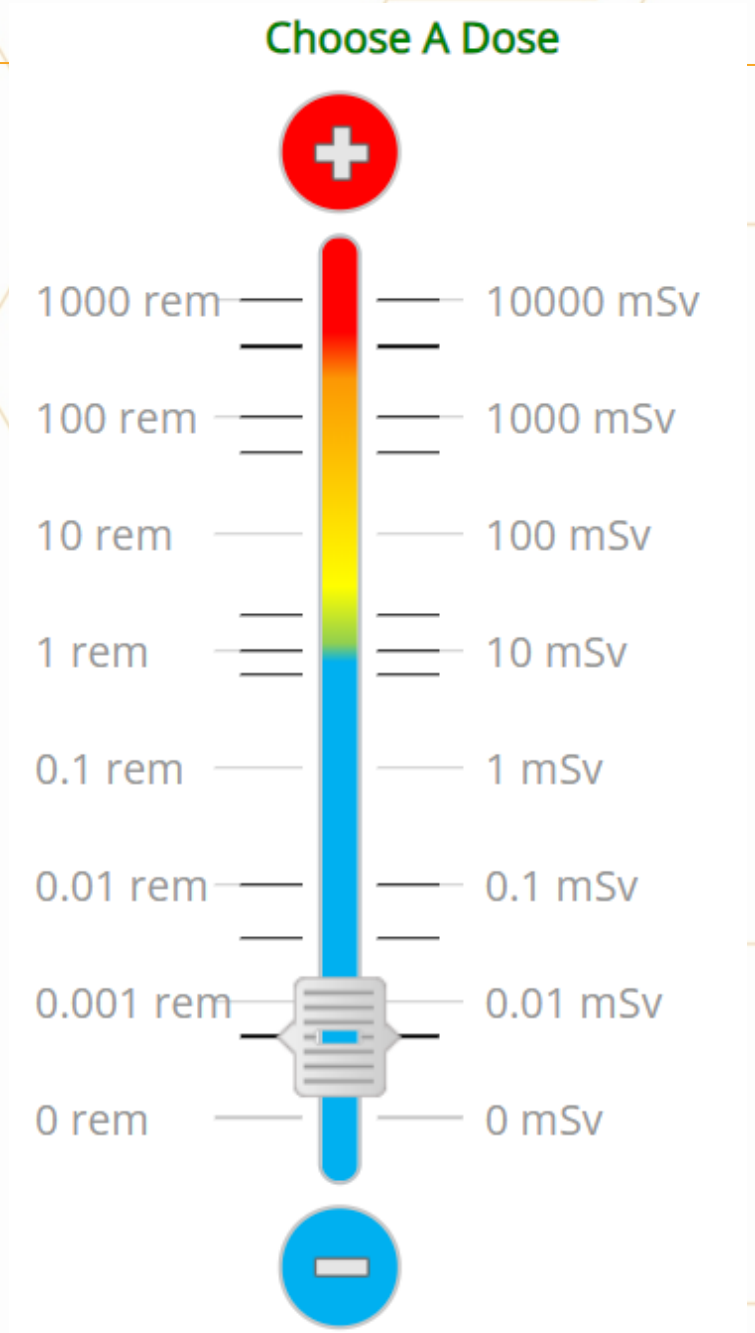
The time required for such radioactive materials to reduce to half is called *effective half-life* (T_e), and the following relationship is found between T_p and T_b:

$$1/T_e = 1/T_p + 1/T_b$$

A major problem with internal exposure is caused by radioactive materials that have a long half-life and emit *α*-particles.

Radioactive materials that are easily incorporated into the body but are difficult to be excreted, and also those that tend to be accumulated in particular organs/tissues cause problems as they result in increasing internal exposure doses.

https://www.env.go.jp/en/chemi/rhm/basic-info/1st/02-01-05.html

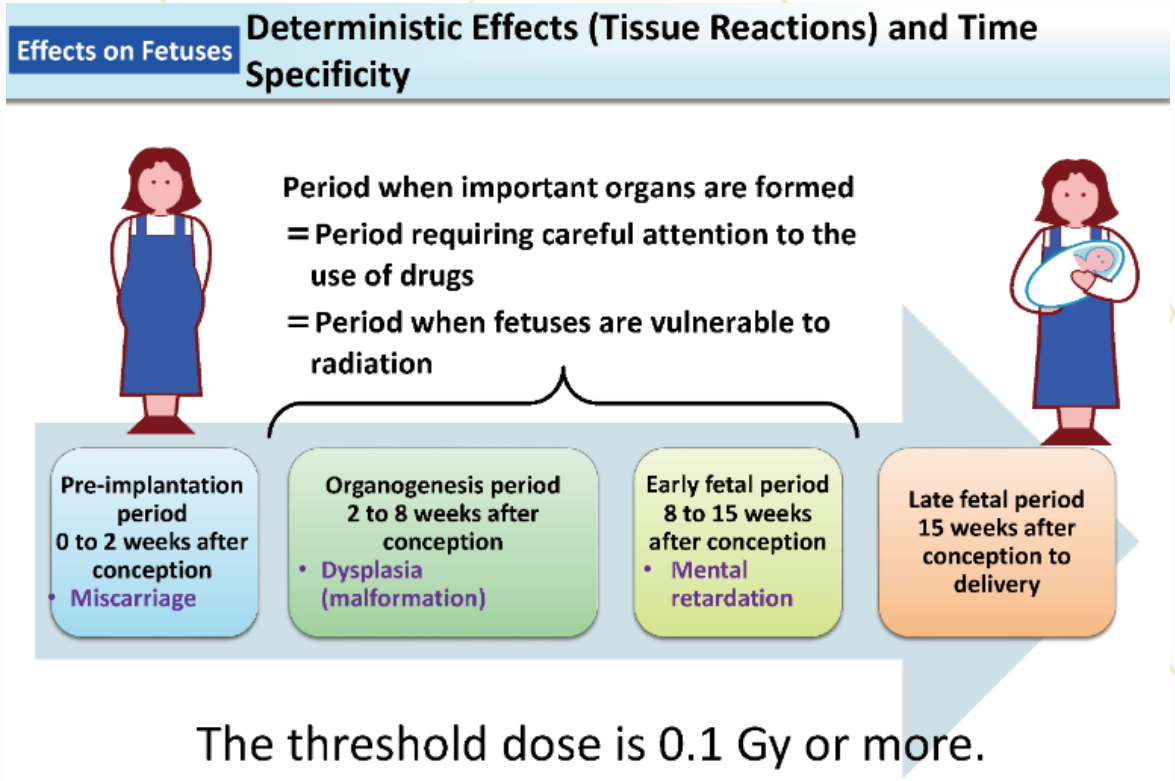


An interactive version of the thermometer tool:

https://www.cdc.gov/nceh/radiation/emergencies/radiationthermometer.htm

Rem (rem)	Millisievert (mSv)	Overview
1000	10,000	Dose that results in death for 100% of those who receive it. People who are close to the site of a radiation emergency may be at risk for this dose.
400	4,000	Dose that results in death for 50% of those who receive it. People who are close to the site of a radiation emergency may be at risk for this dose.
100	1,000	Lowest dose that could cause acute radiation syndrome. Dose for which risk of getting a fatal cancer increases from about 22% to about 27%.
50	500	Dose that causes damage to blood cells.
2	20	Recommended threshold for relocating people (if projected dose from radioactive contamination is greater for the coming year, relocate).
1	10	Dose received during a typical Computerized Tomography scan.
0.62	6.2	Average dose per year for people in the U.S. from: • naturally occurring background radiation – 310 mrem • medical exposures – 300 mrem • consumer products – 10 mrem
0.01	0.1	Typical dose from a chest x-ray.
0.0035	0.035	Dose from high altitude solar and cosmic radiation during a flight from New York City to Los Angeles.
0.0005	0.005	Typical dose from a dental X-ray (bitewing and full mouth survey)

https://www.cdc.gov/nceh/radiation/emergencies/radiationthermometer.htm



Therefore, the International Commission on Radiological Protection (ICRP) states in its 2007 Recommendations that a fetal absorbed dose less than 0.1 Gy should not be considered as a ground for abortion. Exposure to 0.1 Gy of radiation is equivalent to exposure to 100 mSv of γ-rays or X-rays at one time.

Deterministic effects (tissue reactions) include fetal effects for which the threshold dose is especially low. When a pregnant woman is exposed to radiation and radiation passes through her womb or radioactive materials migrate into her womb, her unborn baby may also be exposed to radiation.

It is known that fetuses are highly sensitive to radiation and incidence of effects has time specificity. Radiation exposure exceeding 0.1 Gy at an early stage of pregnancy (preimplantation period) may lead to miscarriage.

After this period, the possibility of miscarriage decreases, but radiation exposure exceeding 0.1 Gy during the period, when important organs are formed (organogenesis period), may cause dysplasia (malformation). Radiation exposure exceeding 0.3 Gy during the period, when the cerebrum is actively growing (early fetal period), poses risks of mental retardation.

The period when fetuses are highly sensitive to radiation coincides with the period during which pregnant women are advised not to take drugs carelessly. During this period before the stable period, fetuses are vulnerable to both drugs and radiation. Fetal effects are caused by radiation exposure exceeding 0.1 Gy.

Incidentally, fetuses' exposure doses are not always the same as their mothers' exposure doses. Risks of stochastic effects such as cancer or heritable effects also increase depending on exposure dose levels.

https://www.env.go.jp/en/chemi/rhm/basic-info/1st/03-05-01.html

Survey on children born from mothers who were pregnant at the time of the Chernobyl NPS Accident

Survey targets

(i) 138 children who were exposed to radiation in the womb and their parents(a group of children exposed to radiation in the womb: exposed group)

(ii) 122 children in non-contaminated regions in Belarus and their parents(control group: non-exposed group)

Children's mental development	When aged 6 to 7		When aged 10 to 11	
	(i) Exposed group	(ii) Control group	(i) Exposed group	(ii) Control group
Difficulty in speech	18.1%	8.2%	10.1%	3.3%
Disorder of emotion	20.3%	7.4%	18.1%	7.4%
IQ=70～79	15.9%	5.7%	10.1%	3.3%

○ A significant difference in mental development was observed between the exposed group and the control group, but there was no correlation between exposed doses and intelligence quotients. Therefore, the difference was considered to be attributable to social factors associated with forced evacuation.

○ There was correlation between parents' extreme anxiety and their children's emotional disorders.

It is considered that radiation exposure during pregnancy does not directly affect intelligence quotients of fetuses and children after growth.

Source: Prepared based on Kolominsky Y et al., J Child Psychol Psychiatry, 40 (2): 299-305, 1999

Effects on children - Chornobyl NPS Accident

Researchers conducted surveys targeting 138 children born from mothers who were pregnant and were residing near the nuclear power plant at the time of the Chornobyl NPS Accident and 122 children born from mothers who were pregnant at the time of the accident but were exposed to little radiation. The surveys were conducted twice when survey targets were aged 6 to 7 and when they were aged 10 to 11 in order to study effects of radiation exposure in the womb on their mental development.

In both surveys, incidences of difficulty in speech and disorder of emotion were larger among the exposed group than among non-exposed group with statistically significant differences.

Regarding intelligence quotient, fewer children in the exposed group were above the average compared with the non-exposed group and children on the borderline between normal levels and mental retardation were clearly larger in number.

However, no correlation has been found between estimated absorbed doses to the thyroid in fetal life and intelligence quotient, and possibilities of other factors are suggested such as social-psychological and sociocultural factors (school education and guardians' academic levels, etc.) associated with forced evacuation from contaminated regions. The possibility that radiation exposure during pregnancy has directly affected the intelligence quotients of fetuses and children after growth is considered to be low. A survey targeting parents using a stress evaluation index revealed clear correlation between parents' anxiety and children's emotional disorders.

https://www.env.go.jp/en/chemi/rhm/basic-info/1st/03-05-03.html

Effects on Fetuses Knowledge on Malformation Induction - Chernobyl NPS Accident -

Has the Chernobyl NPS Accident increased malformation?

Comparison of European congenital malformation/twin registry database between before and after the Chernobyl NPS Accident

European Surveillance of Congenital Anomalies (EUROCAT): 18 regions in 9 countries:

No change in incidence of malformations before and after the accident

Finland, Norway, Sweden:

No change in incidence of malformations before and after the accident

Belarus:

Increase in registration of malformations of aborted fetuses regardless of whether from the contaminated areas or not

Possibility of reporter bias* 1

Ukraine: participated in EUROCAT in this century

Increase in neural tube defects in an isolated Polish community in the Rivne province

It is necessary to evaluate the influences of folate depravation, alcoholism, consanguineous marriage, etc., in addition to radiation.* 2

Source : * 1 :Stem Cells 15 (supple 1): 255, 1997 * 2 :Pediatrics 125:e836, 2010

There have been various reports on the incidence of congenital anomalies before and after the Chornobyl NPS Accident.

Comparison of databases of the European Surveillance of Congenital Anomalies (EUROCAT), and of Finland, Norway, and Sweden showed no change in incidence of malformations before and after the accident.

In the northern part of the Rivne region of Ukraine, there are people who live a self-sufficient life in a contaminated area. There is a report that neural tube defects have been increasing among them, and analysis is underway to determine whether it has been caused by radiation.

https://www.env.go.jp/en/chemi/rhm/basic-info/1st/03-05-01.html

Mother's dose (Gy)	Father's dose (Gy)			
	< 0.01	0.01-0.49	0.5-0.99	≥ 1
< 0.01	2,257/45,234 (5.0%)	81/1,614 (5.0%)	12/238 (5.0%)	17/268 (6.3%)
0.01-0.49	260/5,445 (4.8%)	54/1,171 (4.6%)	4/68 (5.9%)	2/65 (3.1%)
0.5-0.99	44/651 (6.8%)	1/43 (2.3%)	4/47 (8.5%)	1/17 (5.9%)
≥ 1	19/338 (4.9%)	2/30 (6.7%)	1/9 (11.1%)	1/15 (6.7%)

Surveys targeting newborns of atomic bomb survivors were conducted between 1948 and 1954 in order to examine the possibility that genetic mutations in the genome of germline cells induced by radiation exposure due to the atomic bombing may impair growth of fertilized embryos, fetuses or newborn babies. However, radiation effects were not observed.[*1]

Furthermore, in the United States and Canada[*2,*3] and in Denmark[*4,*5], abnormalities at birth among children of childhood cancer survivors were epidemiologically surveyed.

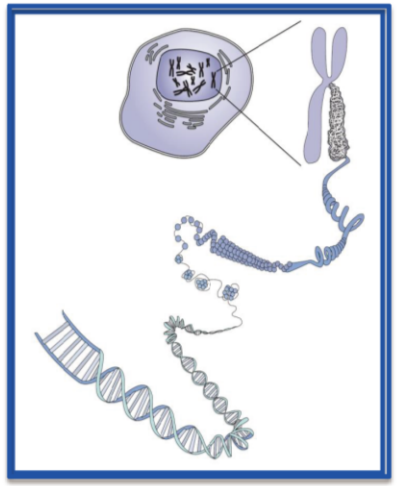
These surveys also do not show any risks of congenital anomalies or stillbirths caused by fathers' radiation exposure.

On the other hand, it was found that mothers' exposure to radiation exceeding 10 Gy in the ovary or womb increased premature births and stillbirths caused by deterioration of uterine function[*3].

*1: M. Ohtake et al.: *Radiat. Res.* 122: 1-11, 1990.
*2: L.B. Signorello et al.: *J. Clin. Oncol.* 30: 239-45, 2012.
*3: L.B. Signorello et al.: *Lancet* 376(9741): 624-30, 2010.
*4: J.F. Winther et al.: *J. Clin. Oncol.* 30: 27-33, 2012.
*5: J.F. Winther et al.: *Clin. Genet.* 75: 50-6, 2009.

Risks of heritable effects for human beings

■ Radiation effects on gonads (reproductive cells)
◎ Gene mutations
Changes in genetic information in DNA (point mutation)
◎ Chromosome aberrations
Structural chromosomal aberrations
* Increases in hereditary diseases in the offspring have not been proved among human beings.



■ Risks of heritable effects (up to children and grandchildren)
= Approx. 0.2%/Gy (Two out of 1,000 people per gray)
(2007 Recommendations of the International Commission on Radiological Protection (ICRP))

This value is indirectly estimated using the following data:
- Spontaneous incidences of hereditary diseases among a group of human beings
- Average spontaneous gene mutation rate (human beings) and average radiation-induced mutation rate (laboratory mice)
- Correction factor for extrapolating potential risks of induced hereditary diseases among human beings based on radiation-induced mutation rate among laboratory mice

■ Tissue weighting factor for gonads(ICRP Recommendations)
0.25 (1977) → 0.20 (1990) → 0.08 (2007)

In animal testing, when parents are exposed to high-dose radiation, congenital disorders and chromosomal aberrations are sometimes found in their offspring. However, there has been no evidence to prove that parents' radiation exposure increases hereditary diseases in their offspring in the case of human beings.

The ICRP estimates risks of heritable effects as 0.2% per gray. This is even less than one-twentieth of the risk of death by cancer. Furthermore, the ICRP assumes that the exposure dose that doubles the spontaneous gene mutation rate (doubling dose) is the same at 1 Gy for human beings and laboratory mice. However, heritable effects have not been confirmed for human beings and there is the possibility that this ICRP estimate is overrated.

Targeting children of atomic bomb survivors, life-span surveys, health effects checks, and surveys on various molecular levels have been conducted. Results of these surveys have made it clear that risks of heritable effects had been overestimated. Accordingly, the tissue weighting factor for gonads was reduced in the ICRP Recommendations released in 1990 and further in the ICRP Recommendations released in 2007.

https://www.env.go.jp/en/chemi/rhm/basic-info/1st/03-06-01.html

Heritable Effects

Chromosomal Aberrations among Children of Atomic Bomb Survivors

Stable chromosome aberrations among children of atomic bomb survivors

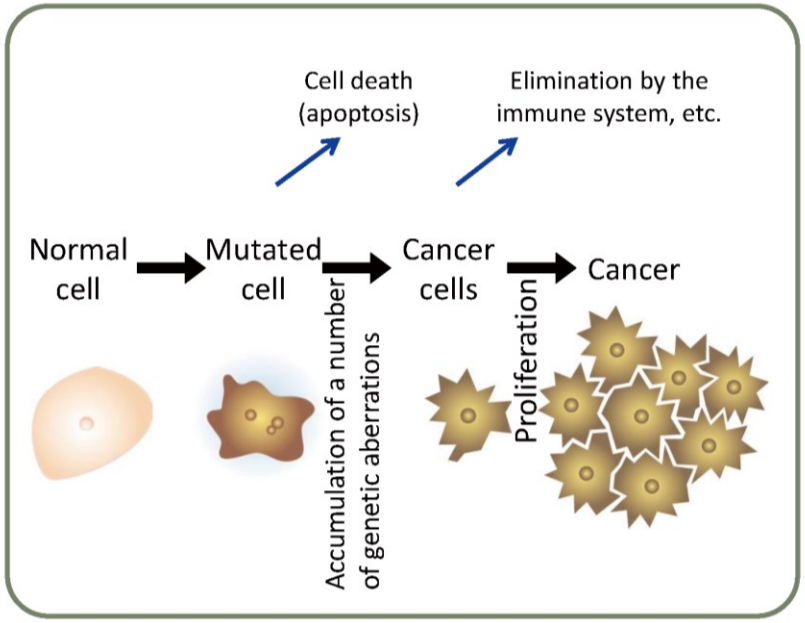
Sources of aberrations	Number of children with chromosome aberrations (percentage)	
	Control group (7,976 children)	Exposed group (8,322 children) Average exposure dose: 0.6 Gy
Derived from either of the parents	15 (0.19%)	10 (0.12%)
Newly developed cases	1 (0.01%)	1 (0.01%)
Unknown (Examination of parents was not possible.)	9 (0.11%)	7 (0.08%)
Total	25 (0.31%)	18 (0.22%)

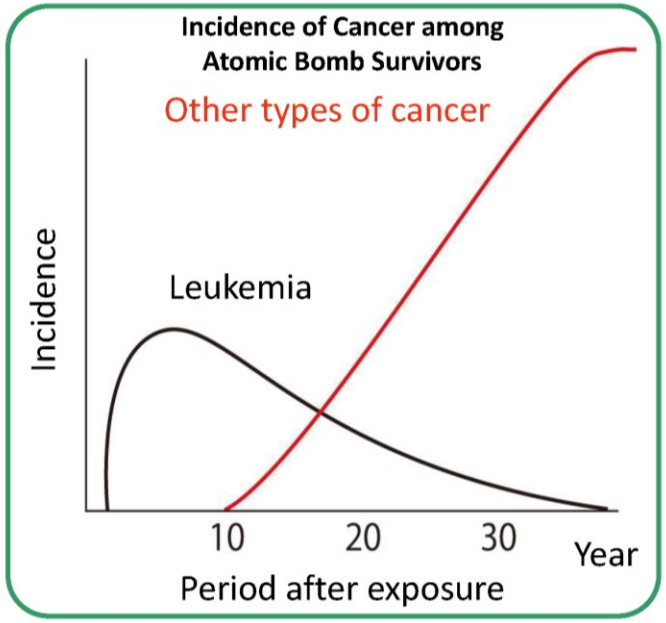
Source: Prepared based on "Chromosomal Aberrations among Children of Atomic Bomb Survivors (1967 - 1985 surveys)" on the website of the Radiation Effects Research Foundation (https://www.rerf.or.jp/programs/roadmap/health_effects/geneefx/chromeab/)

Surveys of health effects on children of atomic bomb survivors examine incidence rates of serious congenital disorders, gene mutations, chromosome aberrations and cancer, as well as mortality rates from cancer or other diseases. However, no significant differences were found between the survey targets and the control group regarding any of these. Stable chromosome aberrations do not disappear through cell divisions and are passed on from parents to their offspring. As a result of a survey targeting 8,322 children (exposed group), either or both of whose parents were exposed to radiation within 2,000 m from the center of the explosion (estimated exposure doses: 0.01 Gy or more), stable chromosome aberrations were found in 18 children. On the other hand, among 7,976 children (control group), both of whose parents were exposed to radiation at locations 2,500 m or farther from the center of the explosion (estimated exposure doses: less than 0.005 Gy) or were outside the city at the time of the atomic bombing, stable chromosome aberrations were found in 25 children.

However, a later examination of their parents and siblings revealed that most of the detected chromosome aberrations were not those newly developed but those that had already existed in either of their parents and were passed on to them. In view of this, it became clear that among the survivors of the atomic bombing, no radiation effects were detected, when stable chromosomal aberrations that appeared in the reproductive cells of parents as a result of radiation exposure are transmitted to their offspring.

https://www.env.go.jp/en/chemi/rhm/basic-info/1st/03-06-02.html



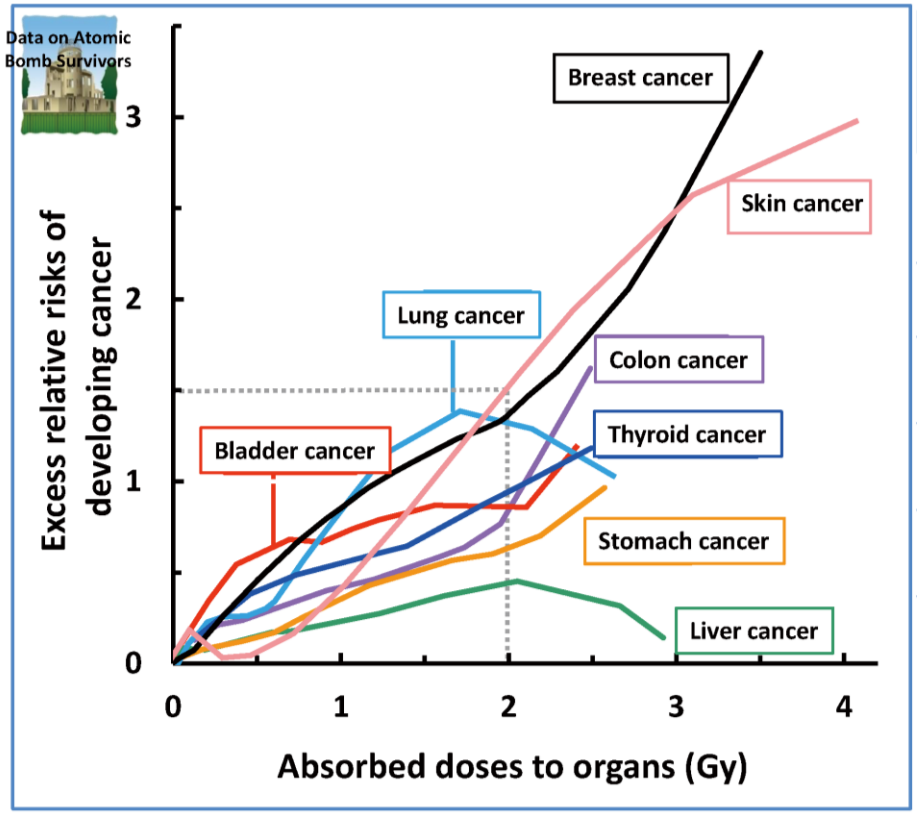


- Radiation is only one of various factors that induce cancer.
- Mutated cells follow multiple processes until developing into cancer cells.
  → It takes several years to decades.

Not only radiation but also various chemical substances and ultraviolet rays, etc. damage DNA. However, cells have a mechanism to repair damaged DNA. Even if repair was not successful, the human body has a function to eliminate cells wherein DNA damage has not been completely repaired.

Nevertheless, cells with incompletely repaired DNA survive as mutated cells in very rare cases. Genetic aberrations may be accumulated in cells that happen to survive and these cells may develop into cancer cells. However, this process requires a long period of time. Among atomic bomb survivors, leukemia increased in around two years, but the incidence decreased thereafter. On the other hand, cases of solid cancer started to increase after an incubation period of around 10 years.

https://www.env.go.jp/en/chemi/rhm/basic-info/1st/03-07-01.html



Source: Prepared based on Preston et al., Radiat Res., 168, 1, 2007

Tissue	Tissue weighting factor w_T*
Red bone marrow, stomach, lungs, colon, breasts	0.12
Gonad	0.08
Bladder, esophagus, liver, thyroid	0.04
Bone surface, brain, salivary gland, skin	0.01
Total of the remaining tissues	0.12

Source: 2007 Recommendations of the International Commission on Radiological Protection (ICRP)

* The tissue weighting factor is larger for organs and tissues for which risks of radiation effects are higher.

This figure shows how cancer risks have increased for each organ depending on exposure doses, targeting atomic bomb survivors. The horizontal axis indicates the absorbed doses to organs through a single high-dose exposure at the time of the atomic bombing, while the vertical axis indicates excess relative risks, which show how cancer risks have increased among the exposed group compared with the non-exposed group.

For example, when the absorbed dose to organs is 2 Gy, the excess relative risk for skin cancer is 1.5, meaning that the risk increased in excess of 1.5 times compared with the non-exposed group (in other words, among the group of people exposed to 2 Gy of radiation, the relative risk of developing skin cancer is 2.5 times higher (1 + 1.5) than among the non-exposed group).

As a result of these epidemiological studies, it was found that the mammary gland, skin, and colon, etc. are tissues and organs that are easily affected by radiation and develop cancer. The 2007 Recommendations of the ICRP specify tissue weighting factors while taking into account the radiosensitivity of each organ and tissue and the lethality of each type of cancer.

https://www.env.go.jp/en/chemi/rhm/basic-info/1st/03-07-02.html

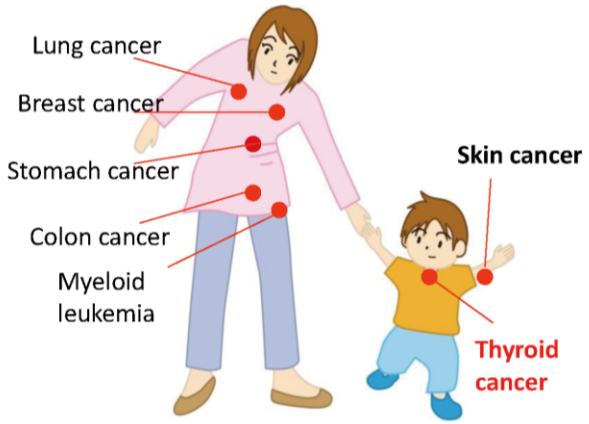
	Committed effective dose coefficients for I-131*1 (μSv/Bq)	Committed effective doses when having taken in 100 Bq of I-131 (μSv)	Equivalent doses to the thyroid when having taken in 100 Bq of I-131*2 (μSv)
3 month-old infants	0.18	18	450
1 year-old children	0.18	18	450
5 year-old children	0.10	10	250
Adults	0.022	2.2	55

*1: Committed effective dose coefficients are larger for children due to difference in metabolism and physical constitution.
*2: Calculated using the tissue weighting factor of 0.04 for the thyroid

Source: Prepared based on International Commission on Radiological Protection (ICRP), ICRP Publication 119, Compendium of Dose Coefficients based on ICRP Publication 60, 2012

Risks of thyroid cancer and skin cancer are higher for children than for adults.

μSv/Bq: microsieverts/becquerel

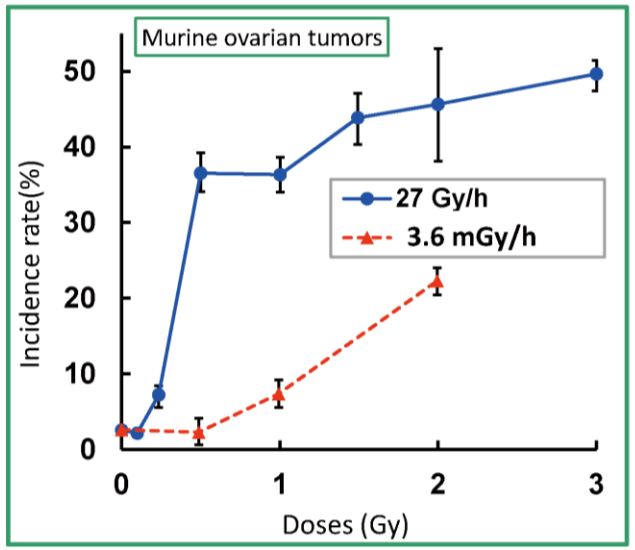


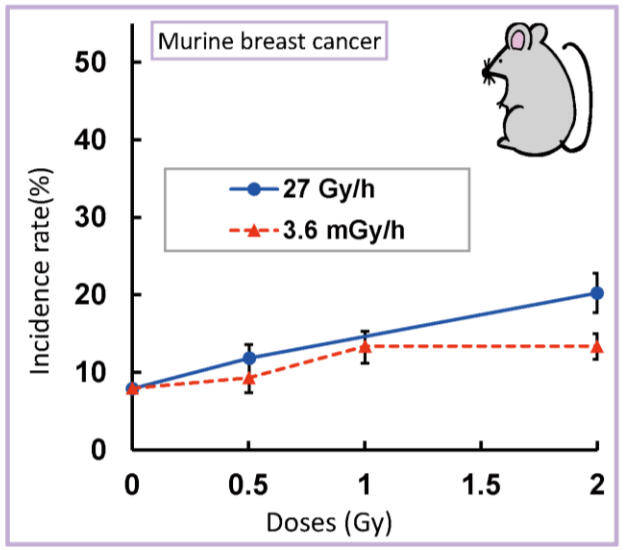
In the case of adults, bone marrow, colon, mammary gland, lungs and stomach easily develop cancer due to radiation exposure, while it has become clear that risks of developing thyroid cancer and skin cancer are also high in the case of children.

In particular, children's thyroids are more sensitive to radiation and committed effective doses per unit intake (Bq) are much larger than adults. Therefore, the exposure dose to the thyroids of 1-year-old children is taken into account as the standard when considering radiological protection measures in an emergency. Additionally, much larger values are adopted as children's committed effective dose coefficients per unit intake (Bq) than those for adults.

https://www.env.go.jp/en/chemi/rhm/basic-info/1st/03-07-03.html

Cancer-promoting effects of low-dose exposures





Source: United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 1993

Risks of low-dose and low-dose-rate exposures

$$= \frac{\text{Risks of high-dose and high-dose-rate exposures}}{\text{Dose and dose-rate effectiveness factor}}$$

Organizations	Dose and dose-rate effectiveness factors
UNSCEAR 1993	Less than 3 (1 to 10)
National Academy of Sciences (NAS) 2005	1.5
International Commission on Radiological Protection (ICRP) 1990 and 2007	2

Surveys targeting atomic bomb survivors have examined effects of large-amount radiation exposure at one time, while occupational exposures and exposures caused by environmental contamination due to a nuclear accident are mostly chronic low-dose exposures.

Therefore, animal testing using mice has been conducted to ascertain differences in oncogenic risks between a single large-amount radiation exposure and low-dose exposures over time. Although test results vary by type of cancer, it has become clear that radiation effects are generally smaller for low-dose exposures over a long period of time.

Dose and dose-rate effectiveness factors are correction values used in the case of estimating risks of low-dose exposures, for which no concrete data is available, on the basis of risks of high-dose exposures (exposure doses and incidence rates) or estimating risks of chronic exposures or repeated exposures based on risks of acute exposures.

Researchers have various opinions on specific values to be used for considering radiological protection, but the ICRP uses 2 as the dose and dose-rate effectiveness factor in its Recommendations and concludes that long-term low-dose exposure would cause half the effects as those caused by exposure at one time, if the total exposure dose is the same.

https://www.env.go.jp/en/chemi/rhm/basic-info/1st/03-07-04.html

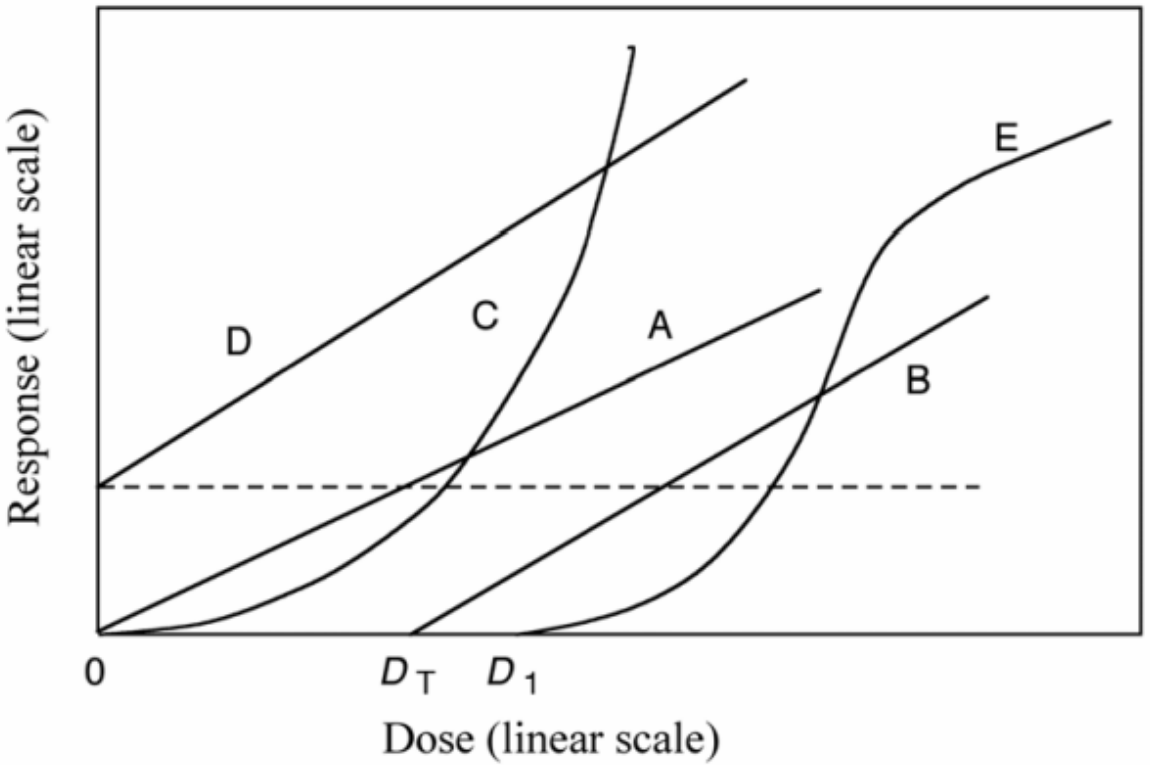
A plot of a biological effect observed (e.g., tumor induction, tissue response) against the dose given is called a **dose-response curve**. Generally, as dose increases so does the effect.

Three types of dose-response relationships are known:

- Linear;
- Linear-quadratic;
- Sigmoid.

The dose-response curves may or may not have a threshold.

A threshold dose is the largest dose for a particular effect studied, below which no effect will be observed.



Sketch of typical dose response curves for cancer induction (curves A, B, C, D) and for tissue response (curve E). Curve (A) represents linear relationship - no threshold; curve (B) linear relationship with threshold D_T; curve (C) linear-quadratic relationship - no threshold (assumed for stochastic effects, e.g., carcinogenesis); curve (D) linear relationship - no threshold (area below dashed line represents the natural incidence of the effect, e.g., carcinogenesis); and curve (E) sigmoid relationship with threshold D_1, as is common for deterministic effects in tissues, e.g., tumor control, treatment morbidity.

https://www.irsn.fr/sites/default/files/documents/professionnels_sante/documentation/syllabus_chapitre_14.pdf

Threshold acute absorbed doses of γ-rays

Disorders	Organs/Tissues	Incubation period	Threshold value (Gy)*
Temporary sterility	Testis	3 to 9 weeks	Approx. 0.1
Permanent sterility	Testis	3 weeks	Approx. 6
	Ovary	Within 1 week	Approx. 3
Deterioration of hemopoietic capacity	Bone marrow	3 to 7 days	Approx. 0.5
Skin rubor	Skin (large area)	1 to 4 weeks	3 to 6 or lower
Skin burn	Skin (large area)	2 to 3 weeks	5 to 10
Temporary hair loss	Skin	2 to 3 weeks	Approx. 4
Cataract (failing vision)	Eyes	20 years or longer	Approx. 0.5

* Threshold doses for symptoms with clear clinical abnormalities (doses causing effects on 1% of people)

Source: Prepared based on the 2007 Recommendations of the International Commission on Radiological Protection (ICRP), and ICRP Report 118 (2012)

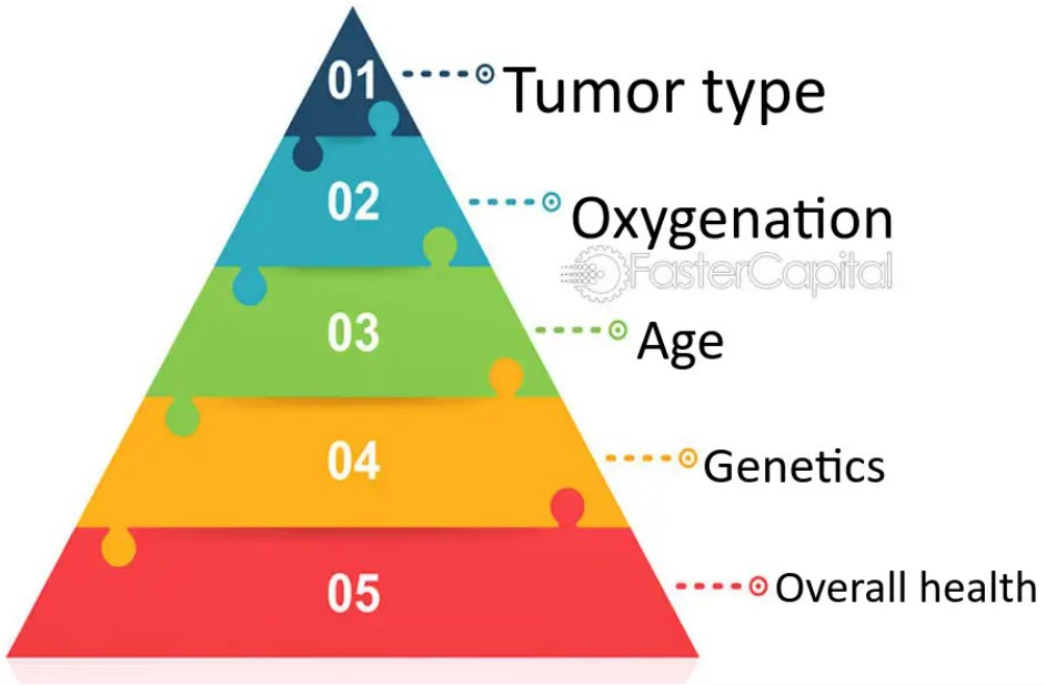
The most sensitive organs include the testes. When the testes are exposed to γ-rays or other types of radiation exceeding 0.1 Gy (100 mGy) at one time, this may cause temporary sterility with a temporary decrease in the number of sperm, which is due to radiation damage to cells in the testes that create sperm.

Also, if bone marrow is irradiated by more than 0.5 Gy (500 mGy) at one time, the hematopoietic function is impaired, and a total number of blood cells may decrease.

Some deterministic effects (tissue reactions), such as cataract, take several years to appear.

The threshold dose for cataract had been set at 1.5 Gy, but the ICRP revised this value downward to approx. 0.5 Gy and set a new equivalent dose limit for the eye lens for occupational exposures.

https://www.env.go.jp/en/chemi/rhm/basic-info/1st/03-03-04.html



Factors Affecting Radiosensitivity

Tumor type: Different types of tumors have different levels of radiosensitivity. For example, lymphomas and seminomas are highly sensitive to radiation, while melanomas and sarcomas are less sensitive.

Oxygenation: Tumor cells that are well oxygenated are more sensitive to radiation than those that are poorly oxygenated. This is because radiation causes the formation of free radicals, and oxygen helps to enhance their effectiveness. Tumors that are located in areas with good blood supply are more likely to be well oxygenated and therefore more sensitive to radiation.

Age: Younger patients tend to have more radiosensitive tumors than older patients. This is because younger cells are more active and therefore more likely to be affected by radiation. Older patients may require higher doses of radiation to achieve the same effect as younger patients.

Genetics: The genetic makeup of the tumor can also affect its radiosensitivity. Some tumors are more resistant to radiation due to genetic mutations that make them less responsive to the effects of radiation. Genetic testing can help radiation oncologists determine the radiosensitivity of a particular tumor.

Overall health: The overall health of the patient can also affect the radiosensitivity of the tumor. Patients who are in poor health may be less able to tolerate radiation treatment, which can affect the effectiveness of the treatment. For example, patients with lung disease may have difficulty breathing during radiation treatment, which can limit the amount of radiation that can be given.

Risks

- The magnitude of the influence of damage
- The possibility of any damage (probability)
- The combination of the magnitude of the influence and the possibility (probability)

Quantitatively expressed probability, not focused on the actual existence of damage

In particular, when considering stochastic effects of radiation,

Risks =
The probability (of contracting cancer or dying of cancer)

Having risks ✕ (Surely) being subject to damage

The term "risk" generally means "dangerousness" or "degree of hazard." However, more strictly, the term is used to refer to "the magnitude of the influence of damage," "the possibility of any damage (probability)," or "the combination of the magnitude of the influence and the possibility (probability)". The focus is not on "whether or not there are any risks" but on "to what extent or by how many times risks increase."

On the other hand, what causes damage is called "hazard." It is important to clearly distinguish hazard information on the existence or non-existence of hazards and risk information on the degree and probability of damage, and properly communicate and utilize these two types of information.

When considering health effects of radiation, in particular, stochastic effects of radiation, it is common to use the term "risk" in the sense of "the probability (of contracting cancer or dying of cancer)".

In this case, it should be noted that "having risks" is not equal to "(surely) being subject to damage".

https://www.env.go.jp/en/chemi/rhm/basic-info/1st/03-04-01.html

Relative risks and attributable risks

Factors	Incidence		Total
	Yes	No	
Exposed group	A	B	A+B
Non-exposed group	C	D	C+D

How many times factor exposure would increase the incidence of an individual:

$$\text{Relative risk} = \frac{\text{Incidence risk among an exposed group}}{\text{Incidence risk among a non-exposed group}} = \frac{\frac{A}{A+B}}{\frac{C}{C+D}}$$

Relative risk larger than 1 represents that risks have increased due to factor exposure.

The value obtained by subtracting 1 from the relative risk is an excess relative risk, showing an increased amount of risks.

How many times factor exposure would increase the incidence rate of a group:

$$\text{Attributable risk} = \text{Incidence risk among an exposed group} - \text{Incidence risk among a non-exposed group}$$

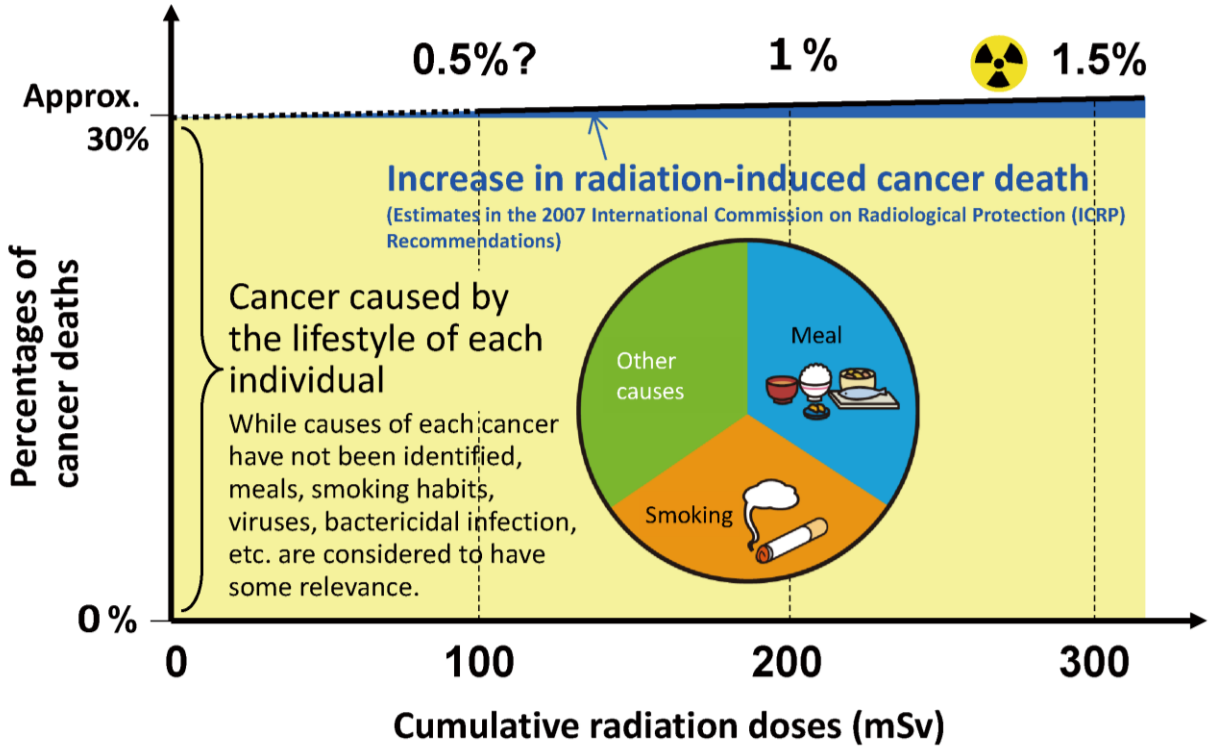
$$= \frac{A}{A+B} - \frac{C}{C+D}$$

A relative risk represents how many times a certain factor increases the risk of an individual exposed there to. In epidemiology, the term "risk" normally refers to a relative risk. The value obtained by subtracting 1 from the relative risk is an excess relative risk and shows an increased amount of risk compared with a group free from risk factors. There is also an **attributable risk** that represents how much a certain factor increases the incidence or mortality rate of a group.

Suppose a group is exposed to some risk factor while another group is not, and there are 2 patients of a certain disease among one million people in the non-exposed group, while there are 3 patients among one million people in the exposed group. Then, an increase in the number of patients from 2 to 3 is construed to mean that the relative risk has increased by 1.5 times from the perspective of how much more an individual is likely to develop a disease. On the other hand, as an attributable risk focuses on increases in the number of patients in a group, the increase is construed as one in a million, that is, an increase of 10^{-6} in risk.

https://www.env.go.jp/en/chemi/rhm/basic-info/1st/03-04-02.html

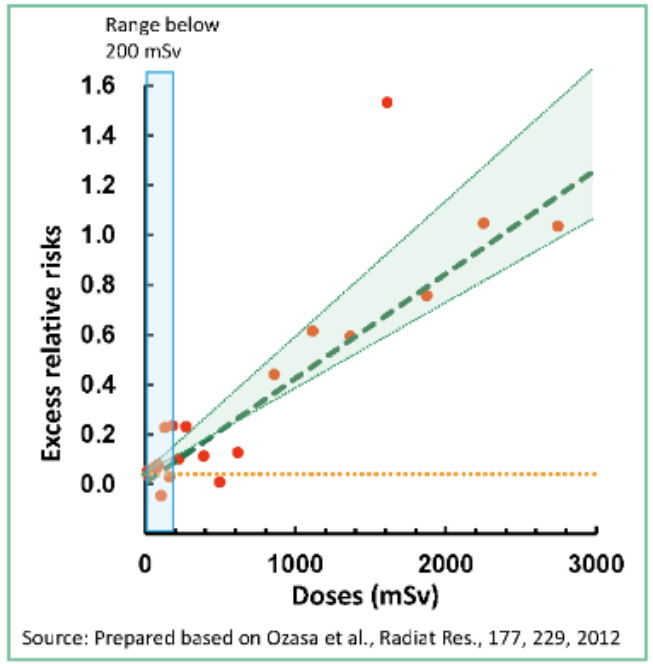
Risks of cancer death from low-dose exposure



Currently, the leading cause of deaths among Japanese people is cancer, with around 30% of the entire population dying of cancer. That is, 300 people in a group of 1,000 will die of cancer. If the probability of death from radiation-induced cancer is added, it can be estimated that if all people in such group of 1,000 people are exposed to 100 mSv, 305 will die of cancer in their lifetime. However, in actuality, the value of 300 out of 1,000 people could vary from year to year and from region to region, and no methods have been established yet to confirm if cancer is really attributable to radiation exposure. It is thus considered very difficult to detect an increase in cancer deaths among people exposed to not higher than 100 mSv, i.e., an increase of up to 5 people in a group of 1,000.

The International Commission on Radiological Protection (ICRP) considers radiological protection based on the idea that in a group of people including both adults and children, the probability of cancer death increases by 0.5% per 100-mSv exposure. This value shows estimated risk of low-dose exposure based on data obtained from atomic bomb survivors.

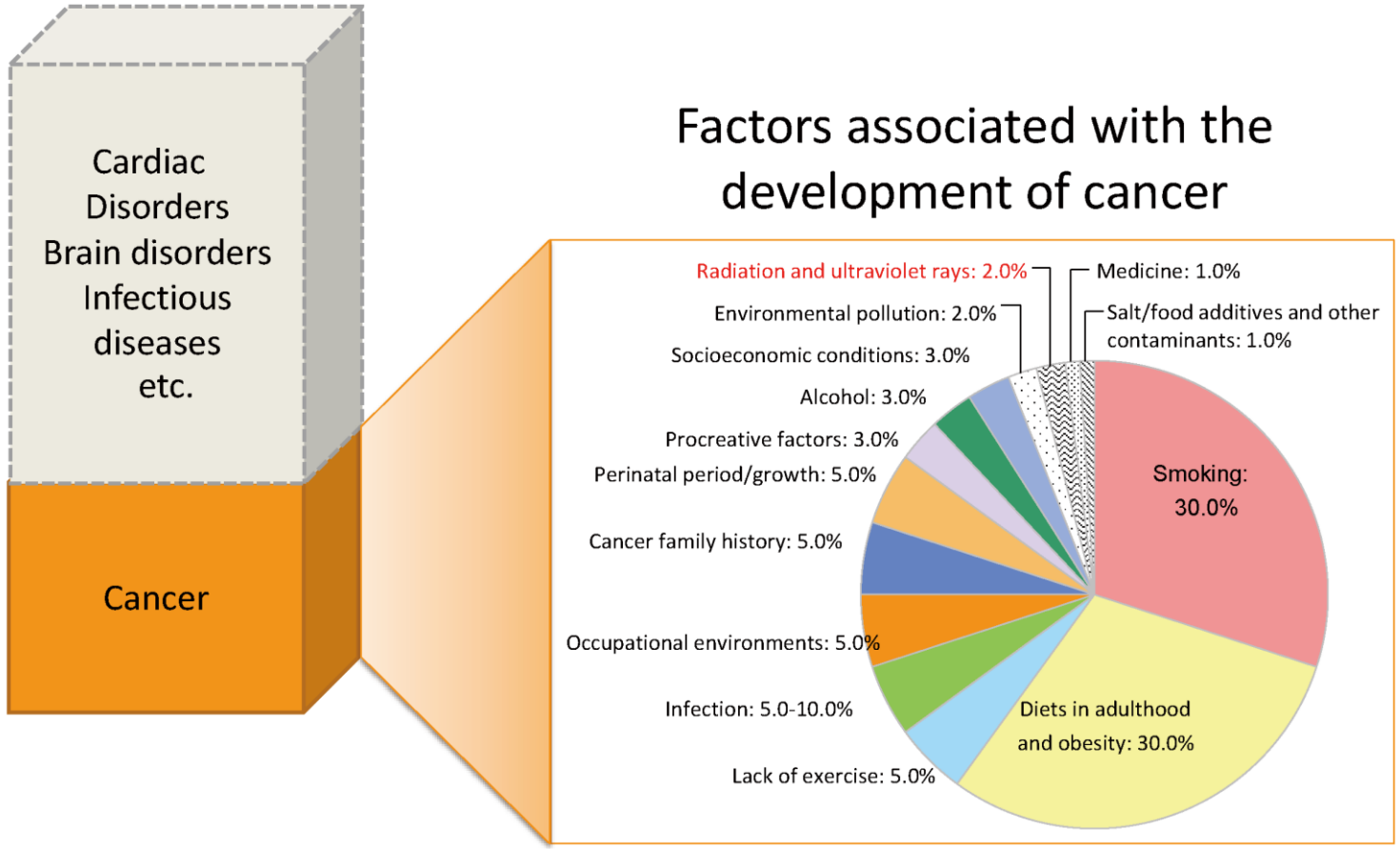
Deaths from solid cancer
(results among atomic bomb survivors)



Source: Prepared based on Ozasa et al., Radiat Res., 177, 229, 2012

Excess relative risks: How cancer risks have increased among a group of people exposed to radiation compared with a group of non-exposed people

https://www.env.go.jp/en/chemi/rhm/basic-info/1st/03-04-03.html



Source: Prepared based on Cancer Causes Control 1996.7.S55-S58

We are surrounded by various risk factors for cancer in our lives. The pie chart provides U.S. data, which gives an idea that meals and smoking habits are closely associated with the development of cancer. If having been exposed to radiation, risks due to radiation are to be added to these factors. Accordingly, it is best to avoid radiation exposure from the viewpoint of reducing risks of cancer.

It may be possible to refuse X-ray examinations or avoid taking flights, but that would make early detection of diseases impossible and make life inconvenient, and such efforts would not dramatically reduce the risks of developing cancer due to the existence of various cancer-causing factors other than radiation in our lives.

https://www.env.go.jp/en/chemi/rhm/basic-info/1st/03-04-04.html

It is estimated that the relative risk increases by 1.8 times due to radiation exposure doses of 1,000 to 2,000 mSv, by 1.4 times due to doses of 500 to 1,000 mSv and by 1.19 times due to doses of 200 to 500 mSv. In the case of radiation exposure below 100 mSv, it is considered to be extremely difficult to detect the risk of developing cancer.

Radiation doses (mSv)	Relative risks of cancer*
1,000 ~ 2,000	1.8 [estimated to be 1.5 times per 1,000 mSv]
500 ~ 1,000	1.4
200 ~ 500	1.19
100 ~ 200	1.08
Less than 100	Difficult to detect

Lifestyle factors	Relative risks of cancer *1
Smokers	1.6
Heavy drinking (450 g or more/week)*2	1.6
Heavy drinking (300 to 449 g or more/week)*2	1.4
Obese (BMI≧30)	1.22
Underweight (BMI<19)	1.29
Lack of exercise	1.15 ~ 1.19
High-salt foods	1.11 ~ 1.15
Lack of vegetable intake	1.06
Passive smoking (nonsmoking females)	1.02 ~ 1.03

It is estimated that the relative risk of cancer for people who smoke or drink a lot is 1.6 times higher than that for people who do not. It is also estimated that factors, such as obesity, lack of exercise, and lack of vegetable intake, will make the relative risks of cancer higher by 1.22 times, 1.15 to 1.19 times and 1.06 times, respectively.

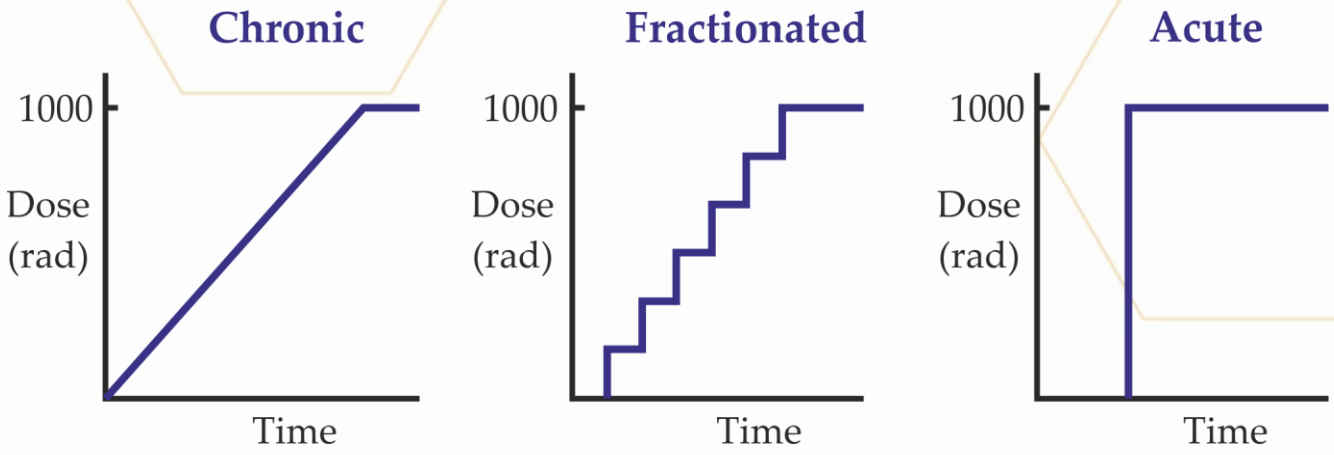
https://www.env.go.jp/en/chemi/rhm/basic-info/1st/03-04-05.html
https://www.env.go.jp/en/chemi/rhm/basic-info/1st/03-04-06.html

Interactive version of cancer probability calculation:

https://www.xrayrisk.com/calculator/calculator-normal-studies.php?id=13

The dose delivery can be classified as a:

- **Chronic Exposure.** The dose is delivered at a low rate over a long time, e.g., 0.1 rad/hr for 10,000 hours (total 1000 rad).
- **Fractionated Exposure**. The dose is delivered in discrete quantities, e.g., 100 rad are delivered per week for 10 weeks (total dose: 1000 rad).
- **Acute Exposure.** The total dose is delivered at once, or in a very short time (total 1000 rad).



For low LET radiation, the magnitude of the effect per unit dose is greatest following acute exposures and least with chronic exposures. This applies to dose rates between 10 and 5,000 rad/hr. Lowering the dose rate below 10 rad/hr doesn't further reduce the magnitude of the effect. Increasing the dose rate above 5,000 rad/hr has no additional effect.

For high LET radiation, this "dose rate effect" is less pronounced or absent.

There is some evidence that chronic exposures with high LET radiation may be more carcinogenic than acute exposures, i.e., an inverse dose rate effect.

https://www.env.go.jp/en/chemi/rhm/basic-info/1st/03-04-05.html
https://www.env.go.jp/en/chemi/rhm/basic-info/1st/03-04-06.html

	Low LET (gammas, X-rays, betas)	High LET (neutrons, alphas)
Dose rate effect	dependent	independent or inverse dependence
Dose response	often linear quadratic	often linear
DNA damage	primarily indirect	primarily direct
	DNA damage simpler	DNA damage more complex
DNA repair	easier	harder
Effect of oxygen	sensitizes tissue	none
Effect of radical scavengers	reduces damage	none

The **Law of Bergonie and Tribondeau** (1906) characterizes those tissues in the body that are most radiosensitive.

Like all laws in biology, it is a generalization and has exceptions. Although radiobiologists tend to dismiss the "law", it does have its uses.

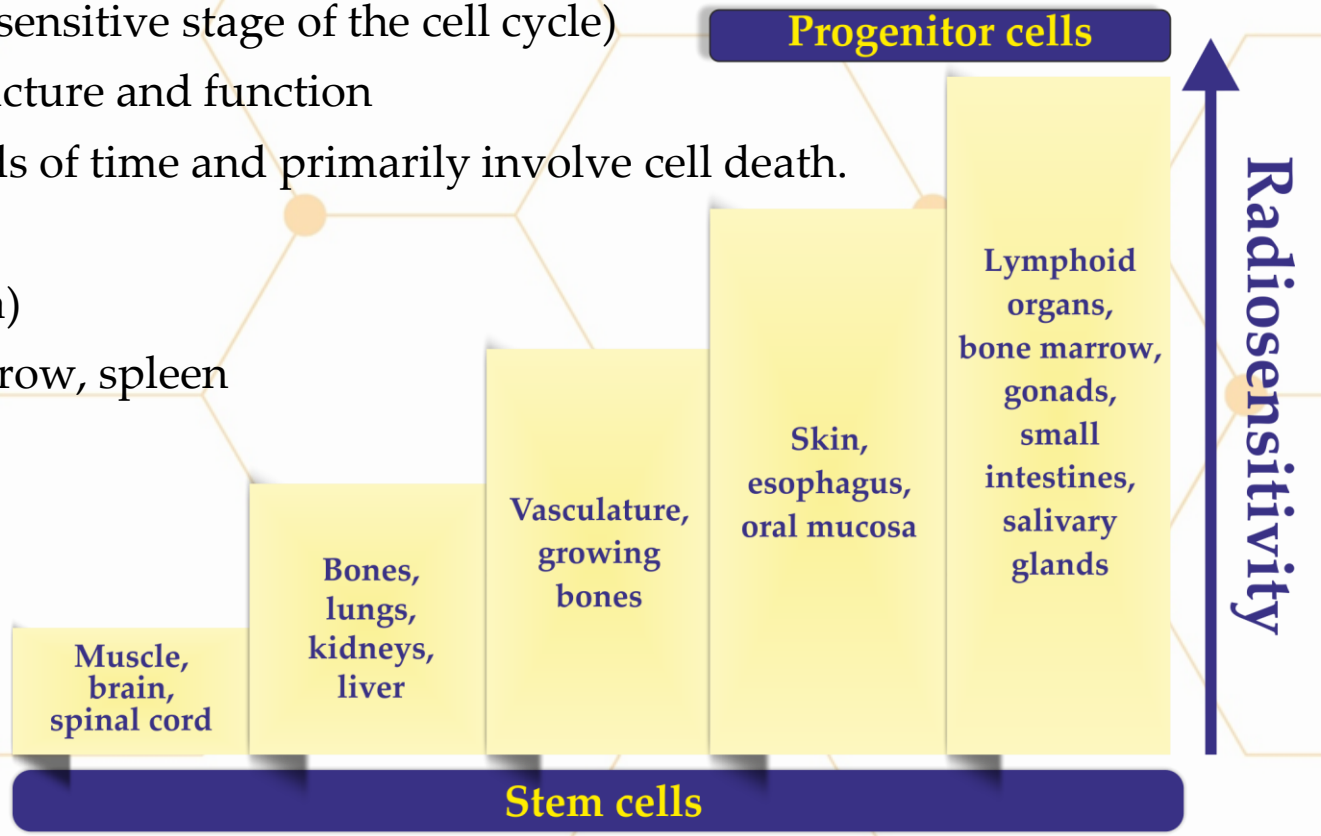
The law states that the most radiosensitive tissues possess cells that are:

- dividing at the time of exposure (mitosis is the most sensitive stage of the cell cycle)
- of an undifferentiated type, i.e., unspecialized in structure and function

These early effects are due to large doses in short periods of time and primarily involve cell death.

Examples of radiosensitive tissues:

- germinal cells of the ovary and testis (spermatogonia)
- hematopoietic (blood forming) tissues: red bone marrow, spleen
- lymph nodes
- epithelium of skin
- epithelium of gastrointestinal tract
- lymphocytes (exception to the "law")
- oocytes (exception to the "law")



http://dx.doi.org/10.1177/0022034509343143

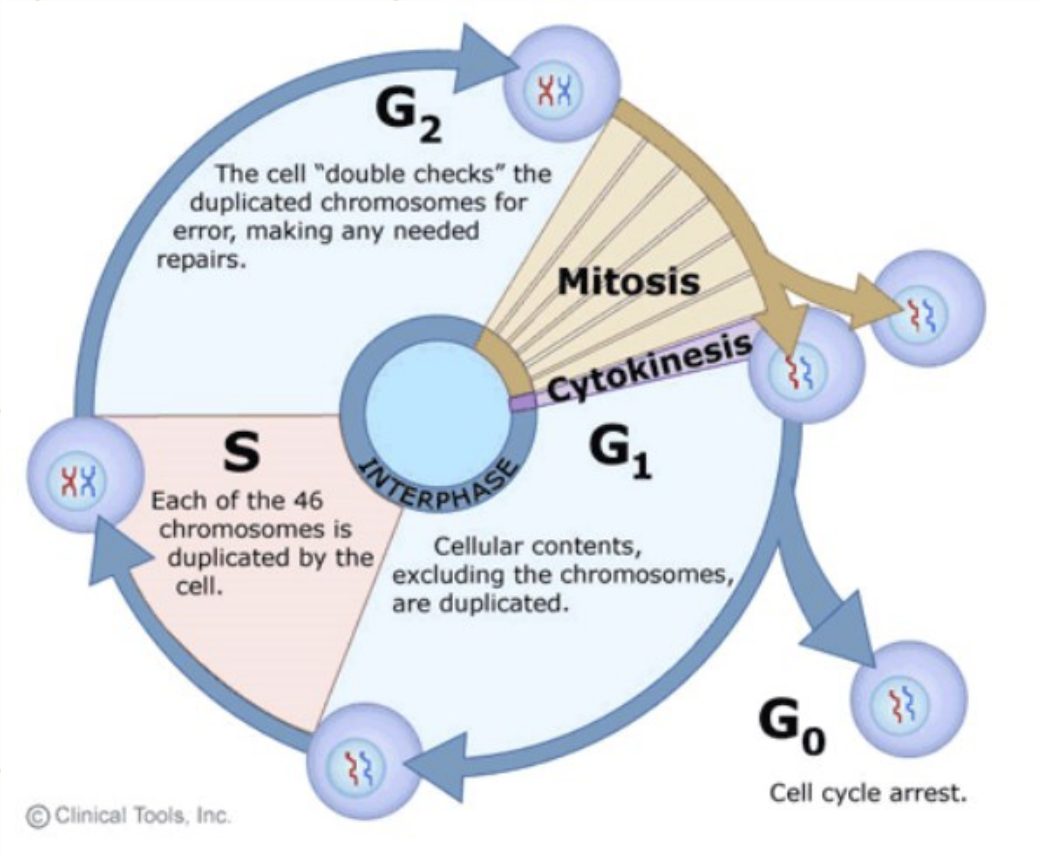
For low LET radiation, the most sensitive stages of the cell cycle, with respect to cell death, are mitosis and late G1 (at the G1 -S border).

This might be because the chromosomes are condensed during mitosis and the repair mechanisms have poor access to the DNA molecule.

For high LET radiation, all phases of the cell cycle appear equally sensitive.

In radiation therapy, the cancer cells most likely to be killed are those in the sensitive stage of the cell cycle. Cells in other stages of the cell cycle survive. This is how radiation exposures can synchronize cells in the cell cycle. Subsequent radiation exposures to the synchronized cancer cells are particularly effective.

One possible effect of this is to give the cell more time to repair damage prior to division.



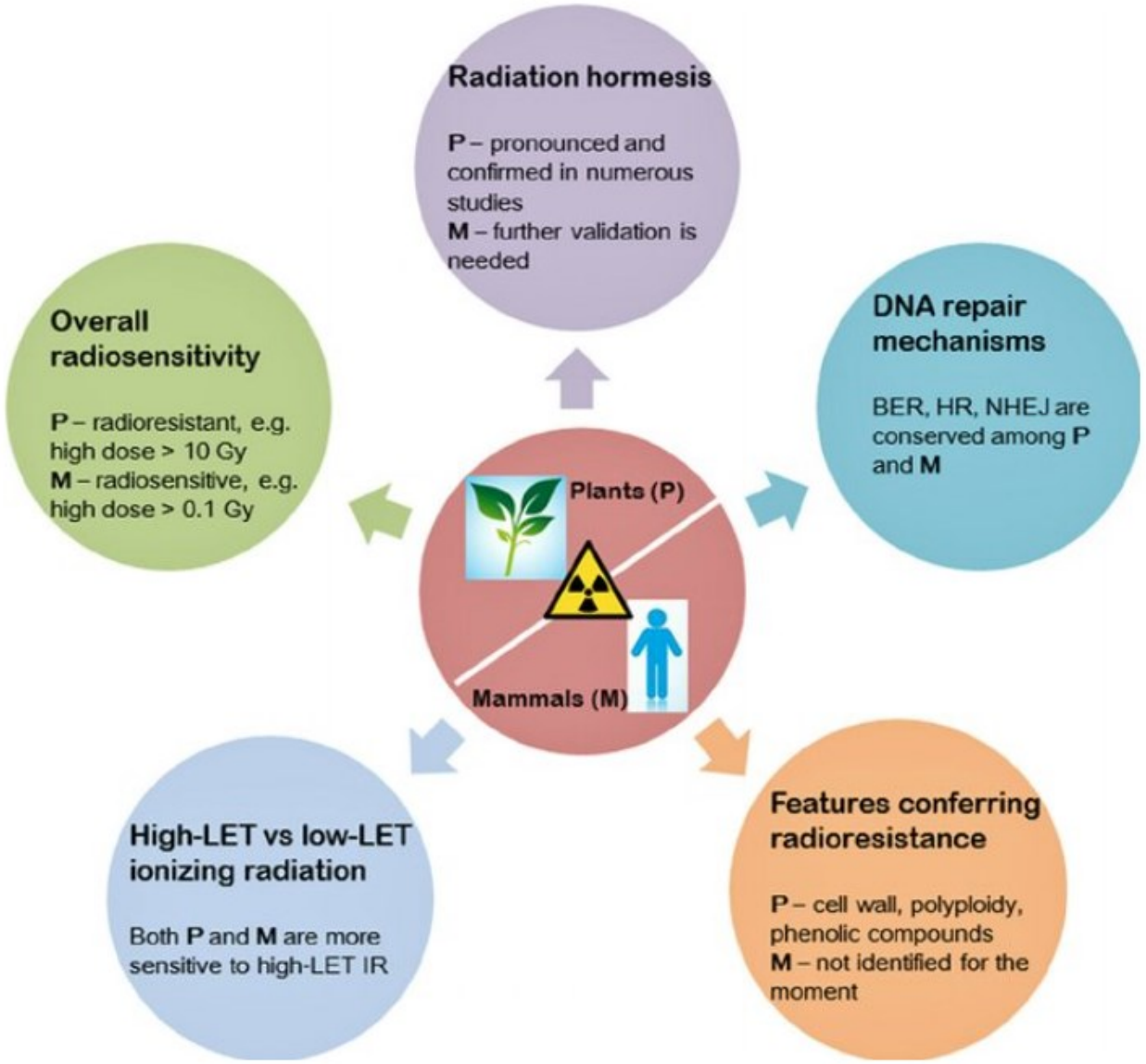
https://le.ac.uk/vgec/topics/cell-cycle/the-cell-cycle-higher-education

Low doses of radiation appear capable of initiating changes in cells that reduce the consequences of subsequent exposures.

For example, a conditioning dose of 5 to 200 mGy (500 to 20,000 mrad) to lymphocytes can result in an adaptive response some four to six hours later.

This adaptive response results in a lower-than-expected number of chromosomal aberrations following a second "challenge" dose.

This adaptive response seems to involve the activation of certain genes that increase the production of enzymes involved in DNA repair.



Cells with normal concentrations of oxygen (40+ mm Hg) tend to be 2-3 times as sensitive to low LET radiation as hypoxic (low in oxygen) cells. For a given effect, this difference is referred to as the oxygen enhancement ratio (OER).

Poorly vascularized tissue, i.e., tumors, tend to be hypoxic.

Tissues well supplied with blood tend to have normal oxygen tensions. The relationship between oxygen and radiosensitivity is most pronounced below 20 mm Hg. Above this, an increase in oxygen concentration does little to increase the radiosensitivity of a tissue.

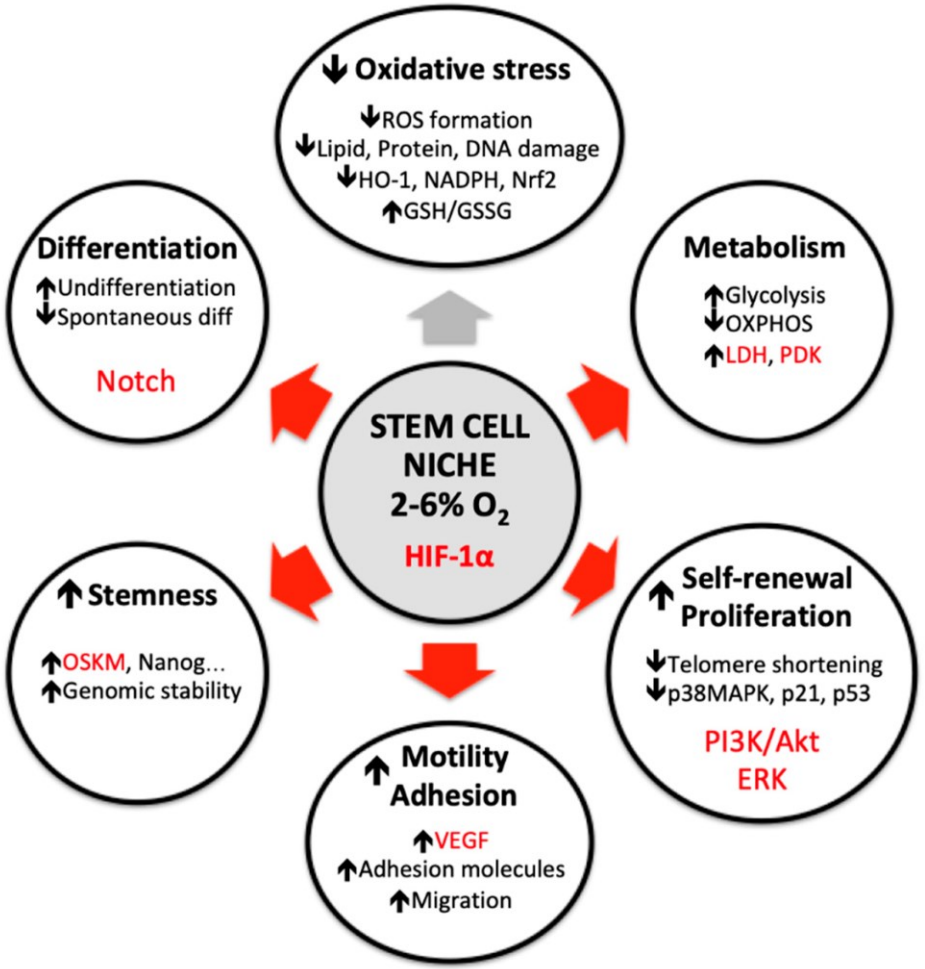
This effect of oxygen is probably due to several things, e.g.,:

- a resulting increase in the production of H_2O_2 and other reactive oxygen species.
- increasing the stability and toxicity of free radicals.

Because oxygen is electronegative, it can combine with the free electrons produced during the radiolysis of water.

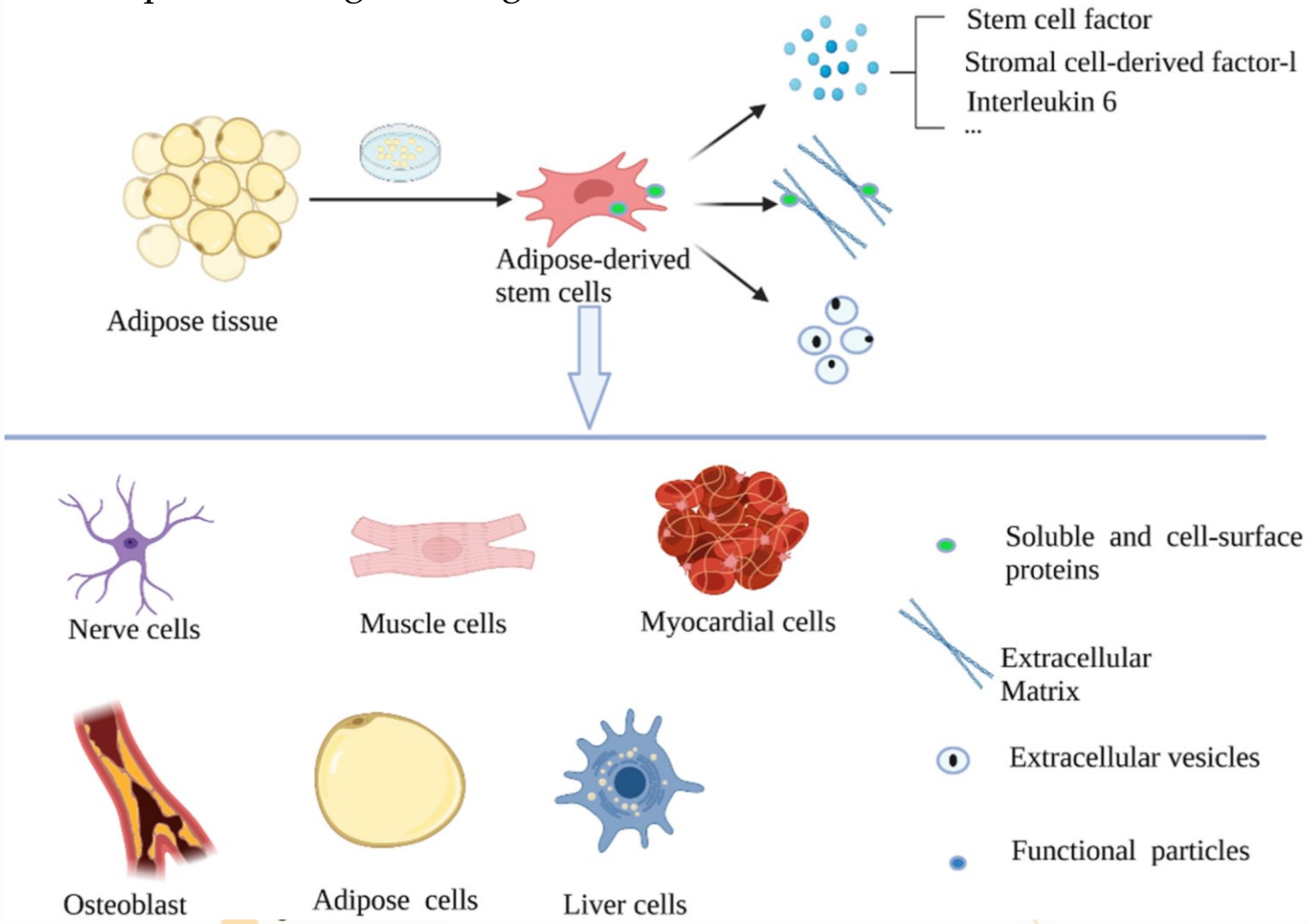
This might slow down the recombination of certain radiolytic products and increase the capacity for damage by extending the latter's effective lifespan.

Oxygen might combine with DNA damage sites and interfere with repair.



Certain chemicals, injected in substantial quantities 30 minutes or so prior to an acute exposure, can significantly reduce the effective dose of the radiation. Post-irradiation and oral administrations are less effective.

The dose reduction factor (DRF) is the ratio of the LD_{50}s for unprotected and protected animals. Typical DRFs for these radioprotective agents range from 1.5 to 2.0.



Examples of radioprotective drugs include cysteine, cystamine, and glutathione. A sulphydryl group is common to many of these agents.

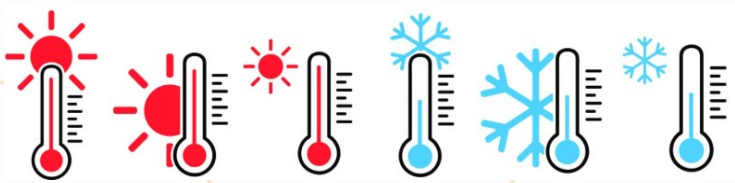
The interest in radioprotective drugs usually focuses on the protection afforded to large acute exposures. This is evidenced by the fact that the DRF is defined in terms of the LD_{50}.

Nevertheless, some of these chemicals (e.g., Amifostine) may provide protection from late effects such as cancer. The protective mechanisms vary.

Radioprotectants can work by scavenging (quenching) free radicals, enhancing cellular repair mechanisms, stabilizing membranes, enhancing hypoxia, etc.

https://www.sciencedirect.com/science/article/pii/S2096691122000383

Radioprotector	Toxicity LD_{50} (mg/kg)	Protective doses (mg/kg)	DRF
Cysteine	1700	1200	1.7
MEA	200	150	1.7
Cysteamine	220	150	1.7
AET	480	400	2.1
WR-638	1120	500	2.0
WR-2721	950	500	2.7
WR-3689	1120	450	2.2
WR-77913	3574	2200	2.0
WR-151327	785	315	1.9
Mercapto-propionyl glycin	2100	20	1.4
Glutathione	4000	4000	1.3



In many experiments, a dramatic increase in radioresistance has been produced by lowering an animal's body temperature.

For example, in mice the LD_{50} can be doubled by reducing the body temperature to 5°C.

The increase in radioresistance is apparently due to a reduction in oxygen tension that accompanies a lower body temperature.

In some cases, the lowered temperature merely serves to delay the effect, not reduce it. If the effect is simply delayed, it may be due to a reduced mitotic rate; once the animal warms up and mitosis resumes, mitotic cell death can occur.

In some species, females tend to be slightly more radioresistant than males. That this is related to differences in hormonal levels.

For example, human males are more susceptible to radiation-induced leukemia, while females are more susceptible to radiation-induced thyroid cancer.

Lymphocytes of males and females differ in their radiosensitivity, something that can introduce uncertainty into cytogenetic dosimetry.

Variability in female hormonal levels has been linked to variations in lymphocyte radiosensitivity.

More radiosensitive

Embryo

Fetus

Child

Adult

Less radiosensitive

For animals, the more primitive the species, the more radioresistant the organism. The more advanced the organism, the more radiosensitive it is.

With plant species, the larger the **interphase chromosome volume (ICV)**, the greater the radiosensitivity. The ICV is defined as the average volume of the nuclei divided by the number of chromosome characteristic of the species.

More radiosensitive

mammals

reptiles, fish, amphibians

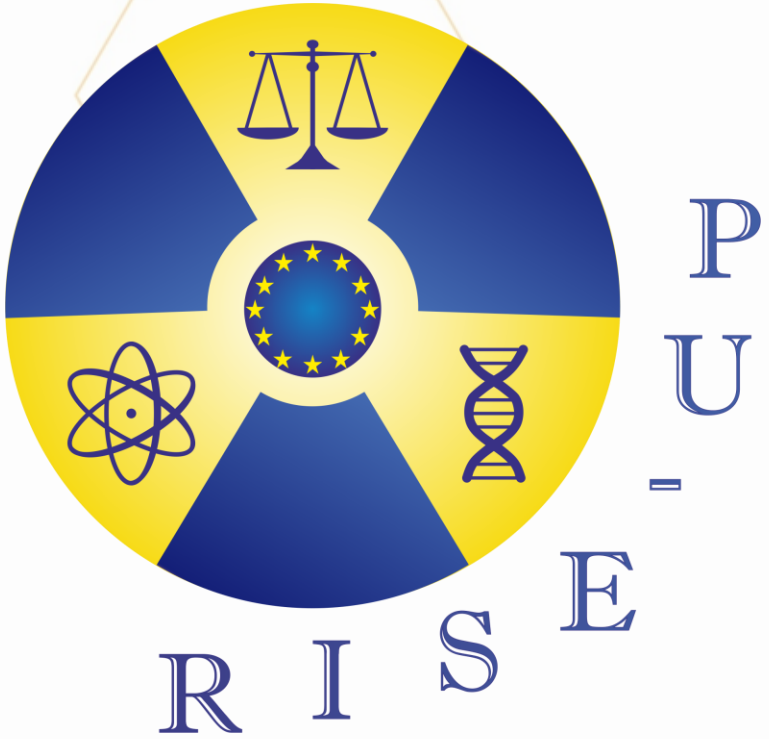
insects

protozoa

bacteria

Less radiosensitive

Species	LD-50 (rad)	Species	LD-50 (rad)
amoeba	ca. 100,000	guinea pig	200-400
paramecium	ca. 300,000	pig	275-400
ctenophore	ca. 1,200	goat	350
snail (Radix)	2,000	dog	325-365
snail (thais)	17,000	laboratory mouse	400-600
cockroach	10,000	cattle	534
beetle (Tribolium)	ca. 100,000	monkey	500-600
fruit fly (Drosophila)	ca. 100,000	burro	585-785
wasp (Bracon)	ca. 300,000	hamster	610-725
salmon	1,500	man	250-500
swordtail	1,000	rabbit	750-825
goldfish	670-800	laboratory rat	600-800
“frog”	700	bobcat	ca. 500
“newt”	1,500-3,000	raccoon	ca. 600
turtle	850-1,500	gray fox	ca. 700
“snakes”	300-400	opossum	ca. 750
lizard	1,200-2,000	wild mouse	1125
pigeon	2,000-3,160	harvest mouse	1130
parakeet	ca. 2,300	cotton rat	1200
chicken	600-1,630	pocket mouse	1200-1300
canary	1,015	bat	ca. 15,000



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