General Pathology - Etiology

Prof. Enrico De Smaele

Lab. Molecular Oncology
Department of Experimental Medicine
Email enrico.desmaele@uniroma1.it

Meets the students: by appointment (e-mail), preferencially videoconference

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The scope of General pathology

1. The core of pathology:

The four aspects of a disease process that form the core of pathology :

(1) Etiology: causes of the disease

(2) Pathogenesis: the mechanisms of its development

(3) Morphological changes: the structural alteration induced in the cells and organs of the body.

(4) Clinical significance: the functional consequences of the morphologic changes.

General Pathology is at the origin of the scientific medicine

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Without Pathology

Diseases could be characterized merely by a group of clinical symptoms:

- **limited understanding of the causes of the diseases**
- **No understanding of the mechanisms of the diseases**

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Julius Friedrich Cohnheim
(1839 -1884)

"I do not expect that any of you have visited already the hospital sections. On the contrary, I believe I can promise you that the study of the physiology of the diseases (i.e. pathology) will give you the best training and the best introduction to the clinical studies.

"You will be given the possibility to understand many things, that otherwise you will only memorize without understanding"

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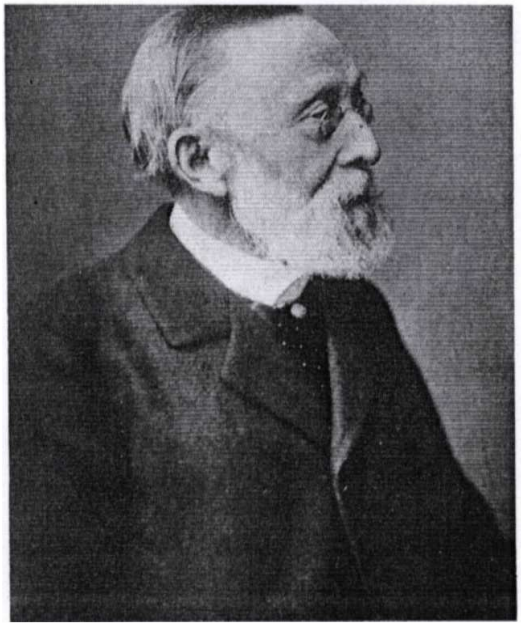
Rudolf Virchow (1821-1902)



one of the 19th century's foremost leaders in medicine and pathology

"a whole organism does not get sick—only certain cells or groups of cells"
He encouraged his students to use microscopes and "think microscopically".

"**all diseases involve changes in normal cells, that is, all pathology ultimately is cellular pathology**."

Diseases could be characterized not merely by a group of clinical symptoms but by typical anatomic changes.

Emerg Infect Dis. 2008 14(9): 1480–1481.

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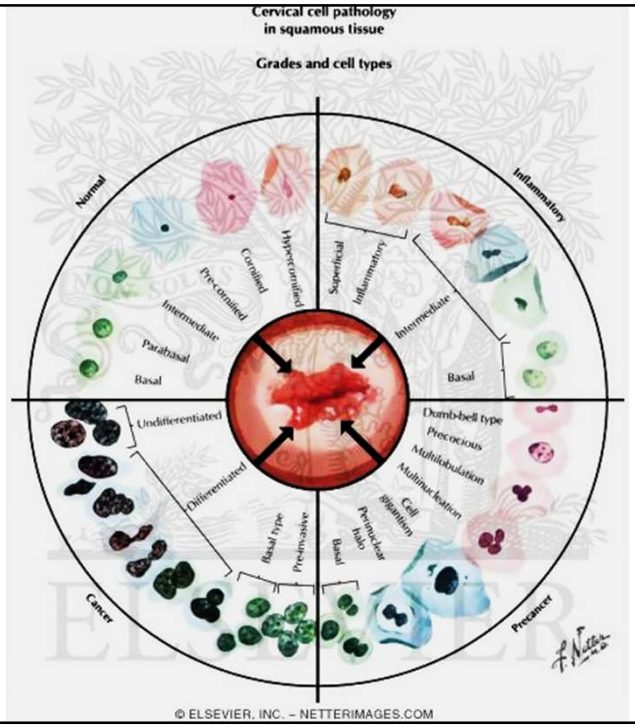

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Short History of Pathology

Autopsy → Organ pathology (1761)

↓

Light Microscopy→ Cellular pathology (1854)

↓

Ultrastructural pathology - EM (1960s)

↓

The "boom":

Immunopathology, Molecular pathology,

Genetic pathology, Quantitative pathology..

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Techniques used by General Pathology

1. Human pathology. Sampling:
   - (1) Autopsy
   - (2) Biopsy: surgical or diagnostic pathology
   - (3) Cytology: smear, fine needle aspiration
2. Experimental pathology
   - (1) Tissue and cell culture
   - (2) animal models

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Observation

Gross appearance:

- size, shape
- weight
- color
- consistency
- surface
- edge, section

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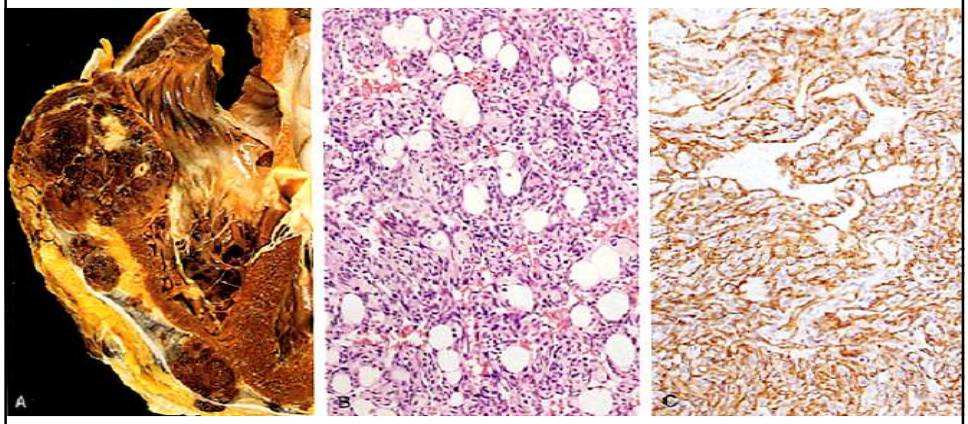
Histological and cytological observation:

most common and basic formalin fixed

→ HE (hematoxylin and eosin) stained



Hemangioma of ventricular wall

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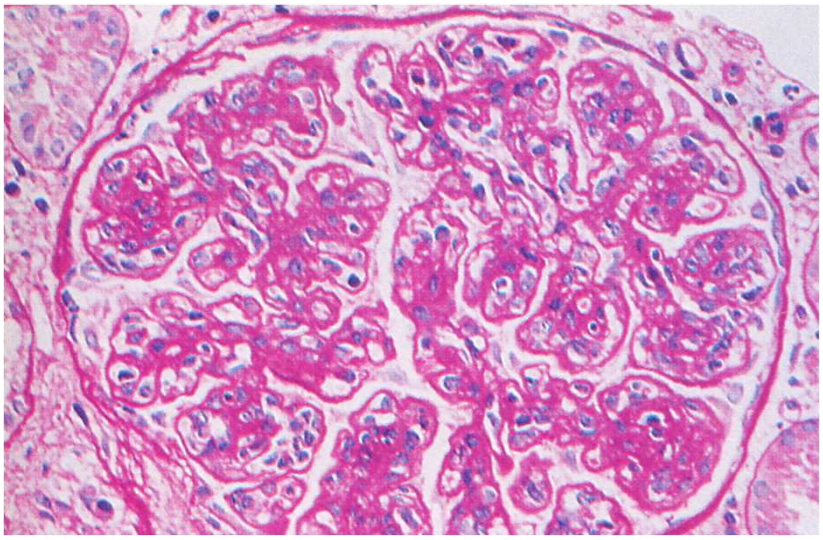
Histochemistry and cytochemistry



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Immunohistochemistry

1. Antigen-Antibody specific reaction
2. Applications:

(1) Localization analysis

cytokeratin →cell membrane

(2) Clinical diagnosis and distinguishing diagnosis by tumor histogenesis

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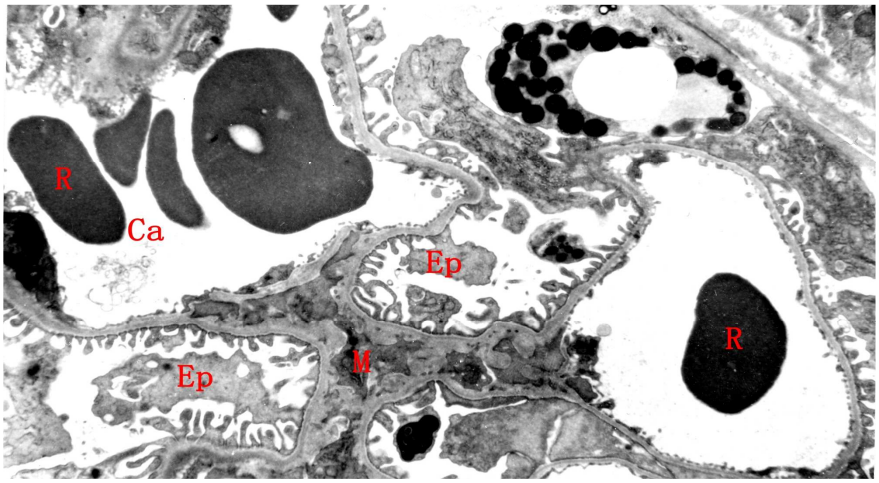
Ultrastructural observation

TEM (transmitting electron microscope)



Filtering membrane

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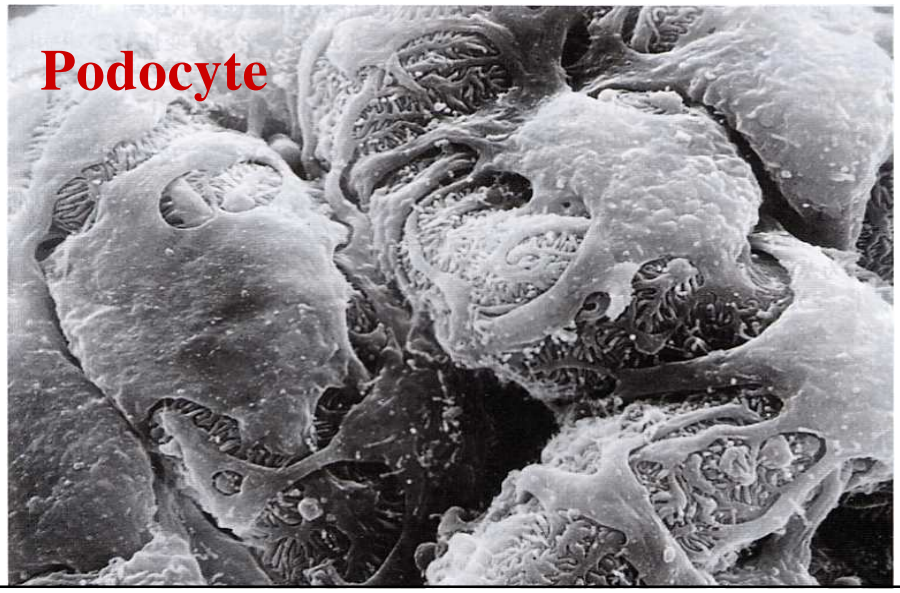
SEM (scanning electron microscope)



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Molecular biology techniques

1. Polymerase chain reaction (PCR)
2. DNA sequencing
3. Biochip technique
   (1) Gene chip (DNA chip) “genomics”
   (2) Protein chip (protein microarray) “proteomics”
   (3) Tissue chip (tissue microarray)

Etc etc..

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General Pathology

Patogenic “agents”

↓

Mechanisms

↓

cellular Stress

↓

cellular Response : ***growth alterations, cell damage, cell death***

↓

Reactions of the tissues: ***inflammatory processes***

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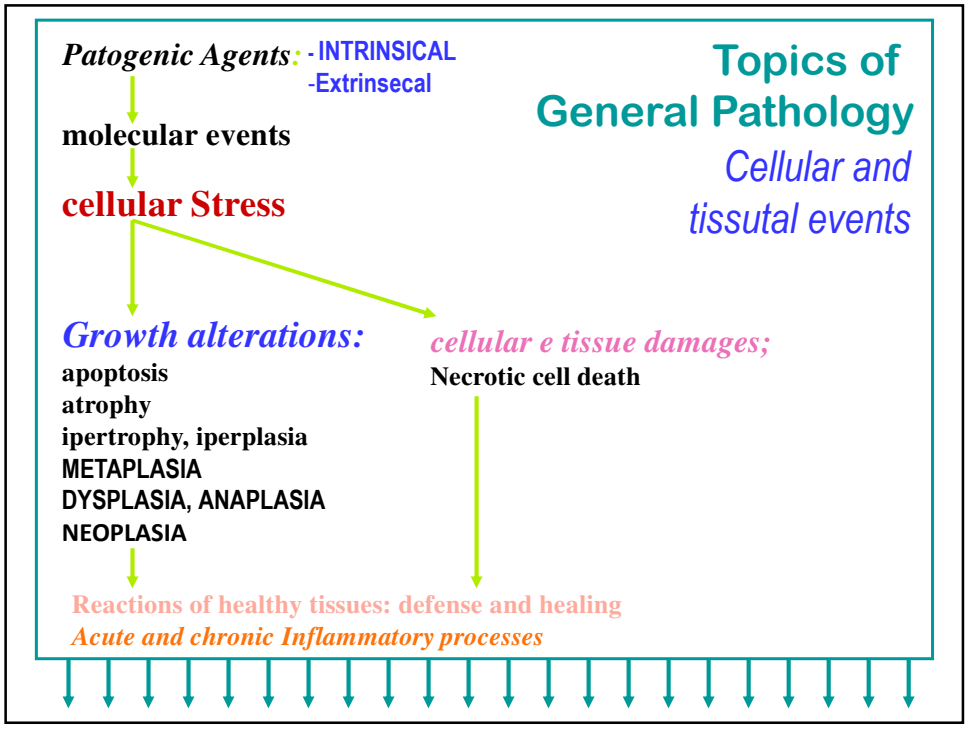
Patogenic Agents: - INTRINSICAL
-Extrinsecal
molecular events
cellular Stress
Topics of
General Pathology
Cellular and
tissutal events
Growth alterations:
apoptosis
atrophy
ipertrophy, iperplasia
METAPLASIA
DYSPLASIA, ANAPLASIA
NEOPLASIA
cellular e tissue damages;
Necrotic cell death
Reactions of healthy tissues: defense and healing
Acute and chronic Inflammatory processes

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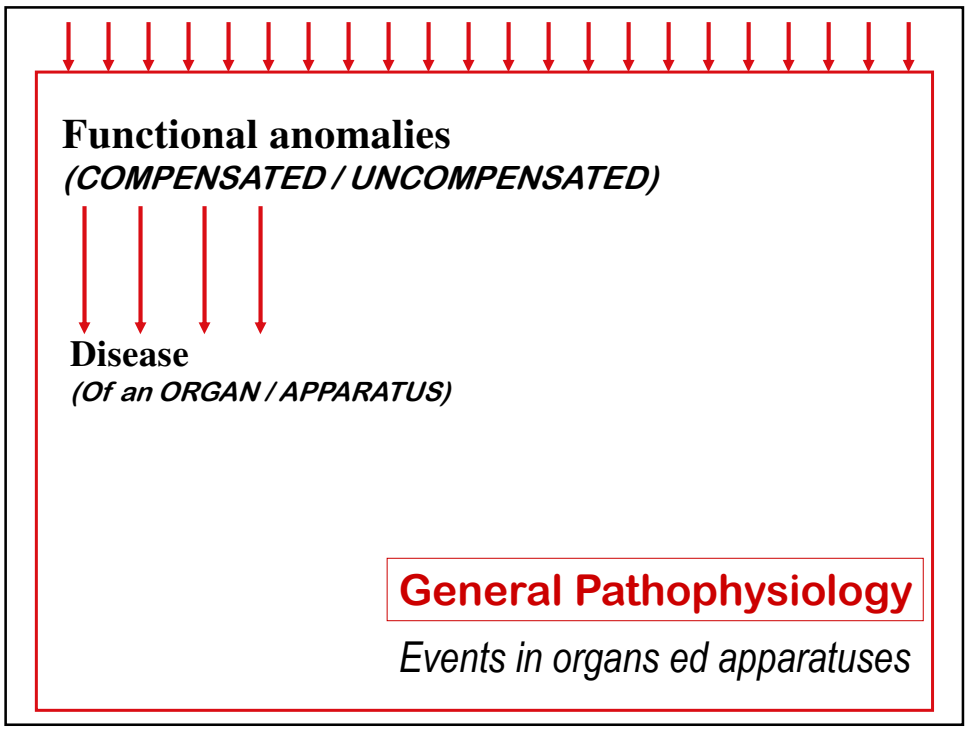
Functional anomalies
(COMPENSATED / UNCOMPENSATED)
Disease
(Of an ORGAN / APPARATUS)
General Pathophysiology
Events in organs ed apparatuses

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What is a Disease?

- **It is a "**State in which an individual exhibits an anatomical, physiological, or biochemical deviation from the normal"

•Disease may be defined as :

an abnormal alteration of structure or function in any part of the body.

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Classification of Diseases:

- **Developmental** – genetic, congenital.
- **Acquired:**

***Inflammatory** – Trauma, infections, immune, etc.

***Neoplastic** – tumors cancers

***Degenerative** – ageing.

***Metabolic**.

***Iatrogenic: Drug induced**.

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Learning General Pathology:

- **General Pathology**
  - Common changes in all tissues. e.g.. Inflammation, cancer, ageing, edema, hemorrhage ….etc.
- **Systemic Pathology**
  - Discussing the pathologic mechanisms in relation to various organ systems e.g. CVS, CNS, GIT…..etc.

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What should we Know About A Disease

- Definition.
- Epidemiology – Where & When.
- Etiology – What is the cause?
- Pathogenesis - Evolution of dis.
- Morphology - Structural Changes
- Functional consequences

Pathology

- Management
- Prognosis
- Prevention

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Pathology focuses on 4 aspects of disease:

- ***ETIOLOGY:*** **Cause of disease.**
- ***PATHOGENESIS:*** **Mechanisms of development of disease.**
- ***MORPHOLOGY:*** **The structural alterations induced in cell and tissues.**
- ***FUNCTIONAL CONSEQUENCES:*** **Functional results of the morphologic changes, as observed clinically.**

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What is Etiology?

Etiology (aitia= cause, logos= speech) is the study of the causes of a specific event.

In the medical field, etiology is the search for the factors that play a role in the origins of the diseases, and the study of the relative relevence and the relationships between them.

We distinguish between Endogenous and exogenous causes.
Very often, diseases do not have a single cause, but a "multiple" etiology: multifactorial diseases the origine and the evolution of the diseases are due to simultaneous or sequential causative events (etiological events).

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Etiology:
"What is the cause?"

- ***Environmental agents:***
  - Physical
  - Chemical
  - Nutritional
  - Infections
- Immunological
  - Psychological
- ***Genetic Factors:***
  - Age
  - Genes

Multifactorial:
e.g. Diabetes, Hypertension, Cancer

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Etiology

Definitions:

- ***An etiologic agent :***

is the factor (bacterium, virus, etc.) responsible for lesions or a disease state.

- ***Exciting Causes of Disease:***

Factors which are directly responsible for a disease (hypoxia, chemical agents…. etc.).

- ***Predisposing Causes of Disease:***

Factors which make an individual more susceptible to a disease (damp weather, poor ventilation, etc.)

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Etiology

•One etiologic agent ⟶ one disease, as Malaria.

• Several etiologic agents ⟶ one disease, as diabetes .

• One etiologic agent ⟶ several diseases, as smoking.

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Etiology

"Study of the cause of a disease"

Knowledge of *etiology* remains the backbone of:

- **Disease *diagnosis***
- **Understanding *the nature of diseases***
- ***Treatment* of diseases.**

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pathogenesis

The sequence of events in the response of the cells or tissues to the etiologic agent, from the initial stimulus to the ultimate expression of the disease, "from the time it is initiated to its final conclusion in recovery or death"

The core of the science of pathology — the study the pathogenesis of the disease.

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Environmental Pathology

- It deals with pathology due to exogenous (external) agents (a.k.a. extrinsical causes)

- Main classification of the exogenous agents:
  - physical (characteristics of the physical environment)
  - chemical
  - biological

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Patology by physical agents

Energy transfers:

Energy coming from external sources:

radiations, heat

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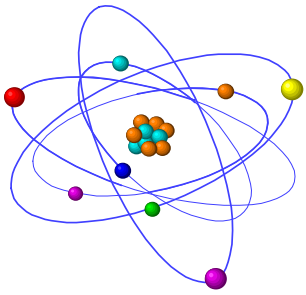
Radiations

- "Radiation is an energy in the form of electro-magnetic waves or particulate matter, traveling in the space."



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Radioactivity

- If a nucleus is unstable for any reason, it will emit and absorb particles and energy.
- There are many types of radiation and they are all pertinent to everyday life, health as well as nuclear physical applications.

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Radiations' sources

- All earth surface system components emit radiation---the sun and the earth are the components we are most interested in.
- The sun emits radiation composed of high energy infrared radiation, visible light, and ultraviolet radiation collectively known as shortwave radiation (SW).
- The earth emits radiation composed of lower energy infrared radiation collectively known as long-wave radiation (LW).

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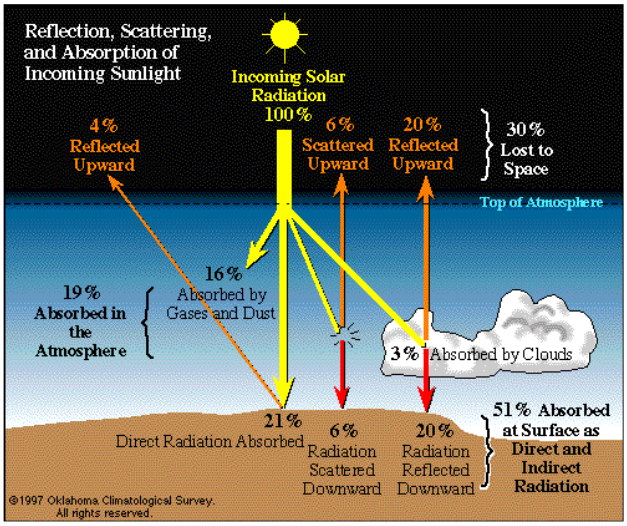
Path of incoming solar radiation



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Radiation from Natural Sources

Source	mrem/year
Cosmic rays	28
The earth	26
Radon	200
The human body	25
Building materials	4

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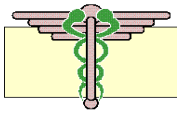
Radiation from Manmade Sources

	Source	mrem/year
	Medical	90
	Fallout	5
	Consumer products	1
	Nuclear power	0.3

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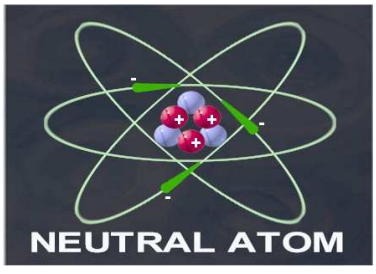
Basic Model of a Neutral Atom.

Atoms are composed of smaller particles referred to as:

- **Electrons** (-) orbiting around a nucleus of **protons** (+) and **neutrons**. Same number of electrons as protons; net charge = 0.

Atomic number (number of protons) determines element.

Mass number (protons + neutrons)



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Radiations can be divided, based on their characteristics, in:

Corpuscular radiations:
energy that propagates in the form of kinetic energy possessed by 'elementary particles of the atom' in motion:
- positively charged (protons),
- no charge (neutrons)
- α e β particles (α and β rays) that are emitted by the disintegration of unstable nuclei of certain atoms as the product of radioactive decay.

Electromagnetic radiations:
energy that propagates without mass in the form of disturbance of an electromagnetic field, and sheds finished energy packets called photons (gamma- rays, X-rays, infrared, UV, visible light)

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Ionizing versus Non-ionizing Radiation

According to the energy levels, radiations have different effects at the atomical level.

- **Ionizing Radiation**
  - Higher energy electromagnetic waves (gamma o x) or heavy particles (beta and alpha).
  - High enough energy to pull electron from orbit, with formation of ions (primary ionization).

- **Non-ionizing ("exciting") Radiation**
  - Lower energy electromagnetic waves.
  - Not enough energy to pull electron from orbit, but can excite the electron.

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IONIZING Radiations:
High energy radiations ⇒ Energy≥ 10 eV (elettronVolt)

-Radiazioni corpuscolate
- γ e X Rays

Non Ionizing Radiations : Energy<10 eV
Lower energy determins shift of electrons in a more external orbital 8higher energy state), with high instability. :

-Infrared Radiations
- Visible Light
- UV Rays

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Non-ionizing Radiation

- Definition:

" They are electromagnetic waves incapable of producing ions while passing through matter, due to their lower energy."

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Examples on Non-ionizing Radiation Sources

- Visible light
- Microwaves
- Radios
- Video Display Terminals
- Power lines
- Radiofrequency Diathermy (Physical Therapy)
- Lasers

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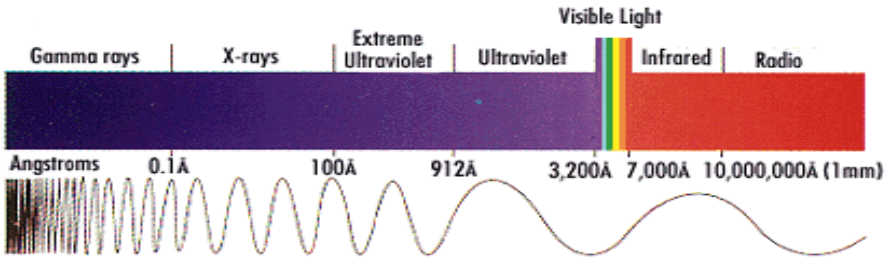
- The electro-magnetic waves vary in their length and frequency along a very wide spectrum.



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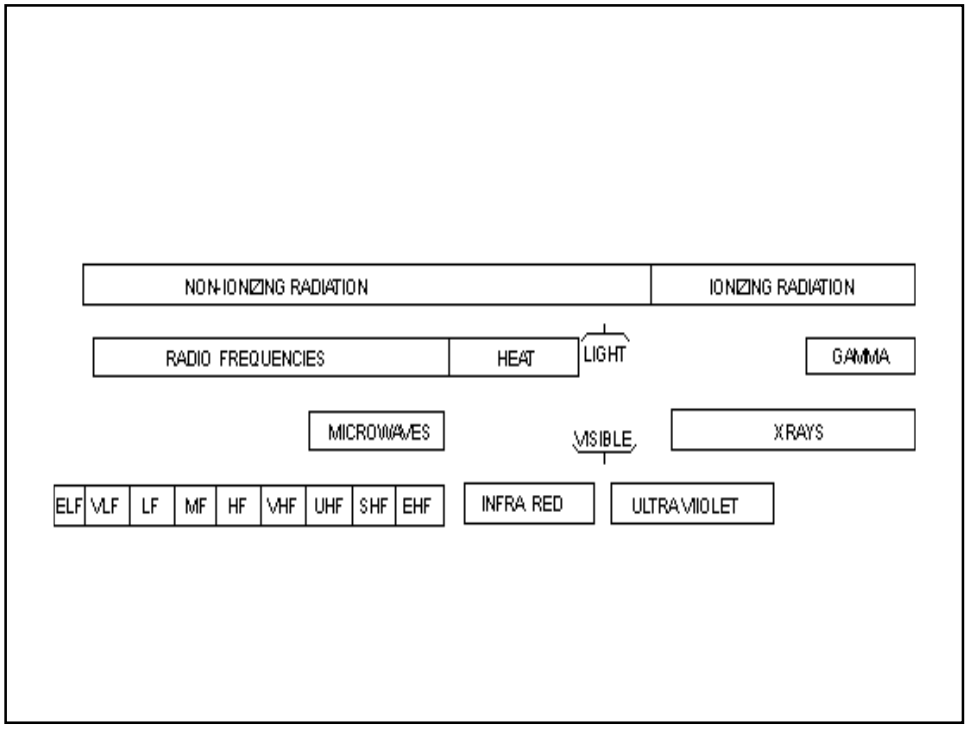
NON-IONIZING RADIATION
IONIZING RADIATION
RADIO FREQUENCIES
HEAT
LIGHT
GAMMA
MICROWAVES
VISIBLE
XRAYS
ELF
VLF
LF
MF
HF
VHF
UHF
SHF
EHF
INFRA RED
ULTRAVIOLET

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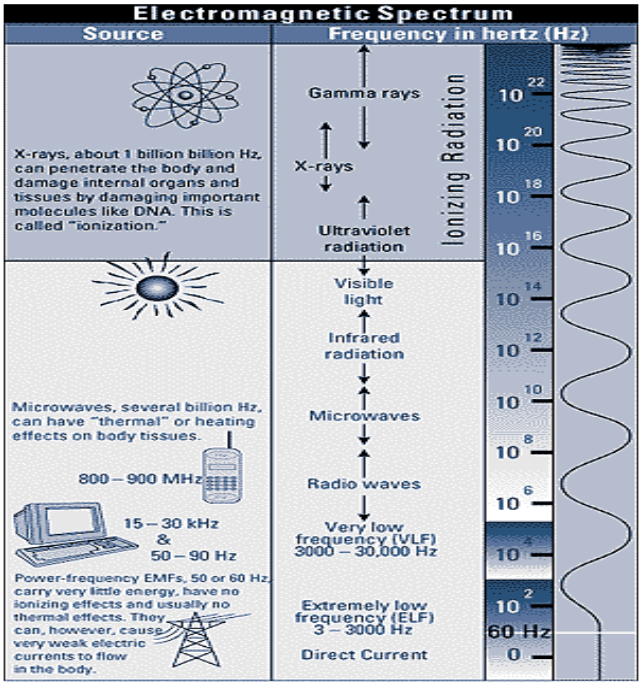
Electromagnetic Spectrum
Source
Frequency in hertz (Hz)
X-rays, about 1 billion billion Hz, can penetrate the body and damage internal organs and tissues by damaging important molecules like DNA. This is called "ionization."
Gamma rays
X-rays
Ultraviolet radiation
Ionizing Radiation
Visible light
Infrared radiation
Microwaves
Radio waves
Very low frequency (VLF) 3000 – 30,000 Hz
Extremely low frequency (ELF) 3 – 3000 Hz
Direct Current
Microwaves, several billion Hz, can have "thermal" or heating effects on body tissues.
800 – 900 MHz
15 – 30 kHz & 50 – 90 Hz
Power-frequency EMFs, 50 or 60 Hz, carry very little energy, have no ionizing effects and usually no thermal effects. They can, however, cause very weak electric currents to flow in the body.
10 22
10 20
10 18
10 16
10 14
10 12
10 10
10 8
10 6
10 4
10 2
60 Hz
0

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Potential Radio Waves Effects

- **Radiofrequency Ranges (10 kHz to 300 GHz)**
  - **Effects only possible at ten times the permissible exposure limit**
  - **Heating of the body (thermal effect)**
  - **Cataracts**
  - **Some studies show effects of teratogenicity and carcinogenicity.**

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EFFECTS OF EXCITING RADIATIONS (<10eV) (UV, IR, luminose):

THERMAL EFFECT (InfraRed)
(radiations absorbed by dark bodies and melanin)

PHOTOCHEMICAL REACTIONS (Light radiations)

Visible light is used for degradation of bilirubin in newborns . I fluorescent blue light (420-480 nanometers) is absorbed by bilirubin (is a yellow compound that adsorbes light at 453 nm wavelenght)

It is adsorbed by: (UV)
-nucleic acids (purins, Adenine e Guanine) (265 nm)
-proteins (280 nm)

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UV effects

- **Bacteria inactivation** (sterilization by UV lamps),
- **Inhibition of cellular division,**
- **mutations,**
- **Cell death,**
- **tumor**

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UV radiations on superficial tissues (Cute)

Biochemical effect: they transform 7-dehydrocholesterol in vitamin D3

Molecular effects:

1. Protein denaturation and enzymes inactivation
2. Thymin Dimers formation in the DNA chains
3. Peroxidation of the lipids in the membranes.

Adsorbed radiation:

-Eritema (inflammation, hyperemia)
-↑ capillary permeability
-Edema
-Necrosis
-Ipercheratosis

Cheratins are present in the skin that adsorbe most of the UV radiations, protecting the deeper layers of tissue. Similarly acts melanins.

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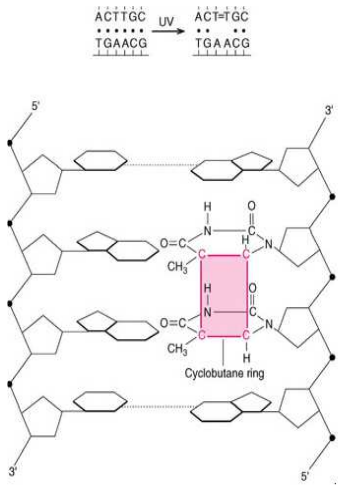
Thymin dimers induced by UV light



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Ionizing radiations

Ionizing radiation is produced by unstable atoms. Unstable atoms differ from stable atoms because they have an excess of energy or mass or both.

Unstable atoms are said to be radioactive.

In order to reach stability, these atoms give off, or emit, the excess energy or mass. These emissions are called radiation.

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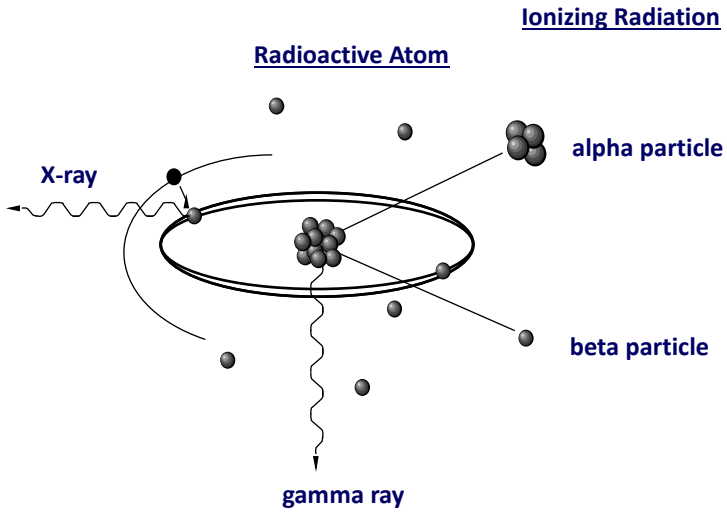
Types or Products of Ionizing Radiation



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Ionizing Radiations

A radiation is said to be ionizing when it has enough energy to eject one or more electrons from the atoms or molecules in the irradiated medium.

" It is a type of radiations that is able to disrupt atoms and molecules on which they pass through, giving rise to ions and free radicals".

This is the case of alpha and beta radiations, as well as of electromagnetic radiations such as gamma radiations, X-rays and some ultra-violet rays.

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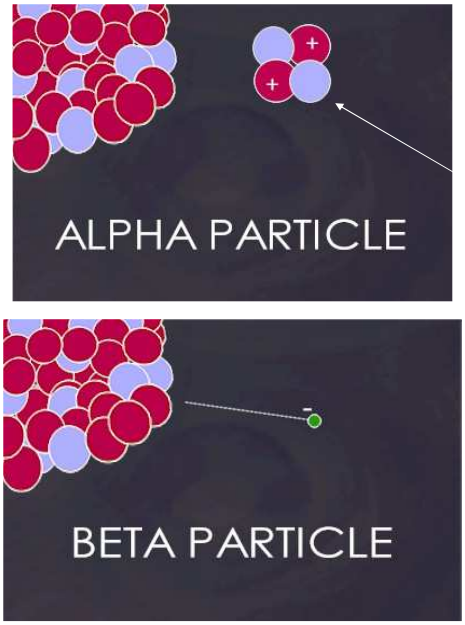

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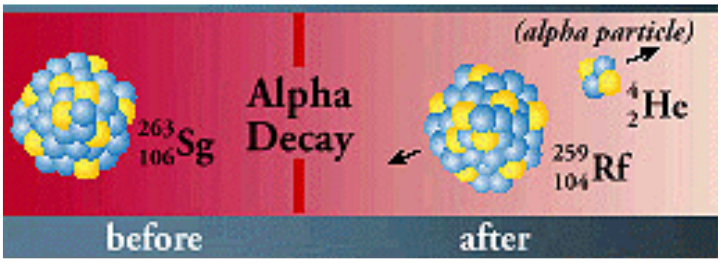
Alpha Particles

Composed by 2 neutrons and 2 protons. 2 positive charges. They travel short distances, have large mass- do not penetrate tisses - only a hazard when inhaled



Typical Energy = 4-8 MeV (million electronvolt); **Limited range** (<10cm in air; 60µm in tissue); High LET (linear energy transfer) causing **heavy damage** (4K-9K ion pairs/µm in tissue).

Easily shielded (e.g., paper, skin) so an **internal radiation** hazard.

Eventually lose too much energy to ionize; become He.

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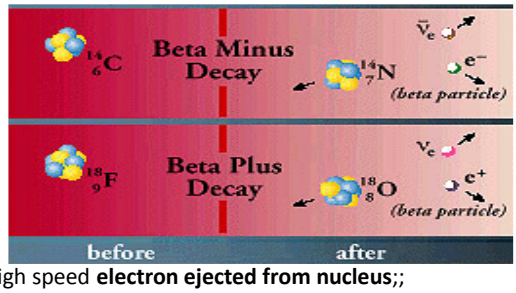
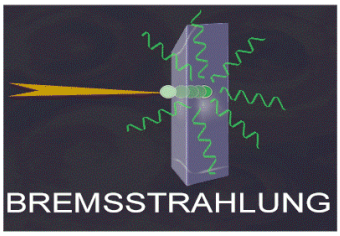
Beta Particles:

Electrons having small mass and variable energy. Electrons form when a neutron transforms into a proton and an electron or viceversa 8in this case we have a positron (positive charge; it behaves similarly):





High speed **electron ejected from nucleus**;;

Typical Energy = several KeV to 5 MeV; Range depends on energy: about 4 meters/MeV in air, 0,5 cm/Mev in H2O, a few mm in tissue;

Low LET causing **light damage** (6-8 ion pairs/µm in tissue).

Primarily an internal hazard, but high beta can be an external hazard to skin.

In addition, the high speed electrons may lose energy in the form of X-rays when they quickly decelerate upon striking a heavy material. This is called **Bremsstralung** (or Breaking) **Radiation.** Aluminum and other light materials are used for shielding.

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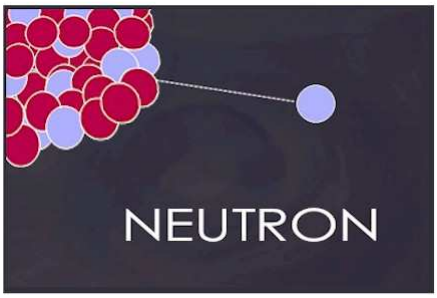
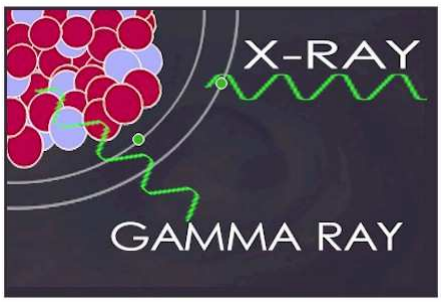


Neutrons: Have the same mass as protons but are uncharged



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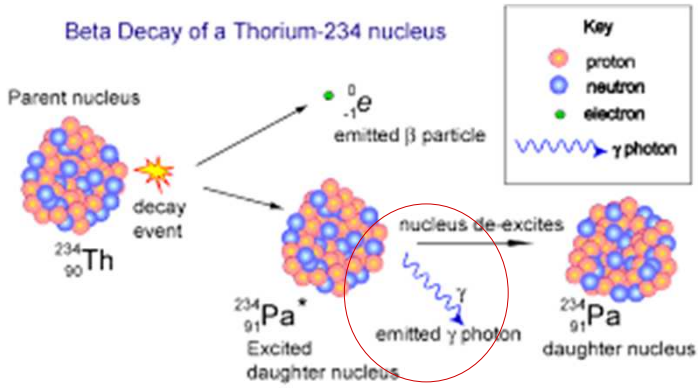
Gamma Rays

Gamma rays are photons emitted **from the nucleus**, often as part of radioactive decay. Gamma rays typically have higher energy than X-rays.

They result when the nucleus releases energy, usually after an alpha, beta or positron transition



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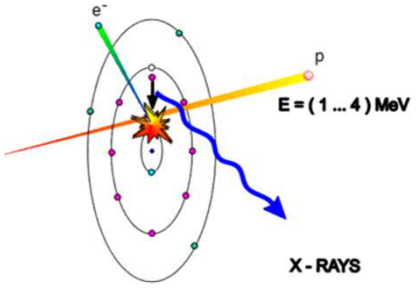
X-Rays

X-rays are photons (Electromagnetic radiations) emitted **from electron orbits**.

X-Rays occur whenever an inner shell orbital electron is removed (i.e. by collision with a proton) and rearrangement of the atomic electrons results with the release of the elements characteristic X-Ray energy

The proton will knock an electron out of one the inner electron shells. This is depicted in the picture as the pink proton flies off in one direction and the green electron goes in the other. After this event an electron will jump down from higher electron shell to the lower one. This releases energy in the form of x-rays.



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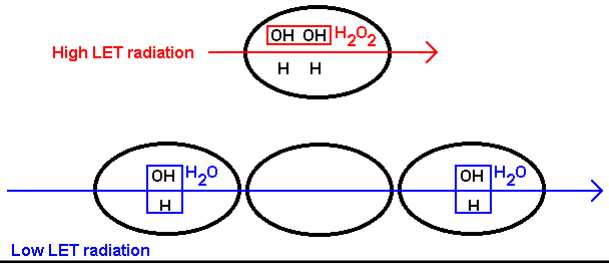
Energy transfer and ionization

LET (linear energy transfer) is the amount of energy released by a radioactive particle or wave over the length of its decay track. Specific Ionization is the number of ion pairs produced per unit track length.

High LET radiation (like **alpha** & **beta particles**) ionizes water into **H** and **OH** radicals over a very short track. In the example, two events occur in a single cell so as to form a pair of adjacent **OH** (hydroxyl) radicals that recombine to form **peroxide**, **H2O2**, which can produce oxidative damage in the cell.

Low LET radiation (like **X-** or **gamma rays**) also ionizes water molecules, but over a much longer track. In the example, two events occur in separate cells, such that adjacent radicals are of the opposite type: the **H** and **OH** radicals reunite and reform **H2O**.



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EFFECTS OF RADIATIONS
at cellular/molecular level

primary (direct) Effects:

Direct effects of radiations on the elements (atoms, molecules) composing cellular structures: excitation and ionization.

Secondary (indirect) Effects:

Raising of the temperature of the target molecules

Triggering of chemical reactions (induced by charged molecules, water ioniziation etc)

The consequences are structural alterations of the Cells:

- Molecular alterations
- Biochemical alterations
- Alterations in function of structure/cell :

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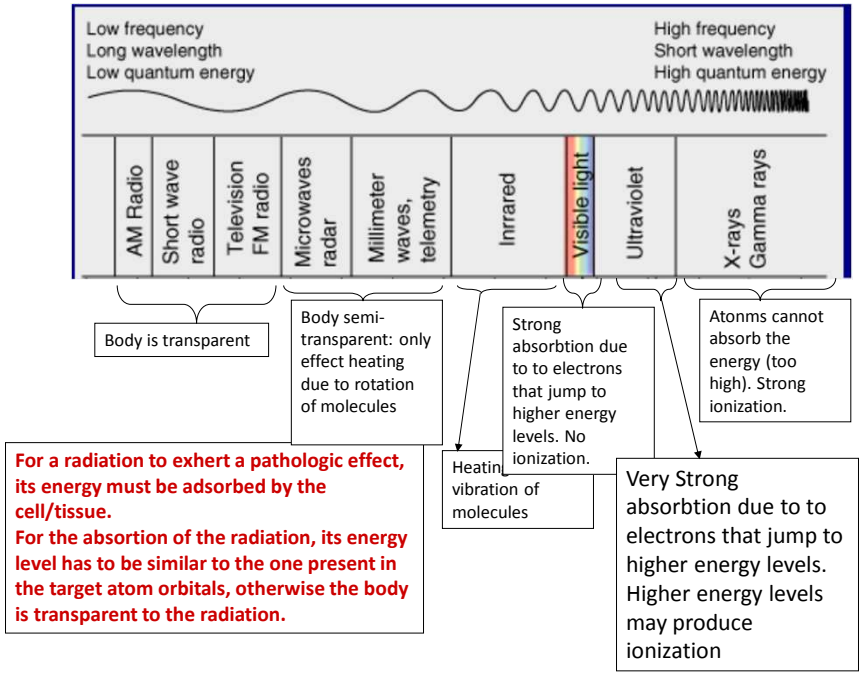

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Primary effects:

direct energy transfer to cell constituents whose atomes are ionized.
Modification of the intramolecular distribution of electric charges, which in turn lead to changes in structures and conformations:

proteins (denaturation)
- breakage of disulfide bonds
- breakege of hydrogen bonds
- variation in the chemical-physical properties of the proteins (viscosity, electric conducibility, etc)

nucleic acids (degradation)
- damage to the double strand DNA (high energy transfer) leads to degradation of the molecule
- damage to the single strand: the broken end presents afree radical which may bind another free end with a free radical of the opposite charge, generating cross linking of the DNA molecules

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Secondary effects:

-**free radicals production (atoms or molecules that have a single electron in the most external orbital):**

INSTABILE
Highly reactive
They tend to activate chain reactions

Free radicals are formed when the energy from the radiation is sufficient to break the covalent bond between two atoms, and one electron remain attached to one of the two separated entities, leaving the other with a missing electron.

$H_2O \longrightarrow H_2O^+ + e^-$ $\qquad$ $H_2O \longrightarrow H^* + OH^*$

$H_2O^+ + H_2O \longrightarrow H_3O^+ + OH^*$ (aqueous cation plus Hydroxyl radical)

$OH^* + OH^* \longrightarrow H_2O_2$ (Hydrogen peroxide)

$OH^* + S^+ \longrightarrow OH^- + S^+$ (oxidized organic compound)

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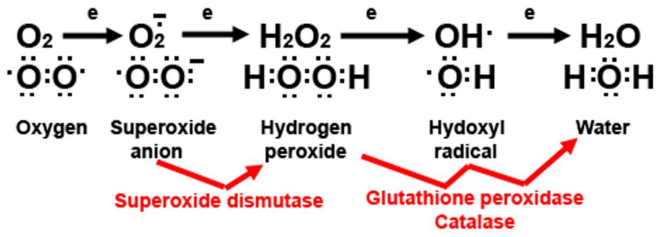
Formation and Elimination of Reactive Oxygen Species (ROS)



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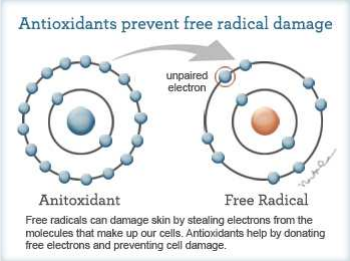
Defence from free radicals:



Meccanismi di difesa sono:

ENZIMI ANTIOSSIDANTI come la superossido dismutasi, la catalasi, la glutatione perossidasi, che eliminano i due reagenti principali, il radicale superossido ed il perossido di idrogeno

SOSTANZE ANTIOSSIDANTI

Possono bloccare le reazioni di innesco dei radicali oppure inattivare (scavengers) i radicali (ad es: Glutatione, Vitamine A, C, E…)

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EFFETTI BIOLOGICI delle radiazioni a livello cellulare

Variabili in base all'organismo preso in considerazione (ad es: batteri → blocco sintesi proteica → morte).

- Globuli rossi → emolisi
- mitocondri → rigonfiamento
- lisosomi→ ↑ permeabilità ⇒ disintegrazione ⇒ liberazione enzimi
- DNA → blocco replicazione (mutageni, sostituzione di 1 o + basi. Attivazione di enzimi riparatori)
- proteine → denaturazione
- Acidi Grassi → perossidazioni e radicali liberi ad azione ossidante

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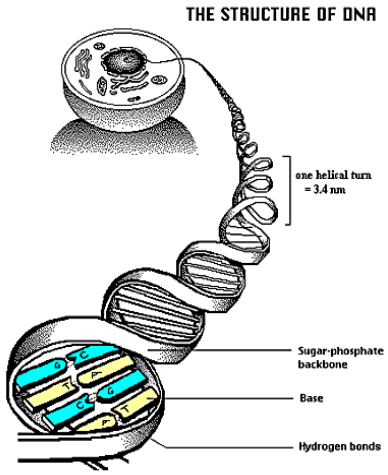
Ionizing Radiation at the Cellular Level

- Causes breaks in one or both DNA strands or;
- Causes Free Radical formation



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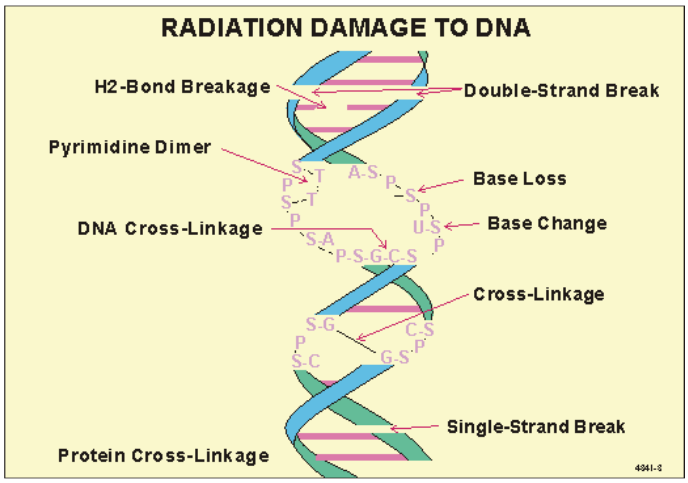

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Sistemi di riparazione del DNA

Meccanismi diretti

-Restaurazione immediata dell'integrità del DNA per correzione dell'alterazione strutturale senza rimozione dei siti distorti

Meccanismi indiretti

-Quattro sistemi enzimatici

- NER (nucleotide excision repair)
- BER (Base excision repair)
- MMR (Mismatch repair)
- MGMT (O6-metilguaninaDNAmetiltransferasi)

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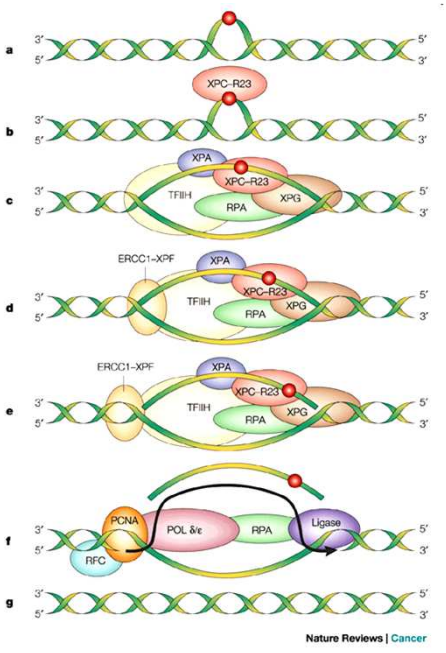
NER (nucleotide Excision Repair)

Meccanismo riparativo più importante, con eliminazione dei danni causati dalla dimerizzazione di pirimidine, dall'alchilazione delle basi, dalla formazione di legami crociati e di addotti di vario tipo.

1) Endonucleasi di riconoscimento individuano l'oligonucleotide alterato in una delle eliche
2) Elicasi srotolano il sito danneggiato
3) Endonucleasi di incisione tagliano i due estremi del sito distorto
4) Endonucleasi di rimozione distruggono il sito del danno lasciando l'interruzione
5) DNA-polimerasi sintetizza un frammento della stessa lunghezza di quello asportato usando come stampo il filamento omologo
6) DNA-ligasi inserisce il materiale di nuova sintesi nella parte di DNA interrotta.



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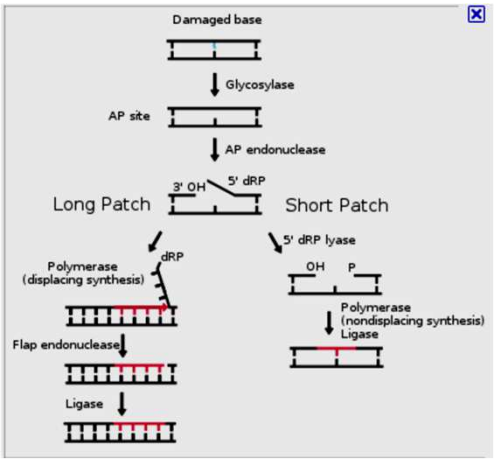
BER (Base Excision Repair)

1) DNA-glicosilasi stacca la base alterata dal deossiribosio
2) Endonucleasi rimuove il pentoso
3) Fosfodiesterasi rimuove il nucleotide senza base lasciando un'interruzione
4) DNA-polimerasi sintetizza un frammento della stessa lunghezza di quello asportato usando come stampo il filamento omologo
5) DNA-ligasi inserisce il materiale di nuova sintesi nella parte di DNA interrotta.



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MMR (Mismatch Repair)

Rimuove e sostituisce nucleotidi non complementari incorporati nel DNA per un errato appaiamento

MGMT(O6-metilguaninaDNAMetiltrasferasi)

Rimuove i gruppi alchilici donati dalle sostanze alchilanti

(gruppo alchile è un alcano (composto organico costituito da C e H: es butano, metano, propano) privo di un atomo di idrogeno e quindi estremamente reattivo

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Effects of radiations at tissue level

- tissue Vulnerability to DNA damages induced by radiation depends on the proliferative state, which is correlated with the life span of the cells and their frequency of replication.

-Labile Tissues +sensitive (+nuclear effects)
(Bone marrow, gonads, neoplastic cells ⇒ therapy(!))

_stabili Tissues +/- sensitive
(liver, kidney, glandular epithelia)

_Perennial Tissues - sensitive (>effects on cytoplasmic organelles)
(neurons and muscle cells)

Consequences can be:
- Inflammation
- Necrosis
- Mutations - neoplasia

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Ionizing radiations

- **HEALTH EFFECTS**
- *Generalizations:* Biological effects are due to the ionization process that destroys the capacity for cell reproduction or division or causes cell mutation. A given total dose will cause more damage if received in a shorter time period. A **fatal dose is (600 R)**

- *Acute Somatic Effects*: Relatively immediate effects to a person acutely exposed. Severity depends on dose. Death usually results from damage to bone marrow or intestinal wall. Acute **radio-dermatitis** is common in radiotherapy; chronic cases occur mostly in industry.

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- *Critical Organs*:
- Organs generally most susceptible to radiation damage include: Lymphocytes, bone marrow, gastro-intestinal, gonads, and other fast-growing cells.
- The central nervous system is relatively resistant.
- Many nuclides concentrate in certain organs rather than being uniformly distributed over the body, and the organs may be particularly sensitive to radiation damage, e.g., isotopes of iodine concentrate in the thyroid gland. These organs are considered "critical" for the specific nuclide.

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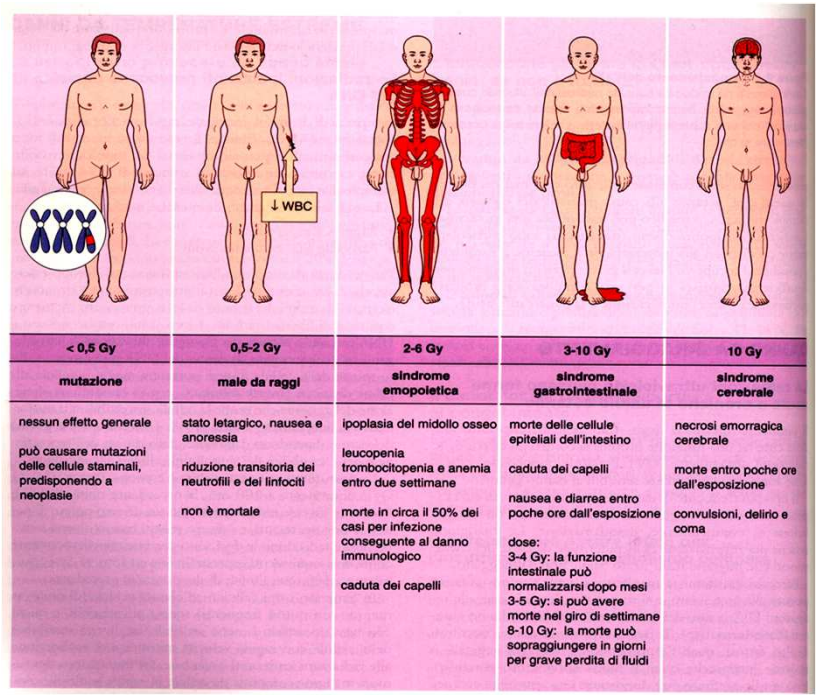

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Pan-Irradiation (whole body irradiation). Ionizing Radiation

Dosage (RADs)	ACUTE Exposure EFFECTs:
0-25	No observable effect.
25-50	Minor temporary blood changes.
50-100	Possible nausea and vomiting and reduced WBC.
150-300	Increased severity of above and diarrhea, malaise, loss of appetite.
300-500	Increased severity of above and hemorrhaging, depilation. Death may occur
> 500	Symptoms appear immediately, then death occurs.

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Pan Irradiation: Delayed effects

- *Delayed Somatic Effects*: Delayed effects to exposed person include: Cancer, leukemia, cataracts, life shortening from organ failure, and abortion. Probability of an effect is proportional to dose (no threshold). Severity is independent of dose. Doubling dose for cancer is approximately 10-100 rems.
- *Genetic Effects*: Genetic effects to off-spring of exposed persons are irreversible and nearly always harmful. Doubling dose for mutation rate is approximately 50-80 rems. (Spontaneous mutation rate is approx. 10-100 mutations per million population per generation.)

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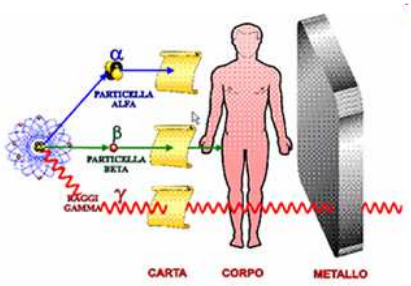
How far can the radiations go?

It depends on the caracteristics of the radiations (mass and energy) and of the body hit

The lenght that can be penetrated is called RANGE
-Normally the charged particles loose a lot of energy during their path
-Big particles have low penetration capability

-I alfa rays/particles have positive charge, and are blocked by a sheet of paper and can be redirected by magnetic fields.
-I beta rays (+ o -) can be blocked by aluminum foil
-I gamma rays are not deviated by magnetic fields and are blocked only by thick layers of lead or concrete walls



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QUANTIFICATION OF RADIATION

Two purposes:

- A. Quantifying Radioactive Decay
- B. Quantifying Exposure and Dose adsorbed

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A. Quantifying Radioactive Decay

Measurement of **Activity** in disintegrations per second (dps);

- 1 **Becquerel** (Bq) = 1 dps;
- 1 **Curie** (Ci) = 3.7 x 10^{10} dps;
- Activity of substances are expressed as activity per weight or volume (e.g., Bq/gm or Ci/l).

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B. Quantifying Exposure and Dose

- Exposure: **Roentgen** 1 Roentgen (R) = amount of **X or gamma** radiation that produces ionization resulting in 1 electrostatic unit of charge in 1 cm^3 of dry a**ir**. Instruments often measure exposure rate in mR/hr.

- Absorbed Dose: **rad** (Roentgen absorbed dose) = absorption of 100 ergs of energy from **any radiation** in 1 gram of **any material**; 1 **Gray** (Gy) = 100 rads = 1 Joule/kg; Exposure to 1 Roentgen approximates 0.9 rad in air.

- Biologically Equivalent Dose: **Rem (Roentgen equivalent man) = dose in rads x QF**, where QF = quality factor. 1 **Sievert** (Sv) = 100 rems. Quantities measured in rem are designed to represent the stochastic biological effects of ionizing radiation, primarily radiation-induced cancer. These quantities are a complex weighted average of absorbed dose, which is a clear physical quantity measured in rads. There is no universally applicable conversion constant from rad to rem. Rem is defined since 1976 as equal to 0.01 sievert

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Your Annual Exposure

Activity	Typical Dose
Smoking	280 millirem/year
Radioactive materials use in a lab	**<10 millirem/year**
Dental x-ray	10 millirem per x-ray
Chest x-ray	8 millirem per x-ray
Drinking water	5 millirem/year
Cross country round trip by air	5 millirem per trip
Coal Burning power plant	0.165 millirem/year

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Exposure Limits

- *OSHA Limits:* Whole body limit = 1.25 rem/qtr or **5 rem (50 mSv) per year.**
- Hands and feet limit = 18.75 rem/qtr.
- Skin of whole body limit = 7.5 rem/qtr.
- Total **life accumulation = 5 x (N-18) rem where N = age**. Can have 3 rem/qtr if total life accumulation not exceeded.
- Note: New recommendations reduce the 5 rem to 2 rem.

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External/Internal Exposure Limits for Occupationally Exposed Individuals

Annual Dose Limits

	Adult (>18 yrs)	Minor (< 18 yrs)
Whole body*	5000 mrem/yr	500 mrem/yr
Lens of eye	15000 mrem/yr	1500 mrem/yr
Extremities	50000 mrem/yr	5000 mrem/yr
Skin	50000 mrem/yr	5000 mrem/yr
Organ	50000 mrem/yr	5000 mrem/yr

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Organ Radiation Pathology

88

Types of Changes

- Acute tissue injury
- Chronic tissue injury
- Seen in both early and late responding tissues.
  Degree of change evident is different

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Acute Tissue Changes

- Acute changes are typically inflammatory
  - Erythema
  - Edema
  - Dry > moist desquamation
  - Hemorrhage
  - Necrosis
- Changes are the result of cells dying in the tissues within the radiation field.
- Cellular death attracts inflammatory cells
  - Radiation injury of these cells further exacerbates the inflammation.
- Severity proportional to the dose received
- Inversely proportional to time span of dose
- Other sources of trauma such as abrasion and infection will increase severity

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Acute Tissue Changes

- Following the acute changes there are two possible outcomes.
  - Regeneration - Replacement of the cells lost by cells of the same type.
    - May be complete or partial and is commonly seen in rapidly dividing cell lines and those arising from blast cells
    - Generally is a low dose phenomenon but may occur in some tissues at relatively high doses.
    - Influenced by the response of other cells in the area (critical cells)

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Acute Tissue Changes

- Following acute tissue injury the tissue may also undergo replacement.
  - Original cell population replaced by different population – usually fibroblasts
  - Results in permanent loss of the original cell population and its function.
  - Occurs in tissues with long cell cycle times
  - Tends to occur more commonly at high doses

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Chronic Tissue Changes

- Changes manifest after healing process
  - May be minimal if regeneration is dominant
  - Depigmentation
  - Hair loss and thinning
  - Atrophy
  - Scar formation and strictures
  - Non-healing ulcers or necrosis

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Chronic Tissue Changes

- Chronic changes may supersede apparent healing.
  - Occurs when a slowly dividing critical cell line dies off after early healing of rapidly dividing cell lines.
    - Classic example is loss of vascular supply to a tissue such as the intestine after mucosal regeneration has occurred.

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Chronic Tissue Changes

- Or, if a subsequent insult (infection, trauma, etc) exceeds the repair tolerance of the tissue
  - Classic example is a non-healing surgical incision made in a radiation field.
  - Another example is bone necrosis is a radiation field months to years after soft tissues in the radiation field have healed.

95

Late vrs. Early Responding Tissues

- Acute and chronic changes are both seen in either:
  - Early (rapidly dividing cell lines)
  - Or late (slowly dividing cell lines) responding tissues
  - Generally speaking the changes are less evident in late responding tissue unless necrosis occurs.

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Other Factors in Radiation Response

- Dose Rate
  - Decreased dose rate decreases effects
- Cellular Kinetics
  - Growth fraction - The percentage of cells actually moving through the cell cycle.
    - Can blunt effects > repopulation
    - Can increase effects > more cells irradiated in Mitosis

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Other Factors in Radiation Response

- Cellular Kinetics
  - Cell loss fraction – number of cells naturally being lost from the cell population.
    - Increased loss Fx. - Accelerates effects
    - Decreased loss Fx. – Blunts effects.
- Cell type
  - Non-cycling population blunts effects markedly.
    - Critical cell line may supersede and cause effects.

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Other Factors in Radiation Response

- Volume of tissue irradiated
  - Increased volume increases effects
- Oxygenation at the cellular level
  - Normal cells are typically 100% oxygenated
  - Tumor tissues may contain hypoxic areas.
- Presence of some chemicals
  - Some chemotherapy agents increase effects
  - Some drugs such as Amophostine mitigate effects

99

General Organ System Responses

Individual Organ/Tissue "sensitivity to radiation injury"

100

Hemopoietic (blood and lymph)

- Refers to the parenchymal cells of the bone marrow and the circulating blood.
- Does not refer to the vessels themselves
- Critical cells are the marrow blast cells and circulating small lymphocytes.
- Non-circulating lymphocytes and other circulating white cells fairly radioresistant
- Red Blood Cells are the most resistant cell in the mammalian body to radiation injury.
- Irradiation of a small region of the body generally has no effect on circulating levels
  - An exception is lymphocyte counts following therapy level doses to the chest.

101

Haemopoietic (blood and lymph)

- Irradiation of a majority of the bone marrow will cause marked decreases in circulating cell levels post irradiation.
- Platelets at 2-4 days
  - White cells at 5-10 days
  - Red cells at 3-4 weeks
- Due to irradiation of stem cells of these cell lines.
- Effect is dose related
  - High dose = increase rate and severity of drop and longer recovery period
  - Lower dose = decreased rate and severity of drop and more rapid recovery.
- At high doses recovery may only be partial or not occur at all.

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Haemopoietic (blood and lymph)

- High dose irradiation of the marrow to sterilize it prior to bone marrow transplant is sometime done for cancer therapy
- Many metallic radioisotopes are bone marrow seekers and can result in marrow toxicity if ingested
  - An example are the phosphonates and calcium containing chemicals.
- Radiation doses to the entire marrow of greater than 8 gray are quite likely to result in marrow death and patient death unless a successful marrow transplant can be performed.
- Doses of the this magnitude are very unlikely to occur in clinical medicine
  - Exception is pre transplant marrow sterilization

103

Skin and Oral Mucosa

- The surface of the skin is covered by cells that are essentially FPM cells
- The deep basement layers of the skin are composed of Stem cells which give rise to the superficial cell layers.
  - Basal cells of the skin
  - Source of skin sensitivity to radiation
  - Skin recovery dependent on this cells
- Little or no reaction below 6-8 gray
- Erythema w/ early and late effects at 10 gray and above.
- Early effects
  - Erythema
  - Dry desquamation
  - Moist desquamation
  - Necrosis

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Skin and Oral Mucosa

- Late effects occur and increase with dose
- Recovers well from fairly high doses but late effects seen:
  - Thinning of skin
  - Pigmentation or depigmentation
  - Loss or thinning of hair.
  - Loss or thinning of subcutaneous fat
  - Cancer induction years later.
- Sources of radiation injury
  - Solar UV
    - Probably major threat for most people
  - Diagnostic x-ray
    - Fluoroscopy – Especially cardiac
    - CT – High speed spiral in juveniles
  - Radiation therapy
    - Modern techniques keep dose low – below 5 gray
    - Exception is when skin is primary target.

105

Digestive System

- Extends from mouth through rectum
- Sensitivity of individual parts rests with the number and reproductive activity of the stem cells in the basal mucosal layer
  - Mouth and esophagus relatively resistant
  - Stomach more sensitive and has more secretory cells
  - Small bowel very sensitive > highly active
  - Colon and Rectum similar to esophagus
- Early effects are mucosal depopulation
  - Clinical soreness and possible ulceration
  - With very high doses bleeding and necrosis
  - Loss of secretory cells
    - Stomach and Intestine – decreased mucus
    - Decreased digestive enzyme production
    - Decreased hormone production
  - Clinical infections

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Digestive System

- Late effects
  - Repopulation – functional recovery ~ partial?
  - Epithelial metaplasia – loss of function
  - Scarring – severe loss of function
    - Chronic clinical signs
  - Stricture - obstruction of GI tract
    - Surgical mediation required.
- Severity of response is dose and volume dependent;
  - High dose and low volume
  - Lower dose and larger volume
- Diagnostic x-ray and nuclear medicine procedures not generally a threat.
- Radiation therapy can result in severe changes

107

Male Reproductive System

- Adult sperm are FPM cells – resistant
  - But, chromosomal damage may be passed on to a fetus. Mutations can result.
  - Germinal cells very sensitive though
    - 2.5 gray to testis causes temporary sterility
    - 5-6 gray to testis causes permanent sterility
- Other secretory and hormonal cells more resistant because RPM and FPM cells
  - Hormonal activity may be retained w/ sterility
- Diagnostic x-ray and nuclear medicine studies not a threat to function
  - Mutation threshold may be lower
- Radiation therapy near testis probably cause temporary sterility
- Radiation therapy including testis causes sterility and possibly loss of function.
  - Functional sperm present 1-2 weeks after 1st dose

108

Female Reproductive System

- Radiation therapy is major sterility threat
  - 6.25 Gray to both ovaries – expect sterility
  - Oocytes do not divide – thus no repopulation
- Radiation therapy is hormonal function threat.
  - Hormonal function decreased/lost above 25 gray
  - May require hormonal supplementation
- Oocytes do not divide like spermatogonia
  - Themselves relatively resistant
  - Chromosomal damage carried on and may become evident after fertilization.
- Ovarian sensitivity more tied to follicular cells which support oocytes during
  - During follicle development there is great cellular growth activity in these cells.
  - Inactive follicular cells are less sensitive

109

Eyes

- Eyes are a major dose limiting structure
- The lens is vary sensitive to radiation
  - Cataract formation is major effect
    - Seen with doses as low as 2 gray
    - Very likely at 4 gray
- Occupational dose from diagnostic x-ray is a threat for cataract formation.
  - Wear eye shields, esp. during fluoroscopy
- Major side effect of RT to head and neck

110

Cardiovascular System

- Vessels
  - Endothelium is target cell type
  - Endothelial injury causes thrombosis and possibly hemorrhage.
  - Endothelium can repopulate to limited degree
    - Exuberant replacement may occlude vessels
  - Endothelium can be default critical cell line
- Other cells in vessel wall are FPM and RPM hence resistant

111

Heart

- Considered resistant
  - Late effects maybe seen years later.
  - Acute or Fibrosing pericarditis most common
  - At higher doses myocardial fibrosis seen
- Late effects seen are slowly progressive
  - Revealed or exacerbated by chemotherapy
- Diagnostic radiation not usually a threat
- Radiation therapy dose/volume related threat

112

Bone and Cartilage

- Mature bone is composed of FPM cells from hierarchical cell lines ~ resistant
  - At high RT doses osteonecrosis and fx. Seen
    - D/t loss of mature osteocytes
- Growing cartilage cells at growth plate are a target at risk. Especially at < 2 yrs old.
  - Causes stunted growth and possibly deformity
- High dose to joint can cause "dry" joint
- Diagnostic exposure in children from Multi-slice spiral CT can be enough to at least cause some growth arrest.

- Radiation Therapy exposure will cause permanent growth arrest in open growth plate of a young person
- Osteonecrosis and fracture possible in adult.

113

Liver and Kidneys

- Large organs which are fairly radiation sensitive
  - RPM cells with limited repopulation at lower doses.
  - Vascular injury may play an important role.
  - Functional subunits arranged in parallel
  - In kidneys fractionation has minimal effect
- Whole organ doses of 30 gray are lethal
- Greater tolerance if partially irradiated
- Major radiation threat is from radiation therapy fields which include these organs
- The kidneys in particular may be at risk for damage from some Nuclear Medicine studies.
  - Kidneys and bladder are major excretion route for many isotopes
  - Liver is excretion route for a few isotopes.

114

Lungs

- One of the most radiosensitive organs
  - RPM populations of epithelium & endothelium
  - 10 gray single dose or 30 gray fractionated to the whole lung cause progressive fibrosis
  - Type II pneumocyte is critical cell > edema
    - Edema is acute toxicity (radiation pneumonitis)
  - Fibrosis is the late effect.
- The lung has large functional reserve >
  - Dose to less than ½ lung has minimal clinical effect

115

Central Nervous System

- CNS is considered quite radioresistant in adults.
  - Development continues to 12 years of age therefore whole brain dose can reduce development
  - Glial cells and vascular endothelium are the critical cells of interest.
- RT usually avoided in children.
- Increasing volume or dose ^ the effects
  - Large volumes irradiated above 40 Gray lead to decreased function.

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