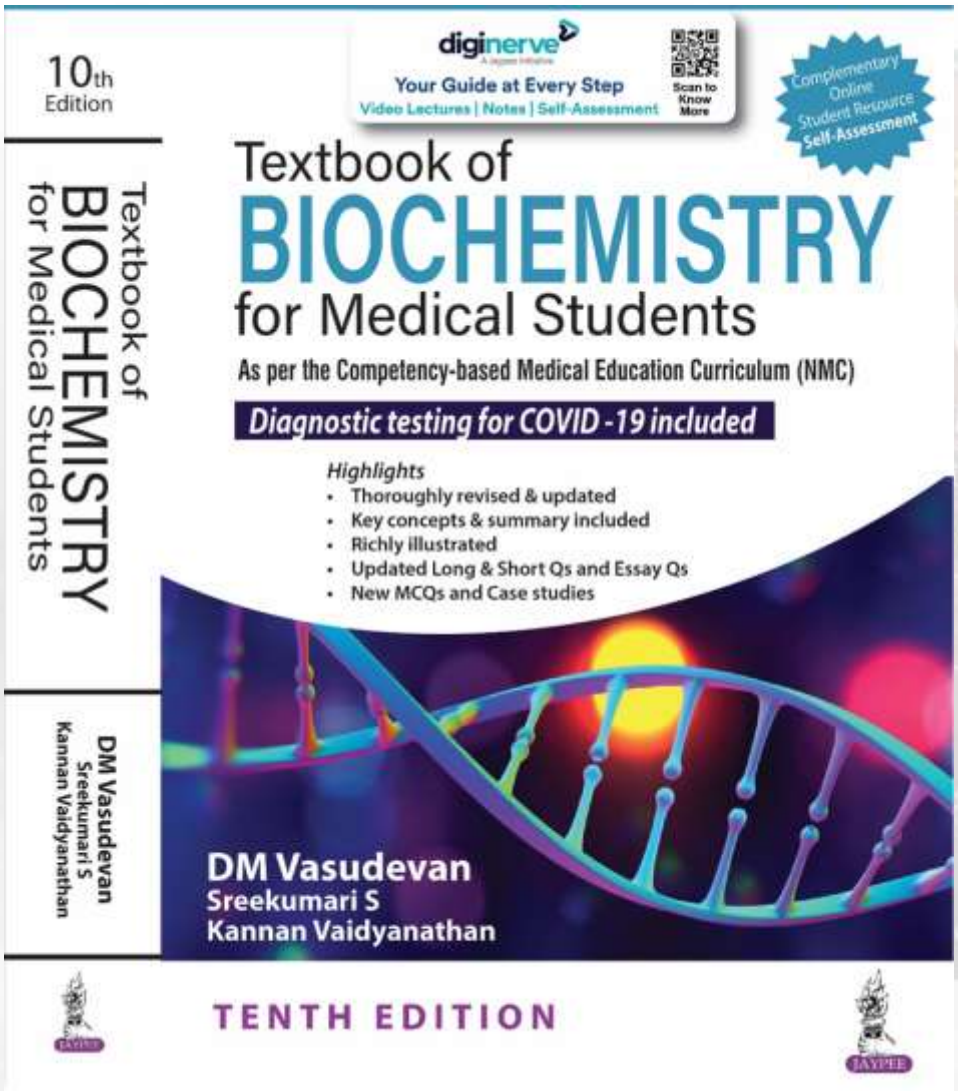


Chapter 45:

Applications of isotopes in medicine

Textbook of

BIOCHEMISTRY

for Medical Students

By DM Vasudevan, *et al.*

TENTH EDITION

Basic Principles

- Atom is the smallest unit of an element having all the properties of that element.
- Atom consists of protons, neutrons and electrons.
- Protons and neutrons are present in the nucleus.
- **Atomic number (Z) is the number of protons in an atom.**
- **Mass number (A) is the number of protons + neutrons (because the weight of electrons is so small that it is negligible).**
- **Nuclides with the same atomic number, but different mass numbers are designated as isotopes. Isotopes are basically the different nuclear species of the same element.**
- **For example Carbon can have ^{13}C and ^{14}C isotopes.**

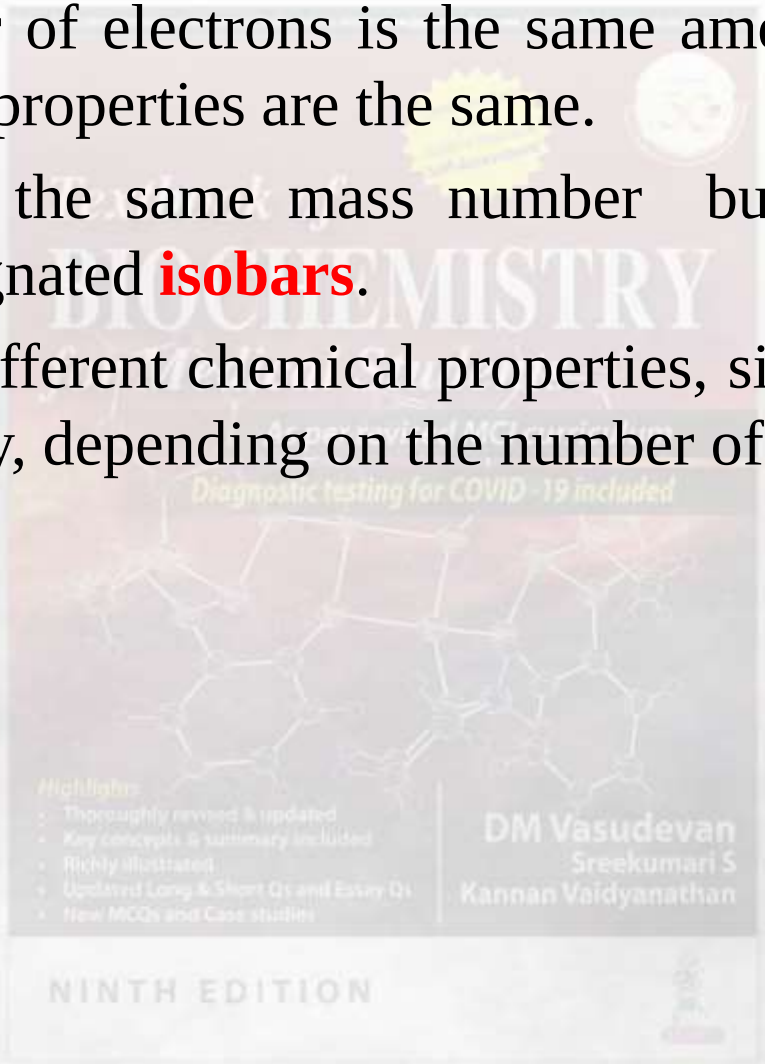
For example, ^{1}H is normal hydrogen with 1 proton. It is present 99.985% of hydrogen ions in nature.

^{2}H is heavy hydrogen or **Deuterium**. It has 1p + 1n. It is present only 0.015% in nature.

^{3}H is **Tritium** with 1p + 2n. It is not present in nature, but may be produced artificially.

These three isotopes of hydrogen will react similarly in chemical reactions, because all of them contain only one electron.

- Since the number of electrons is the same among isotopes, their general chemical properties are the same.
- Elements having the same mass number but different atomic numbers are designated **isobars**.
- They will have different chemical properties, since the number of electrons will vary, depending on the number of protons present.



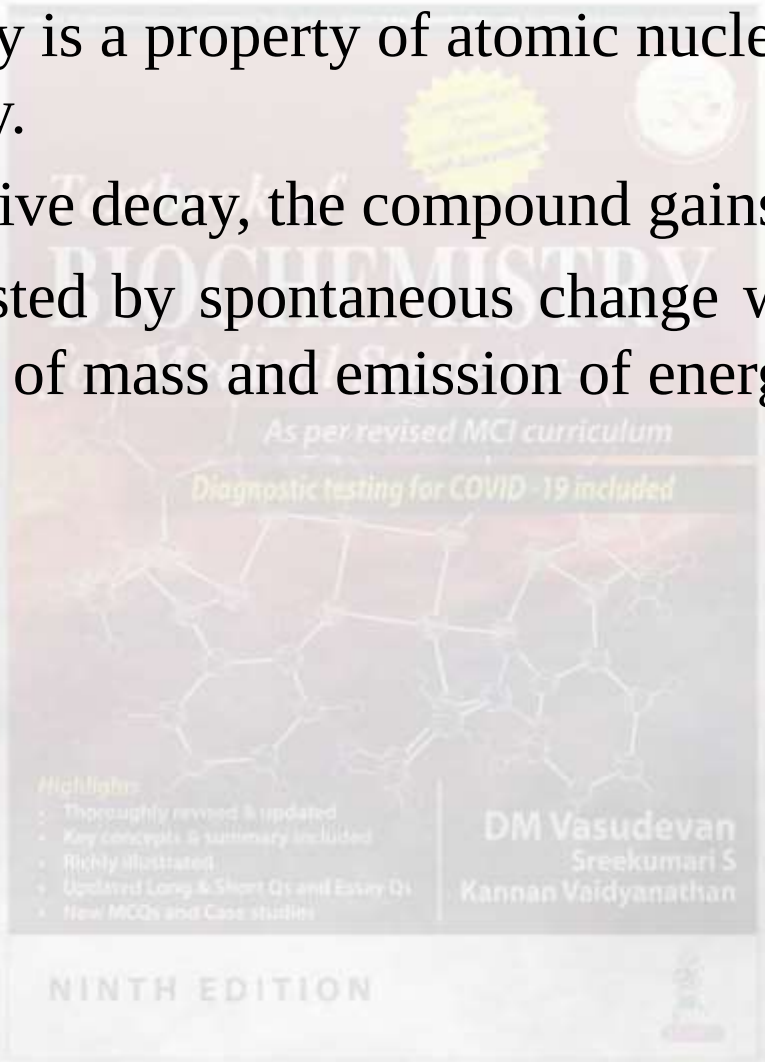
- Naturally occurring isotopes of lighter elements are stable, but those of higher elements are unstable (e.g. lead, bismuth)
- They undergo spontaneous 'transitions' to stable forms, by a process known as **radioactive decay**.
- Decay typically is associated with emission of energy in the form of radiation.
- With increasing atomic number, the difference between number of protons and neutrons increase, thereby decreasing stability.
- In fact, all atoms beyond 83 protons are unstable.

Radiation

- Radiation from atoms and its nucleus may be either particle or electromagnetic in nature.
- Particulate radiations consist of matter, like electron, positron, proton, neutron etc.
- Electromagnetic radiations is characterized by its energy.
- Commonly occurring radioactivity are a, b and g rays.
- X rays and g rays have the highest energy levels.
- Both are electromagnetic radiations.
- Energy is liberated in the form of ‘photons’ which are units of energy release having no mass.

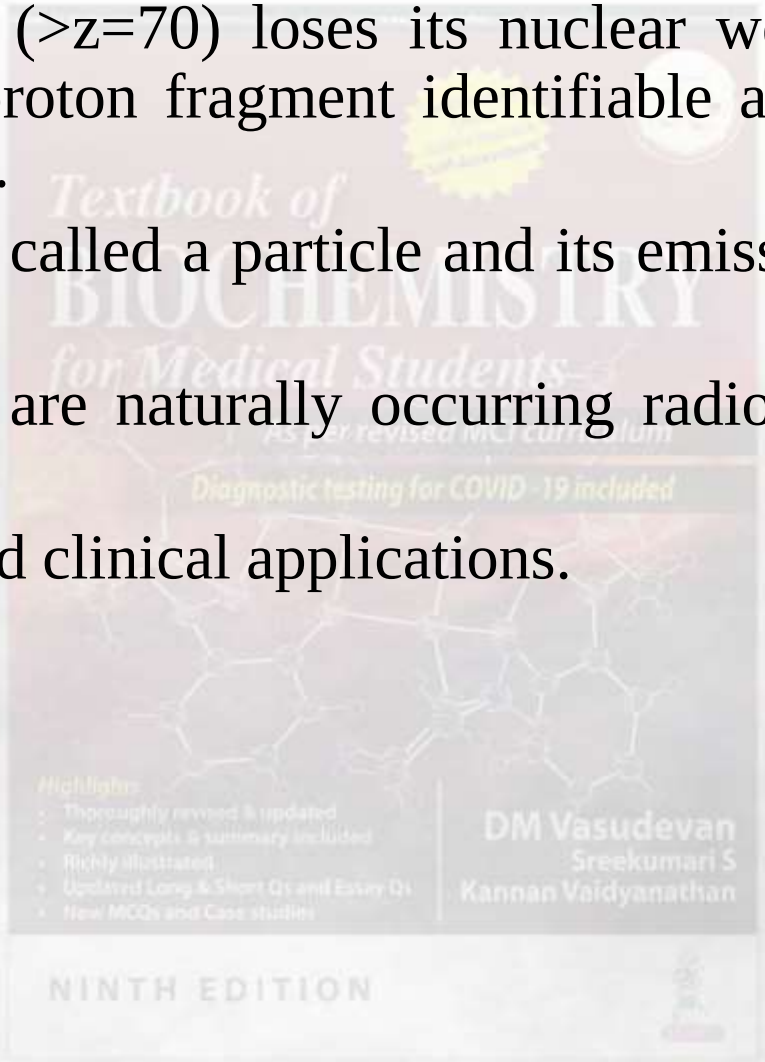
Radioactive Decay

- Radioactive decay is a property of atomic nucleus and an index of nuclear instability.
- Through radioactive decay, the compound gains stability.
- Decay is manifested by spontaneous change within nucleus that results in the loss of mass and emission of energetic radiations.



α Decay

- Heavy elements (>z=70) loses its nuclear weight by shedding a 2 neutron, 2 proton fragment identifiable after emission as a 'helium nucleus'.
- This fragment is called a particle and its emission is known as a decay.
- Most a emitters are naturally occurring radioisotopes of heavy elements.
- They have limited clinical applications.



Alpha Decay

The nucleus of Radium, being unstable, emits 2 protons and 2 neutrons (one helium nucleus) to become Radon-222. Thus, the atomic number is reduced by 2 and mass number is lowered by 4.

For example:

$^{226}Ra_{88} \rightarrow {}^{222}Rn_{86} + {}^{4}He_{2}$ (alpha particle)

The alpha particles will carry 2 positive charges and produce maximum ionization in their path. Thus, they are most damaging to tissues. The alpha radiations are not useful in clinical medicine. The alpha particles do not travel far and can be stopped by a few layers of paper.

β Decay

- There is inter-conversion of protons to neutrons or vice versa through 'positrons'.
- Positrons are the negative electrons or their positive equivalents.
- Negative electron is b particle and this is known as b decay.
- Emission of negative electron leaves the nucleus with an additional positive charge.
- Normally neutron is converted to proton (increasing z), thereby reducing neutron number (e.g. ^{131}I, ^{14}C, ^{3}H, ^{59}Fe).]
- Emission of positive b particle is called positron emission. Here z<1, and neutron becomes proton.
- Examples for positron emission are ^{11}C, ^{18}F and ^{52}Fe.

When a neutron is split, one proton, one electron (beta particle) and one neutrino are generated. The element is changed to one having a higher number in periodic table.

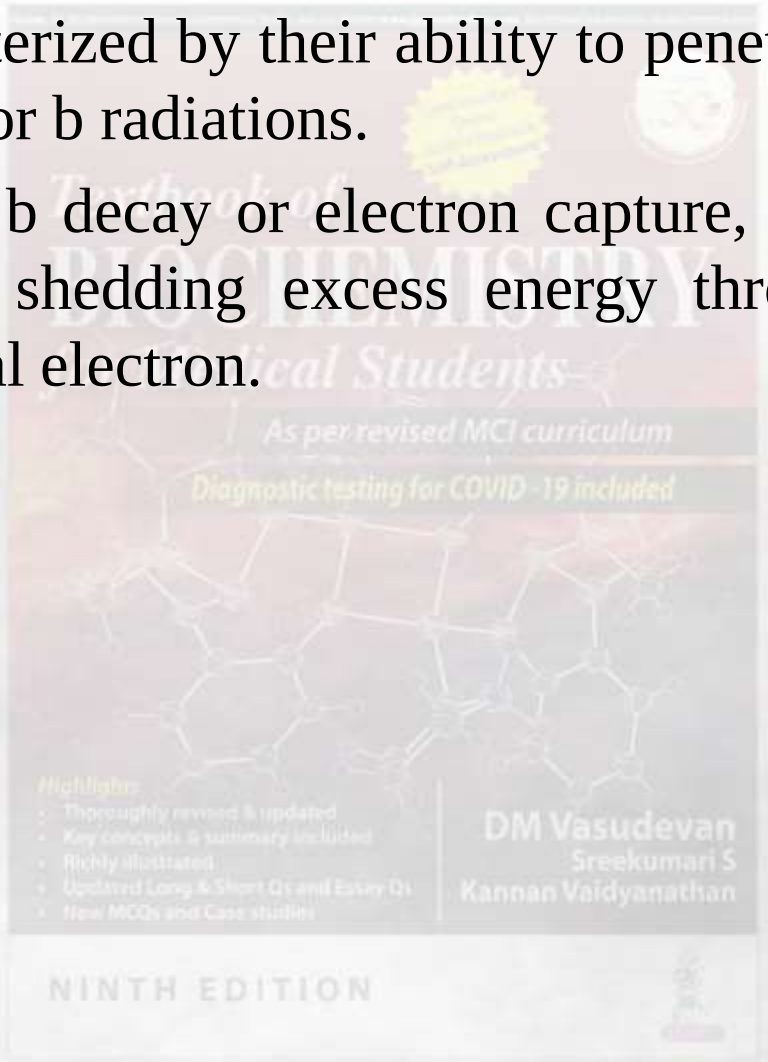
$^{14}C_6 \rightarrow {}^{14}N7 + e^{-} +$ neutrino

One neutron from carbon is changed to a proton.

Therefore mass remains the same, but the element is changed with one number more in atomic number. The electrons thus emitted become the beta rays. So they are negatively charged.

γ Emission and Internal Conversion

- g rays are characterized by their ability to penetrate materials that are blocked by a or b radiations.
- After either a or b decay or electron capture, nucleus returns to ground state by shedding excess energy through emission of g photon or orbital electron.



Gamma Radiation

While alpha and beta radiations are particles, gamma radiation is in the form of electromagnetic waves. Gamma ray has no mass and no charge, and therefore penetration power is maximum. It is used for treatment of cancer cases.

The gamma radiation is produced by:

$^{131}I_{53} \rightarrow {}^{131}Xe_{54}$ (metastable) + b emission

$\rightarrow {}^{131}Xe_{54}$ + g ray

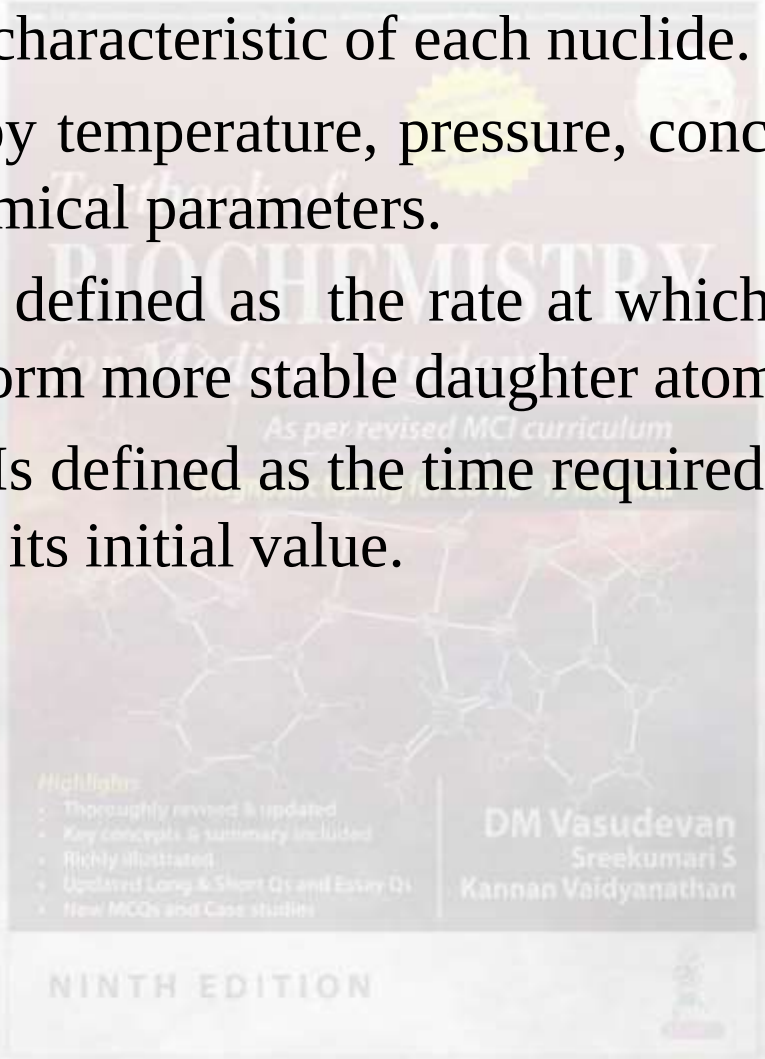
The resulting xenon is at a metastable state. It will release further energy in the form of gamma irradiation within a fraction of second to form the stable xenon.

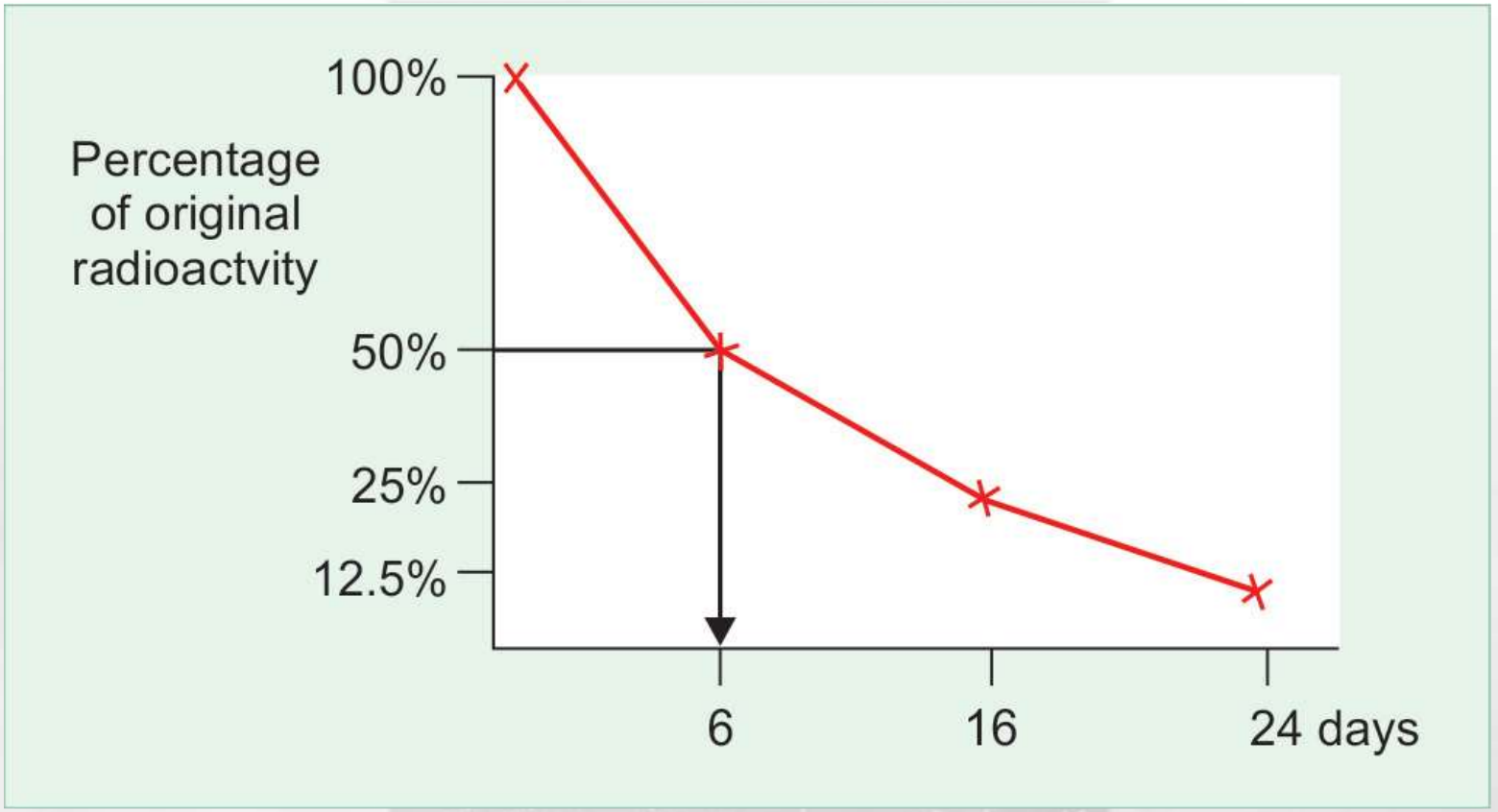
Different forms of radiation

Type	Composed of	Mass	Charge	Ion pairs per cm	Range in air	Stopped by	Application
α	2p+2n	4	+2	20,000	3-8 cm	Few sheets of paper	Radiation hazard
β	e^-	negligible	-1	100	15-100 cm	Few sheets of aluminum	Research/ diagnosis
γ	Electromagnetic waves	Nil	0	1	100 m	Few cm thick lead	Diagnosis/ treatment

Rate of radioactive decay and half life

- Rate of decay is characteristic of each nuclide.
- It is unaffected by temperature, pressure, concentration and other physical and chemical parameters.
- Rate of decay is defined as the rate at which radioactive parent atoms decay to form more stable daughter atoms.
- Half-life ($t_{½}$) – Is defined as the time required for sample activity to decline to half its initial value.





Radioactive decay and half-life of ^{131}I.

Units of radioactivity

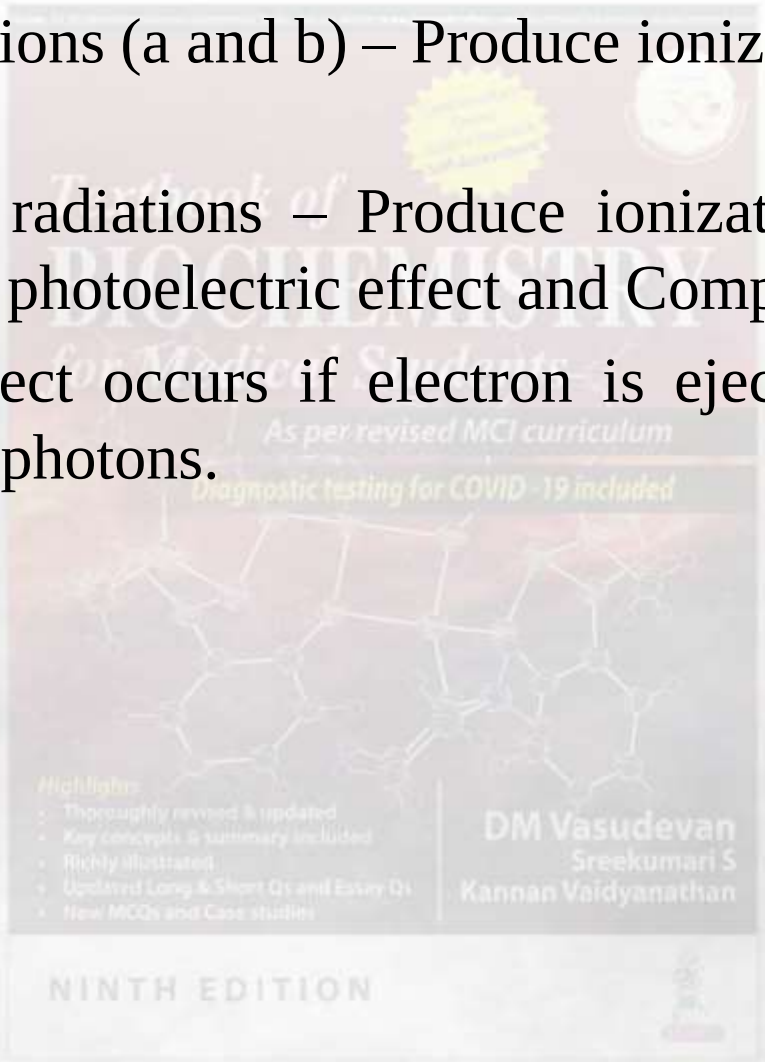
- Becquerel (Bq)– Is the SI unit of radioactivity and is defined as one decay per second (dps). Activity of typical samples is expressed as kiloBecquerels (kBq).
- Curie (Ci) is the older and more conventionally used unit. One curie is 3.7×10^{10} dps.
- One curie equals 37 giga Becquerels (GBq).
- Unit used for absorbed dose: rad = 10mGy). Gray is the SI unit defined as the energy absorbed from ionization of radiation per unit mass of absorber.
- Unit for exposure is roentgen. 1R = 258 mC/kg. SI unit is coulombs/kg (C/kg) defined as amount of charge liberated by ionization of radiation per unit mass of air.
- Dose equivalent – rem. 1 rem=10mSv. SI unit is sievert (Sv).

Matter – Radiation Interactions

- Radioactive emissions transfer energy to atoms and molecules they encounter, chiefly through excitation and ionization.
- Ability of radioactive substances to produce excitation is one of its most important properties.
- It is the basis of its biological effects and is the basis for its detection methods.
- Excitation describes the process whereby energy of incident radiation is transferred to matter through raising of electrons of irradiated materials to higher energy levels.
- If energy absorbed completely removes electron from the atom, it is called ionization.
- Resulting positive ion and electron are referred to as ion pair. Ejected electron is called secondary electron.

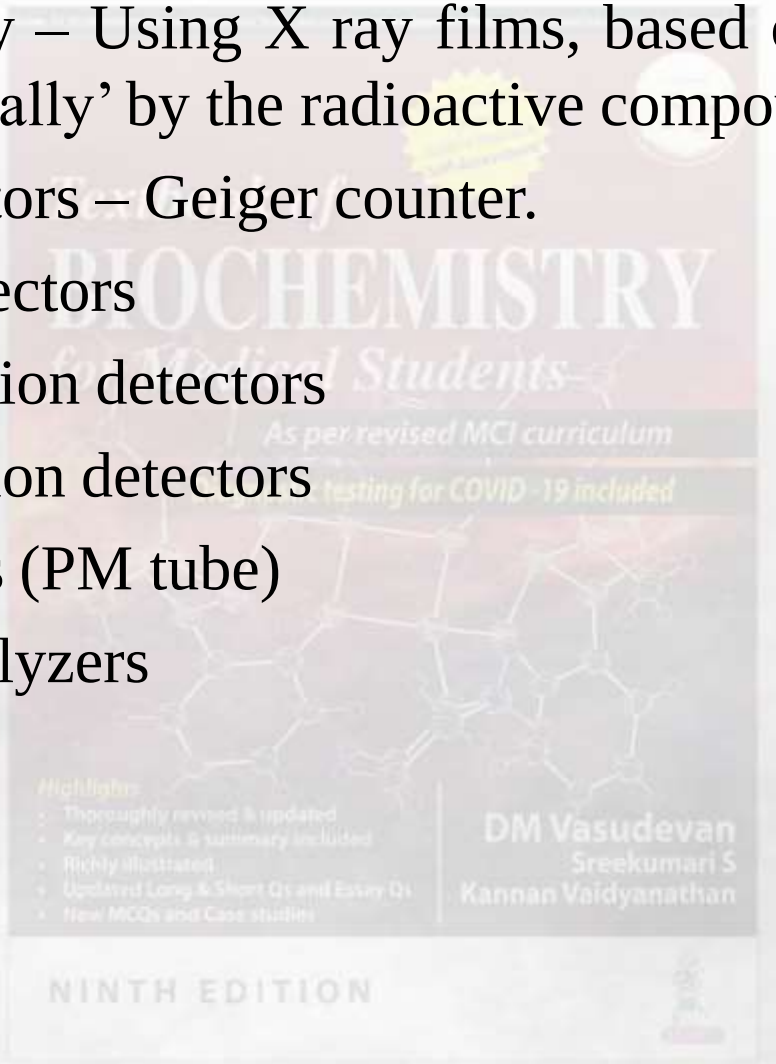
Effects of radioactive species

- Particulate radiations (a and b) – Produce ionization and excitation.
- Electromagnetic radiations – Produce ionization and additional effects known as photoelectric effect and Compton effect.
- Photoelectric effect occurs if electron is ejected, was observed initially for light photons.



Detection and measurement of radioactivity

- Autoradiography – Using X ray films, based on development of films 'automatically' by the radioactive compound.
- Gas-filled detectors – Geiger counter.
- Scintillation detectors
- Crystal scintillation detectors
- Liquid scintillation detectors
- Photomultilpiers (PM tube)
- Pulse height analyzers



Commonly used radioisotopes

Element	Iso-tope	Half-life	Major radia-tion	Important applications
Carbon	^{14}C	5600 years	Beta	Research in metabolism, carbon dating
Hydro-gen	^{3}H	12 year	Beta	Research in cell biology
Phos-phorus	^{32}P	14 day	Beta	Nucleic acid research, treatment for polycythemia
Chro-mium	^{51}Cr	28 day	Gamma	RBC kinetics in diagnosis
Iodine	^{125}I	60 day	Gamma	Radio immunoassay
Iodine	**^{131}I**	**8 day**	**Gamma**	Treating hyperthyroidism and thyroid cancer

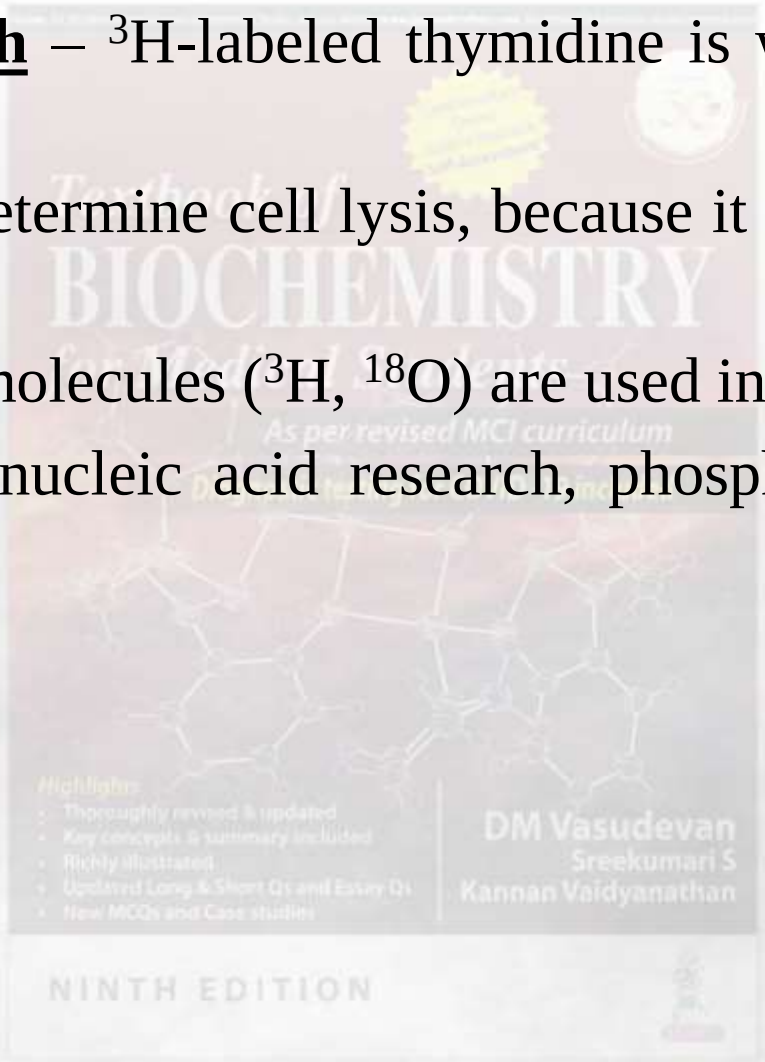
Commonly used radioisotopes

Element	Isotope	Half-life	Major radiation	Important applications
Technetium	^{99}Tc	6 hour	Gamma	Blood flow experiments; gamma imaging
Radium	^{226}Ra	1600 years	Gamma	Interstitial implantation for treating cancer
Cobalt	^{60}Co	5.3 years	Gamma	Teletherapy for cancer
Caesium	^{137}Cs	30 years	Gamma	Teletherapy for cancer

Research Applications of Radioactivity

- **Tracer technique** – Used to study metabolic pathways (e.g. ^{32}P, ^{14}C). They are metabolized similar to normal molecules.
- Metabolic pathways have been 'traced' by these methods only.
- Turnover rate of compounds can be studied using tracer techniques (e.g. ^{131}I for Igs).
- **Isotope dilution technique** – Total body content (body pool), extracellular volume, intracellular compartment volume etc can be studied by this method.
- **Carbon dating technology** – Using ^{14}C, age of fossils and other ancient materials can be ascertained.

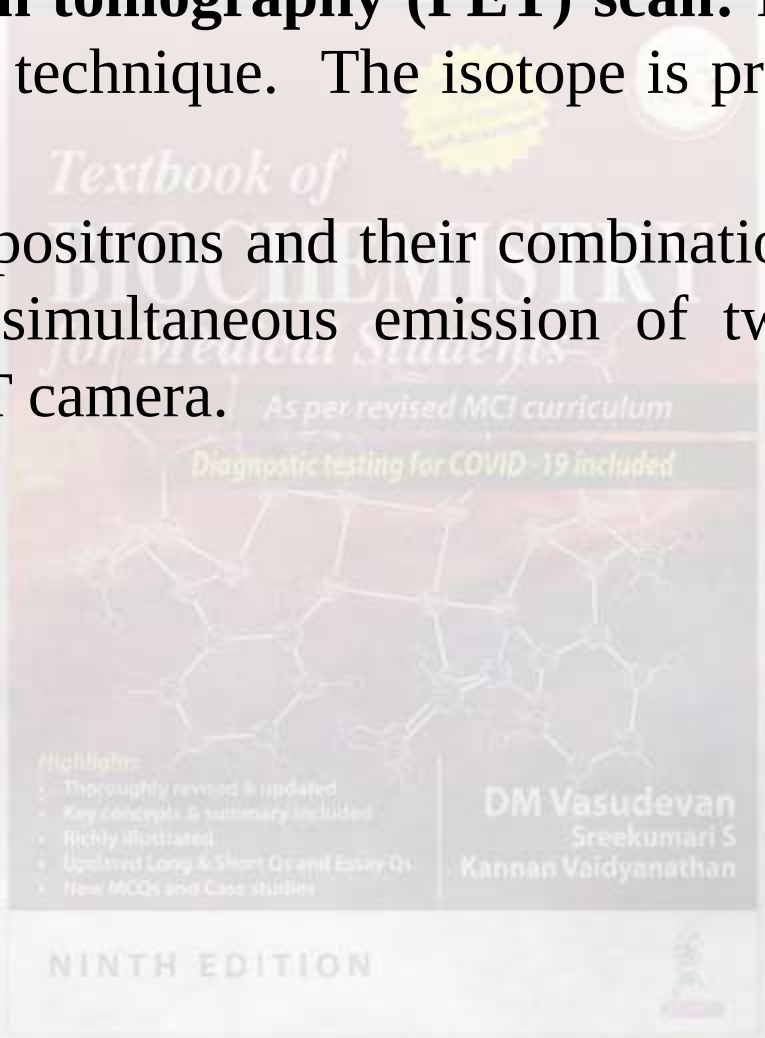
- **Genetic research** – ^{3}H-labeled thymidine is widely used in cell division kinetics.
- ^{51}Cr is used to determine cell lysis, because it is taken up only be living cells.
- Double labeled molecules (^{3}H, ^{18}O) are used in some cases.
- ^{32} P is used in nucleic acid research, phosphorylation (kinase) studies.



Diagnostic applications

- **Thyroid uptake studies** – ^{131}I is used. Normally 25% uptake in 2 hrs and 50% within 24 hrs. Increased uptake in hyperthyroidism and decreased un hypothyroidism.
- **Thyroid scanning** – ^{131}I is used. Increased uptake is seen as heavily shaded areas (thyroid) under the scan. 'Silent nodule' suggestive of thyroid cancer, where there is defective uptake in circumscribed areas can be detected by thyroid scan.
- **Bone and kidney scanning** – ^{90}Sr (strontium)is used for bone scans. Early detection of osteoblastomas can be done.
- ^{131}I labeled hippuric acid or diodrast is used for kidney sacn.
- **Technicium blood flow studies** – ^{99}Tc is used for this purpose. Known as nuclear stethoscope.
- **RBC lifespan studies**– ^{51}Cr used for studying lifespan and intravascular hemolysis studies.
- **Radioimmunoassays** -

- **Positron emission tomography (PET) scan:** It is a more precise and sophisticated technique. The isotope is produced on the spot by a cyclotron.
- The emission of positrons and their combination with an electron resulting in the simultaneous emission of two gamma rays is detected by a PET camera.



Radioactivity in treatment

- Radioactivity is used in treatment of cancers.
- Radiations after absorption by tissues, produce cell damage (induced by mainly ionization).
- Radiotherapy mainly affects cells in division phase so that next cell division is impaired (at DNA level).
- Major problem is toxicity because normal cells are also damaged in the vicinity.
- However, mainly cancer cells which are in S phase are primarily affected.
- Radiotherapy may be of different types depending on source and other characteristics.
- **Unsealed sources** – Substance is kept in liquid form (mainly b rays). ^{131}I is used for thyroid cancer and secondary deposits in thyroids. ^{32}P also used in some cases.
- **Sealed sources** – Utilize g rays.Radioactive material is covered by (platinum) alloys which absorb a and b. Only g rays pass through. This is used for cancer therapy. Source may be implanted into tissue as needle.

- Application of sources directly into cancer tissue is termed **brachytherapy**. ^{137}Cs needles are used now, which have replaced more toxic radium needles.

- **Intracavitary** applications (body of uterus, cervix, vagina) and **interstitial** applications (oral cavity) are commonly practiced.

- **Teletherapy** – Where source is kept away from the body. Initially deep X rays were used. Gamma rays from ^{60}Co and ^{137}Cs are used. They have high penetration power, and deep seated cancers are effectively treated.

Linear accelerator (LINAC):

Cesium-based radiotherapy is no more used, which is replaced by the **linear accelerator**.

Here electrons are accelerated to higher energy levels of 8–12 MV and directed into the cancer tissue. It has more penetrating power and accurate beam focusing capabilities.

As there is no permanent radioactive source in the machine, the radiation hazards are minimal.

Proton beam therapy with IMRT (intensity modulated radiation therapy) does not affect the skin or neighbouring tissues. Proton therapy is now available in almost all renowned cancer centres in India.

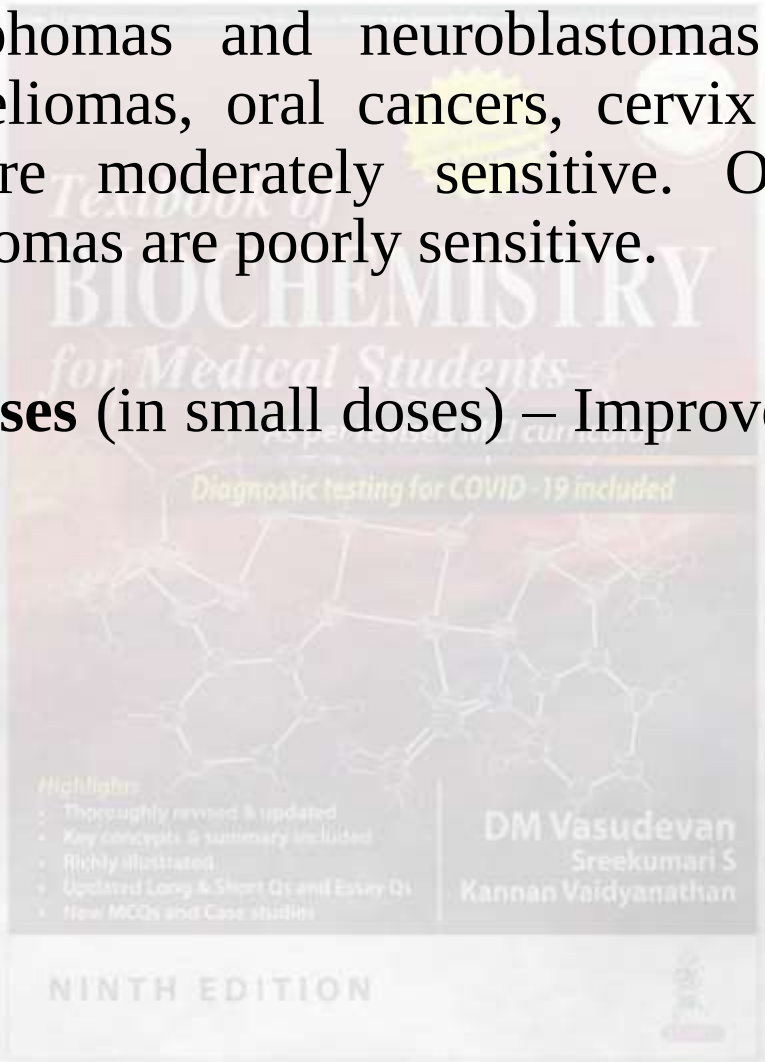
Teletherapy

Linear accelerator

Radiosensitivity

- Hodgkin's lymphomas and neuroblastomas are more **radio-sensitive**. Epitheliomas, oral cancers, cervix cancer, breast and lung cancers are moderately sensitive. Osterosarcomas and malignant melanomas are poorly sensitive.

- **Fractionated doses** (in small doses) – Improves effectiveness and reduces toxicity.

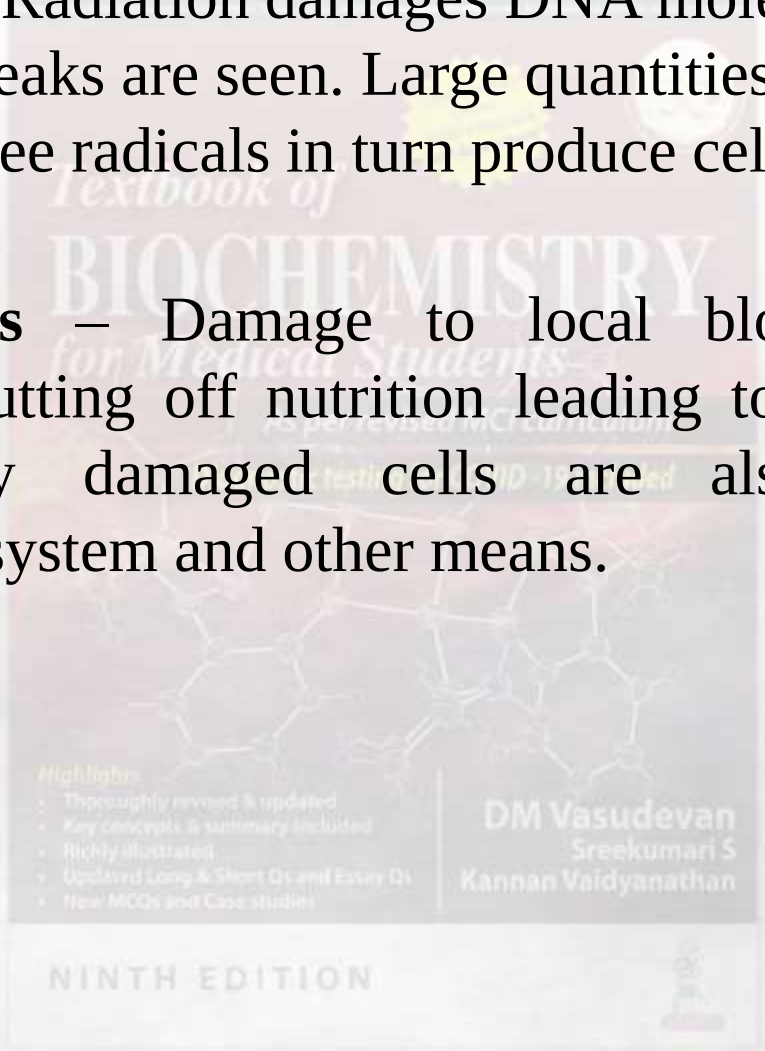


Effect of radiotherapy differs from dose to dose

Day	Dose in rads	Initial no. of cells	Frac-tion of cells in divi-sion	No. of remaining cells	No. of cells killed
1.	400	$1x10^{10}$	10%	$9x10^{9}$	$1x10^{9}$
2.	400	$1x10^{9}$	10%	$9x10^{8}$	$1x10^{8}$
3.	400	$1x10^{8}$	10%	$9x10^{7}$	$1x10^{7}$
4.	400	$1x10^{7}$	10%	$9x10^{6}$	$1x10^{6}$

Effects of radiation on cancer tissues

- **Direct effects** – Radiation damages DNA molecules. Chromosome breaks are seen. Large quantities of free radicals are produced. Free radicals in turn produce cell and DNA damage.
- **Indirect effects** – Damage to local blood supply (neo-angiogenesis) cutting off nutrition leading to cell necrosis and death. Partially damaged cells are also destroyed by immunological system and other means.



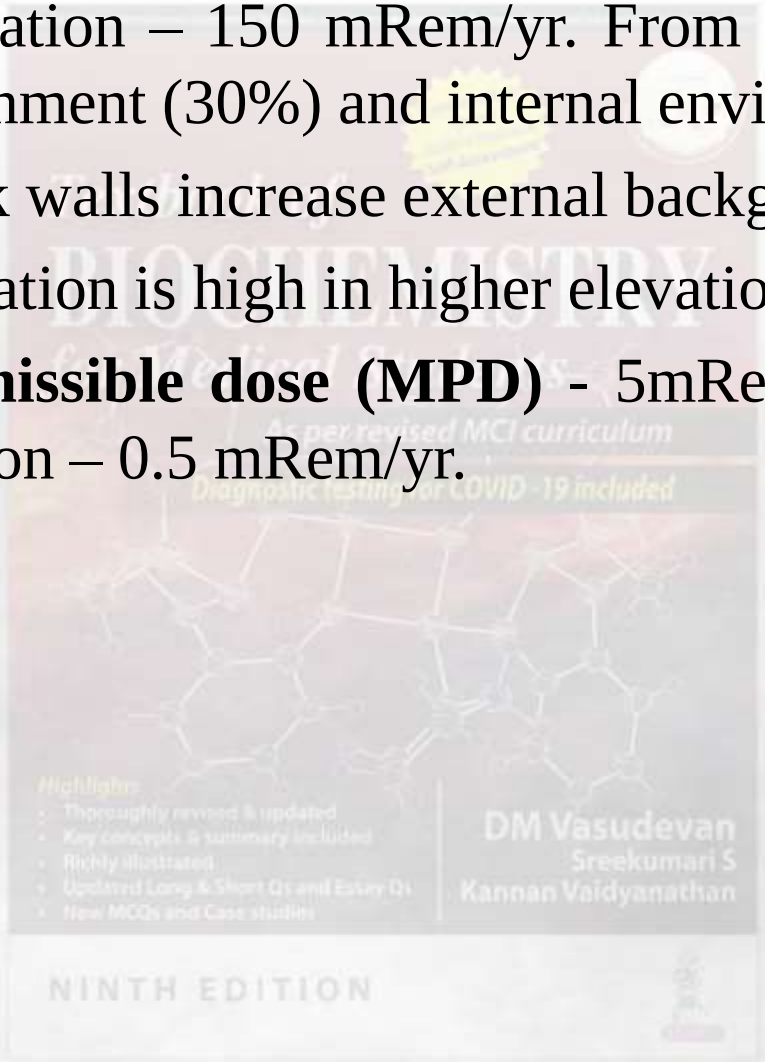
Effects on normal tissues (Adverse effects)

- May be classified into **somatic, genetic** and **teratogenic** effects.
- **SKIN** – Epilation. Sweat glands may be permanently damaged. Eythema, blisters - Acute radio-dermatitis.
- Chronic radiodermatitis – After a few months of exposure. Skin atrophy, hypo-pigmentation, fibrosis, loss of elasticity. Overdose leads to radiation burns, skin sloughing.
- **MUCOSA** – GI mucosa is extremely sensitive. Nausea, vomiting, diarrhea, ulceration and bleeding may result.
- Late sequel include adhesions, fibrosis, stenosis and obstruction.
- **GONADS** –Highly radiosensitive. Genetic alterations may result, esp. pelvic radiation. Complete sterility at 1000 rads.

- **BLOOD CELLS** – Bone marrow and lymphoid tissues are highly sensitive. Leukopenia and thrombocytopenia result.
  Blood counts have to be essentially performed during treatment.
- **RADIATION SICKNESS** – Dose above 1000 rads is fatal. At 150 rads, severe illness is seen in 50% cases.
- **EMBRYO**-Irradiation can affect embryo at the blastocyst stage and can also affect skeletal, CNS, hematopoietic and other systems.
- **Delayed effects** are seen in almost all human systems including skin, GIT, digestive, hematopoietic, CVS, eye, CNS, reproductive, urinary, respiratory, musculo-skeletal and endocrine systems.

Radiation protection and maximum permissible dose

- Background radiation – 150 mRem/yr. From cosmic rays (50%), terrestrial environment (30%) and internal environment (20%).
- Granite and brick walls increase external background.
- Background radiation is high in higher elevation and coastal areas.
- **Maximum permissible dose (MPD)** - 5mRem/yr (Technicians). General population – 0.5 mRem/yr.



Precautions

- Wear radiation badges – Radiation films turn black when exposure is high.
- Keep source as far away as possible.
- Shield radioactive sources – Lead bricks.
- Handling to be done by remote devices.
- Use rubber gloves and aprons.
- Radioactive materials to be handled fast to reduce chance of exposure. Shorter the time spent, shorter the actual exposure.

BIOINFORMATICS

Bioinformatics describe the *use of computers to handle biological information.* Bioinformatics may be regarded as "computational molecular biology".

Databases of existing sequencing data can be used to *identify homologues* of new molecules that have been amplified and sequenced in the lab. The property of sharing a common ancestor, *homology,* can be a very powerful indicator in bioinformatics.

Computational Drug Designing

Discovering and developing any new medicine is a long and expensive process. Drugs work by interacting with target molecules (receptors) and altering their activities. In some cases, the effect of a drug is to stimulate the activity of its target (an agonist) while in other cases the drug blocks the activity of its target (an antagonist). A drug target is a key molecule involved in a particular metabolic or signaling pathway that is specific to a disease condition, or to the infectivity or survival of a microbial pathogen. Some approaches attempt to inhibit the functioning of the in the diseased state by causing a key molecule to stop functioning. Drugs may be designed that bind to the active region and inhibit this key molecule.

NANOMEDICINE

- Nanotechnology is an exciting science which deals with miniaturization of devices and processes at the nanometer (10^{--9} m) scale.
- Human hair varies from 18 to 180 micrometers. Thus nanotechnology is working at a level 100-1000 times smaller than human hair.
- Nanotechnology is the science for understanding and control of matter at dimensions between 1 and 100 nanometers.
- Nanotechnology involves imaging, measuring, modeling, and manipulating matter at nano scale, applicable to both engineering and medicine.
- Unusual physical, chemical, and biological properties can emerge in materials at the nanoscale.

Applications of Nanotechnology

- Drug delivery
- Therapeutics
- Imaging Techniques
- Antimicrobial Techniques
- Nanorobotics
- Cancer
- Gene therapy
- Drug delivery

BIOPRINTING

Bioprinting is the three-dimensional (3D) printing of biological cell patterns (e.g., cells and biomolecules). It works by outputting layer-upon-layer of living cells, which are then fused with advanced additive manufacturing technologies ("bio-ink") to fabricate make tissues that mimic parts of the body such as the skin or bones.