MEDICAL UNIVERSITY – PLEVEN
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CENTER FOR DISTANCE LEARNING

LATE EFFECTS OF RADIATION

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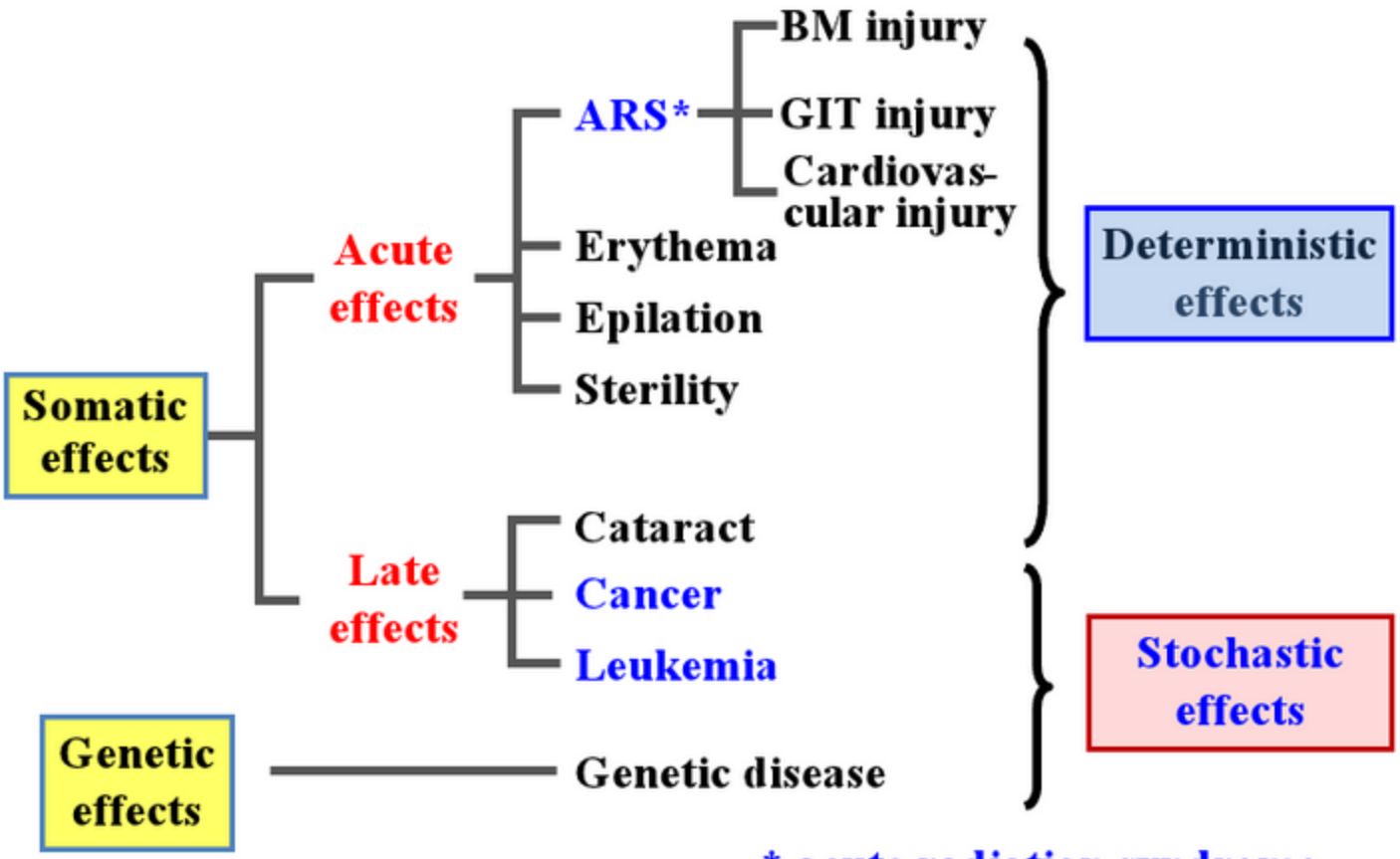
- The **late effects** of the ionizing radiation include the **carcinogenesis and the genetic effects.**
  - These effects have not any threshold, like the **acute radiation injuries** (for example **1 Gy is threshold for the bone marrow syndrome).**
  - **Any dose, no matter how small**, **carries a probability of inducing the late effect - increasing the dose will increase the probability that this effect will occur**, but will not increase the severity of the effect;
  - For this reason the late effects of the radiation are also **called stochastic effects**.

Human Health Effects of Radiation Exposure



* acute radiation syndrome

Early endothelial effects	Late endothelial effects
▪ Apoptosis ▪ Activation: increased expression of cell adhesion molecules and cytokine secretion ▪ Recruitment of inflammatory cells ▪ Pro-coagulant and pro-thrombotic phenotype ▪ Increased permeability ▪ ROS production	▪ Microvessel collapse: rupture and dilatation of capillaries ▪ Thickening of the basal membrane Thrombosis ▪ Chronic pro-inflammatory phenotype ▪ Chronic production of ROS ▪ Senescence

Effects of irradiated endothelium on surrounding normal tissues
▪ Ischemia ▪ Necrosis ▪ Tissue fibrosis

Late effects occur:

1. In individuals who **survive acute high dose** exposure.
2. In individuals **received single low dose**.
3. In individuals **received chronic low doses**.

Unlike the acute effects due to cell killing, **late effects arise in those cells**, which **survive the initial exposure**, but **retain some memory** of this exposure.

CARCINOGENESIS

- The **most important** late somatic effect induced by radiation is **carcinogenesis**.

  - It may arise after low doses such as those received by **occupationally exposed person or by patient undergoing diagnostic tests**, using radiation.

- **The first reported case** of radiation - induced carcinoma was **in 1902**.

  – Within 15 years of the discovery of x-rays, **100 cases of skin cancer** caused by radiation were reported in radiologists and technicians.

  – Many **famous pioneer** workers and scientists as **Marie Curie** and her **daughter Irene** had been victims of radiation induced malignancies.

- **The time** between irradiation and the appearance of cancer is **very long** and differs **for different type of cancers**.
  - **Latent period** for the induction of types of **solid tumors** after irradiation varies **between 20 and 30 years**.
  - The peak of increased **incidences** of **leukemia** after irradiation of population appears **between 7 and 12 years**, but essentially returns to control incidence **by 20 years after exposure**.
  - However, for **some other types** of radiation - induced cancer the individual may be **at risk throughout his life**.

- **After low doses the cells are not killed**, but survive only to undergo later **malignant transformation**. **After high doses** the cells **do not get an opportunity** to express any malignant change, **because they are killed** by the radiation.

For human, the following are **sources of data** on the incidence of radiation - induced cancer:

1. **Occupational exposure**
2. **Atomic bomb survivors**
3. **Medical exposure**
4. **Fallout accidents**

Malignancies in which **radiation has been implicated as a cause are**:

- **leukemia**
- **skin carcinoma**
- **osteosarcoma**
- **lung cancer**
- **thyroid cancer**
- **breast cancer**

a) Leukemia

- **The radiation** increases the incidence of only **specific type of leukemia**; only **acute and chronic myeloid** leukemia have been found to be increased in irradiated **adults**, whereas an increase in **acute lymphatic leukemia** is responsible for the increased incidence in exposed **children**.
  - The incidences of **chronic lymphocyte leukemia do not** appear to be influenced by radiation exposure.

b) Skin carcinoma

- The **first case** of skin cancer is **reported in 1902** on the hand of a technician of x-rays machines.
- The skin carcinoma caused by **radiation cannot be differentiated from skin cancer** caused by other agents. IR is associated with an **increase** in the **incidence** of **squamous cell carcinoma.**

c) Osteosarcoma

Radium, used to paint the clock faces (in the early part of 20th century) **was ingested** by these workers and **accumulated in the skeleton**.

- Although exposure to the radioactive material was brief, the **ingested radium was not excreted**, resulting in a **continuous exposure to the bone**.
- As a result many of those people developed **osteosarcoma**.

- Radiation-induced osteosarcoma occurs in approximately 1% of patients who have been treated with greater than **25** Gy and can occur in unusual locations, such as the skull, spine, clavicle, ribs, scapula and pelvis, osteosarcoma is the most common radiation-induced sarcoma.

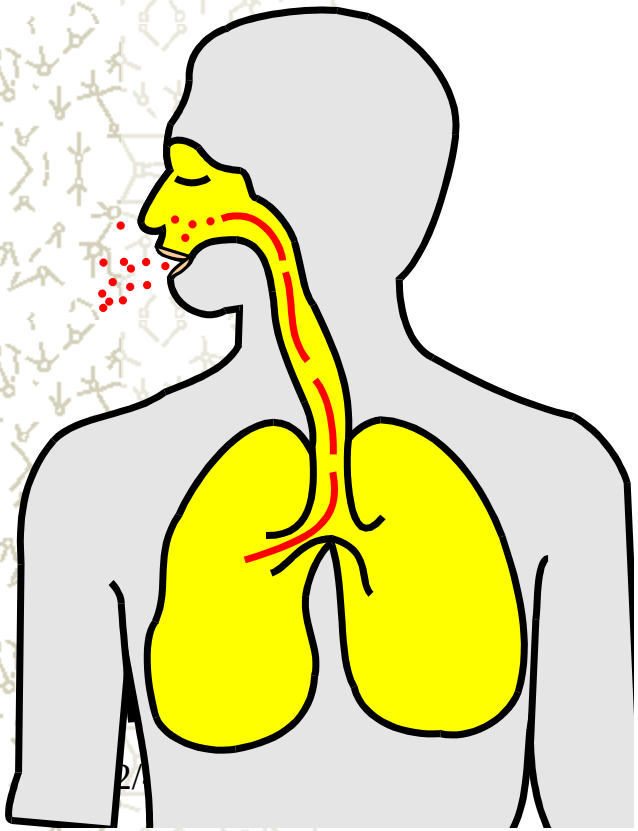
d) Lung carcinoma

- **Pitchblende minors in Germany** more than 500 years ago were known to have a high incidence of a fatal disease referred to **as "mountain sickness"**.
  - In 1924, investigations of this disease revealed it to be **carcinoma of the lung**.
  - The cause of the disease was occupational and was explained with the fact that **the air in the pitchblende mines** was rich in **radon**.

What is Radon?

- Radon is an indoor air pollutant.
- Radon is a colorless, odorless radioactive gas that comes from naturally occurring uranium in the soil.

Radon Exposure



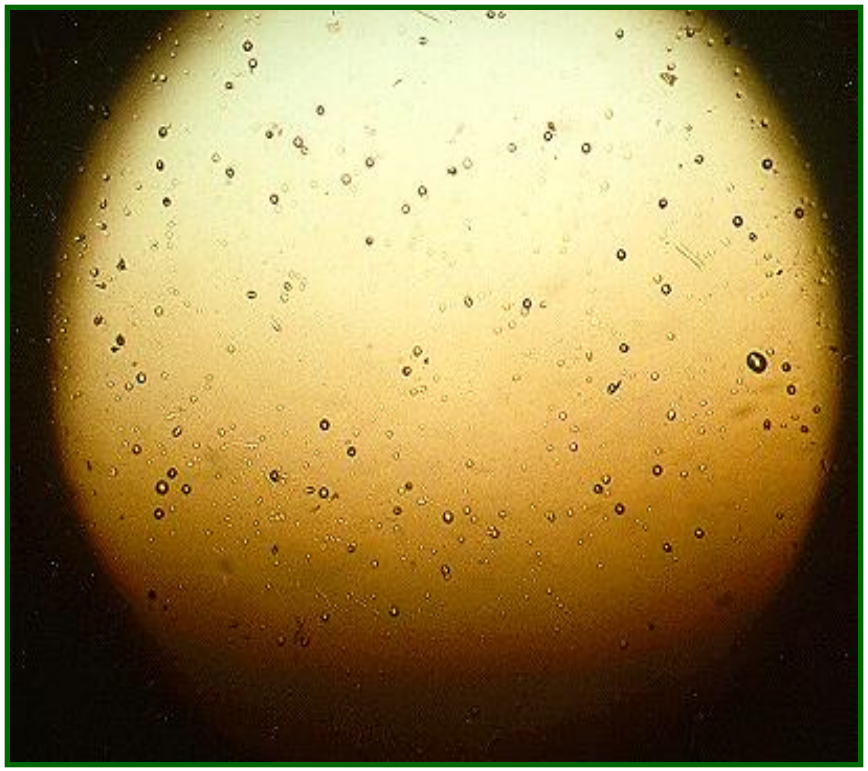
- RD remains in lung tissue and is trapped in the bronchial epithelium and emits alpha particles which strike individual lung cells and may cause physical and/or chemical damage to DNA.
- Radon and Radon Decay Products (RDPs) are breathed in and the Radon is exhaled.

Alpha Particle Damage

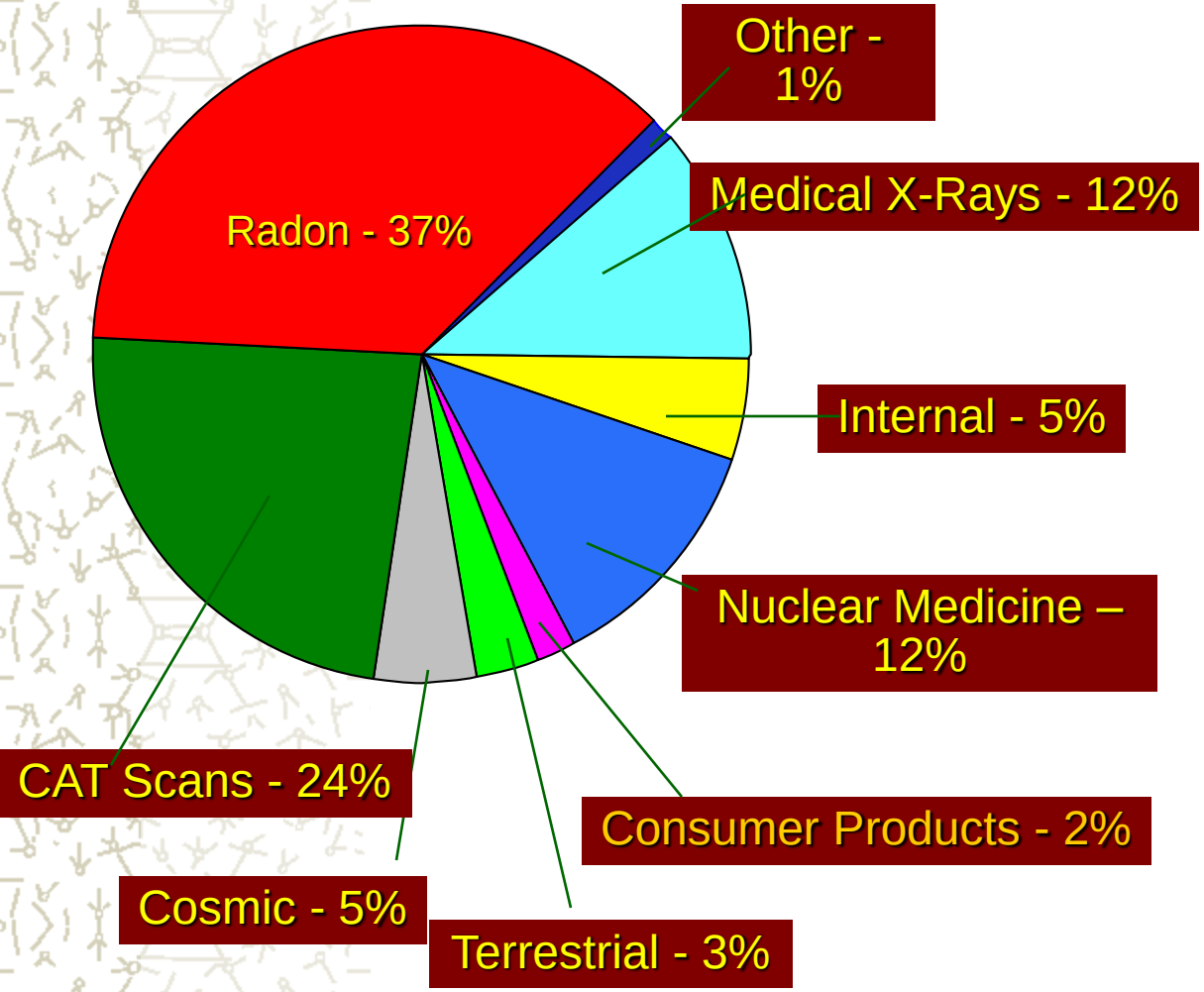
Alpha Particles are strong enough to pit plastic.

Alpha Emitters

americium-241
plutonium-236
uranium-238
thorium-232
radium-226
radon-222
polonium-210



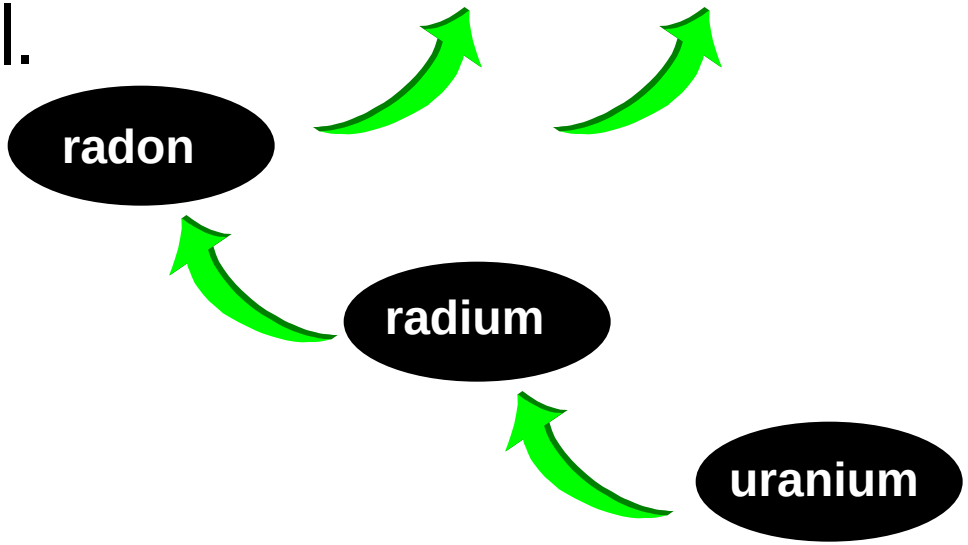
Sources of Radiation Exposure to US Public 2009



- Average Exposure 620 mrem
- Assumes average indoor radon concentration of 1.3 pCi/L.
- Radon is by far the greatest single source of radiation exposure to the general public.

Radon Entry

- Radon enters through any opening between the building and the soil.



- **Radon 222 is a radioactive gas released from soil and rocks during natural decay of Uranium and Thorium**
- Considered second leading cause of lung cancer, may enhance risk of cancer in smokers
- Geology of the area can predict potential high levels in soil and water
- Radon concentrations indoors depend on construction aspects: building materials; cracks or pores in concrete floor and walls; floor-wall joints; loose pipe penetration; air pressure of a house lower than the surrounding soil, and others
- Highest level in basements and ground floor
- Radon usually does not present a health risk outdoors because it is diluted in the open air.

e) Thyroid carcinoma

This carcinoma was observed:

1. **In infants irradiated in the early decades of 20th century** to reduce **"thymus enlargement"**.
2. **In children of the Marshall Islands** who were accidentally exposed to fallout radiation from a nuclear test.
   - In later years this irradiated children revealed an increased incidence of **all types of thyroid diseases**, including **benign** and **malignant tumors**.

Thyroid carcinoma

- 100 fold increase in children after Chernobyl incident

f) Breast cancer

- A study of **three groups of irradiated women** has shown that **radiation increases** the incidence of **breast cancer**. These groups are:

1. Female survivors of the **atomic bomb in Japan**.
2. **Canadian women with tuberculosis** who were subjected to multiple fluoroscopes.
3. **Women treated with radiation** for **benign breast disease** such as **postpartum mastitis**.

GENETIC EFFECTS

- A **certain number of spontaneous mutations** arise in each generation: this is termed the **mutation frequency**.
- Radiation certainly can produce mutation **through unrepaired structural breaks in chromosomes** or through discrete **changes in the order of bases on the DNA chain**.
  - When these mutations occur in **germ cells** the possibility exists that they may be transmitted to future generation.

- The unit of measurement for the determination of radiation effect on mutation frequency is the **doubling dose**. It is defined as that dose of radiation which ultimately doubles the number of spontaneous mutations.

For example, if 5% of the offspring in each generation were observed to have mutations, the doubling dose would eventually produce 10% mutations.

Radiation produces no new mutations, only an increase in the already existing number of mutations is observed.

Müller did **the classic study** of the effect of radiation on mutation frequency **on fruit flies**. In these studies Müller drew following conclusions:

1. Radiation **did not produce any new or unique mutations** - it **simply increased** the **number of mutations** that **spontaneously arise** in each generation.
2. **Between doses of 0,25 and 4 Gy** the frequency of mutation **was linear with dose**.
3. **Radiation-induced** mutations were **recessive**, i.e. they may not be exhibited for many generations.

4. The incidence of mutation was **independent of dose rate**. A given dose produced the **same incidence of mutation**, whether it was given as one "shot" of radiation or extended over a long period of time.
5. **The doubling dose for humans** extrapolated from the experimental data was estimated to be **between 5 and 150 rems**.

- Later, **Russell and Russell** undertook a study using thousands of mice. The most important findings are:

1. There was a **clear dose rate effect in the mouse for radiation induced mutations**.
   - When a given dose was extended over a period of time it produces fewer mutations than the same dose given in one single shot.
2. **The doubling dose** for humans was estimated by extrapolation to be **50 to 250 rem**, significantly higher than that estimated from fruit fly data.

- In addition, three other conclusions were drawn from these data that were relevant to humans:

1. **All mutations** did not show **the same susceptibility** to **induction by radiation**. It indicates that **the doubling dose is not constant** for all type of mutations.
2. **Male** were found to be **more sensitive** than female.
3. The **genetic effects can be reduced** by allowing **a time period to elapse between exposure and conception**.
   - By extrapolating, this period is suggested to be **6 month for humans**.

RADIATION DAMAGE OF THE FETUS

- There are **three general effects** of radiation on the embryo and fetus:

1. **Lethality**
2. **Congenital abnormalities present at birth**
3. **Long-term effects** (late effects) that **are not visible at birth but develop later in life**.

- These effects can be produced in the embryo and fetus **by a mutation in the ovum or sperm** resulting in inherited (genetic) effects, or they can be **directly induced by exposure of fetus** to radiation.

- Radiation effects on developing human embryos have been observed in **the following situations**:
  - **Atomic bomb survivors**
  - **Accidental exposure**
  - **Occupational exposure**
  - **Diagnostic and therapeutic exposure of pregnant patients**

- The clinic observations suggest following conclusions:

1. **Over 2,5 Gy** delivered to human embryos **before 2 to 3 weeks** of gestation may result in a large number of **prenatal death**, but produces very few abnormalities in those children carried to term.
2. Irradiation **between 4 and 11 weeks** of gestation may lead to severe **abnormalities** of many organs, particularly the **CNS** and **skeletal systems**.
3. Irradiation **during 11th to 16th** weeks frequently produces **mental retardation** and **microcephaly**.
4. Irradiation **after 20th** week may result **in functional defects**.

The most common abnormalities are:

CNS	Skeletal	Ocular	Others
exencephaly	stunting	absense	leukemia
microcephaly	abnormal limb	of eye(s)	genital deformities
mental retardation	small head	microphtalmia	
idiocy	deformed arms	cataract	
scull malformation	spina bifida		
hydrocephaly			
mongoloism			

- Fetuses in the **second** and **third trimester are more radioresistant** from those in the first. However, this later stage of development may result in more suitable abnormalities and functional disorders (e.g. sterility) and **late changes** such as **malignancies** and **bone marrow syndrome** of birth.