Radiation and Radioisotopes

- Aarushi Sharma

Every time a doctor locates a hidden fracture, identifies a tumour or measures blood flow inside a beating heart, they often rely on a force we cannot see: radiation. By converting atomic physics into clinical insight, it powers some of the most advanced imaging and therapy systems in medicine.

From Accidental Discovery to Precision Science

In 1895, Wilhelm Conrad Röntgen was working in his lab in Germany, experimenting with cathode rays in a dark room, when he noticed a fluorescent screen glowing, even though it shouldn't have. He realised some new, invisible rays were passing through solid objects. He called them X-rays.

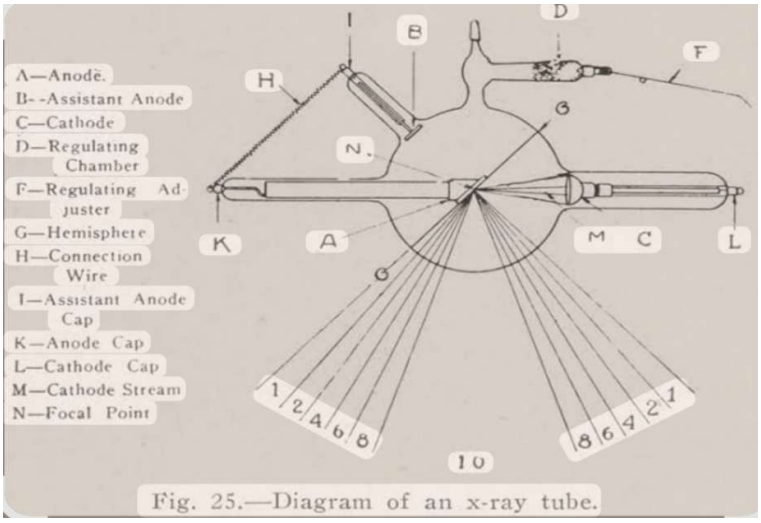


Fig. 25.—Diagram of an x-ray tube.

Within weeks, the doctors realised that these rays pass through soft tissues, bones absorb them and you can **catch the shadows on a photographic plate.** Thus, the first ever medical X-rays was performed on Röntgen's wife's hand, to which she said, "I've seen my death", because it showed underlying bones for the first time, clearly.

With the discovery of Polonium and Radium by Marie and Pierre Curie in 1898, the **basic foundations of radiotherapy were laid**.

From 1930s-1950s, physicists developed artificial radioisotopes in cyclotrons. George De Hevesy used radioactive tracers to track chemical pathways in living beings. This became the foundation of PET scans, SPECT scans and thyroid scans. Medicine suddenly had a way to study the physiology of human body, not just anatomy.

Hence, 1970s onwards, the whole field matured from discovering something glowing to precision targeting tumours with millimetre accuracy.

i) *The Physics of Medical Radiation: Image Formation, Contrast and Tissue Interaction*

To move further, we have to encroach the fundamentals of radiation first.

Radiation exists in 2 broad categories:

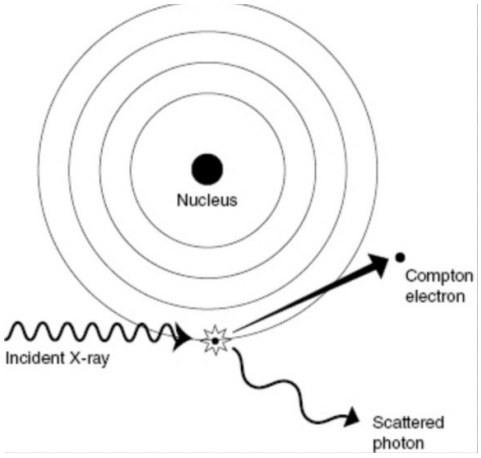
1. **Electromagnetic radiation**: Composed of massless photons which travels at the speed of light. It includes both ionizing and non-ionizing rays. Eg. X-rays and gamma rays.
2. **Particulate radiation**: Consists of particles with mass and often, electric charge. It includes only ionizing radiation. Eg. Alpha and beta particles.

Ionizing radiation has enough photons/particle energy to excite(elevate) or ionize(remove) electrons from atoms. Ionization is *central* to both image formation(via attenuation differences) and tissue damage(via DNA transcription).

The 3 major photon interactions with human tissue are the Photoelectric effect, Compton scattering and Pair production.

In photoelectric effect, the photon is fully absorbed by an inner-shell electron, ejecting from atom. This phenomenon is more prominent in high-atomic-number materials such as bone, and is responsible for the **radiographic contrast** seen in plain X-ray imaging.

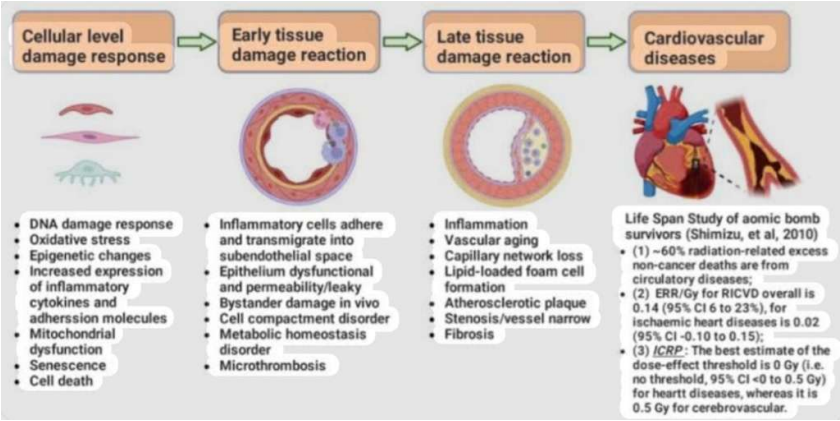
Compton scattering, which dominates in soft tissues with diagnostic energy ranges, involves partial energy transfer to an outer shell electron, with the photon being deflected. This contributes significantly to **image degradation and operator exposure,** since scattered photons reduce image clarity and must be controlled through collimation (to reduce spreading/make them travel in a parallel way) and grid systems.



Particulate radiation deposits energy differently. Alpha particles, because of their large mass and charge, exhibit high linear energy transfer (LET), producing **dense ionization tracks** over short distances. Beta particles, being electrons or positrons, have lower LET and greater penetration. Neutrons interact mainly through nuclear collisions and are biologically highly destructive despite being uncharged.

Linear energy transfer (LET) describes the amount of energy deposited per unit path length. High-LET radiations (alpha particles, neutrons) cause concentrated DNA damage, while Low-LET radiations (X-rays, gamma rays, beta particles) create sparse ionization. Relative Biological Effectiveness (RBE) is a related concept that compares the biological potency of a given radiation type with a reference, typically 250 kVp X-rays.

Cellular response to radiation depends on multiple factors including the phase of cell cycle, oxygenation status and dose rate. According to the **Law of Bergonié and Tribondeau**, rapidly dividing undifferentiated cells show the highest radiosensitivity, which explains why radiation is used so extensively to eradicate cancer cells.



Thus, the differences in these interactions form the foundation of medical imaging and radiotherapy. The ability of different radiation types to deposit energy in specific patterns also explains their varied biological effects: tissues exposed to high-LET radiation suffer more concentrated DNA damage compared to those exposed to low LET-radiation.

ii) <u>Radiopharmaceutical Engineering: Designing Molecules that behave like Biological Spies</u>

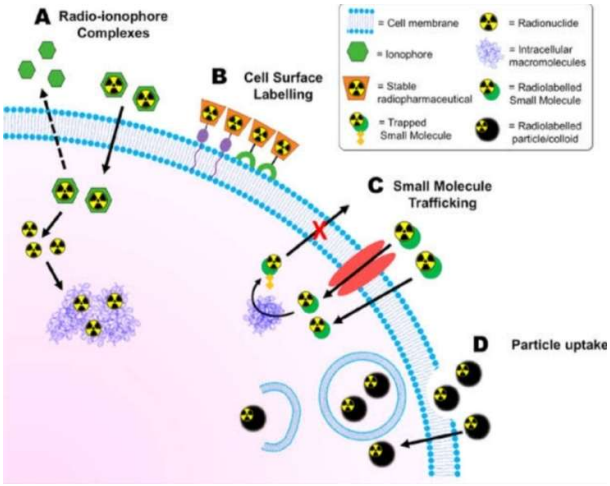
At the core of every radiopharmaceutical is a simple scientific logic: the radioisotope must behave predictably inside the body. It's half-life must be long enough to complete imaging or therapy, yet short enough to limit unnecessary exposure. It's emission type (gamma for imaging, beta or alpha for therapy) determines what it can be used for. The isotope must also form a stable chemical bond with its carrier molecule so it **does not detach or degrade in vivo**. These design principles decide

how far the radiotracer travels, which tissues it accumulates in and how clearly it can be detected. In essence, the physics of the isotope sets the rules, and the chemistry of the ligand decides where the Isotope plays its role.

The engineering of targeted molecules (often called 'magic bullet' as per Paul Ehrlich's original concept) relies on 2 primary strategies:

1.**Passive Targeting**: This leverages the body's natural processes and disease specific anatomical features. For eg. Tumour blood vessels are often 'leaky' and have poor lymphatic drainage, allowing nanoparticles carrying drugs to accumulate in the tumour area more than in healthy tissue, a phenomenon known as the Enhanced Permeability Retention (EPR) effect.

2.**Active Targeting**: This involves modifying therapeutic or imaging agents with specific 'homing devices' called ligands (eg. Antibodies, peptides, small molecules like folic acid) that bind to target molecules (receptors or antigens) highly expressed on the surface of specific diseased cells or tissues. This lock-and-key mechanism ensures high specificity and uptake by the target cells via receptor-mediated endocytosis, minimising impact on healthy cells.



The precision with which different molecules/cells are targeted is truly spectacular. It represents a paradigm shift from conventional therapies and it comes from:

1.**Molecular specificity**: agents are designed to target specific proteins, enzymes, or genetic mutations unique to diseased cells, largely sparring healthy tissue.

2.**High affinity**: targeting ligands (like antibodies) have a very high binding affinity for their targets, ensuring a strong and selective interaction, much like a specific key fits only one lock.

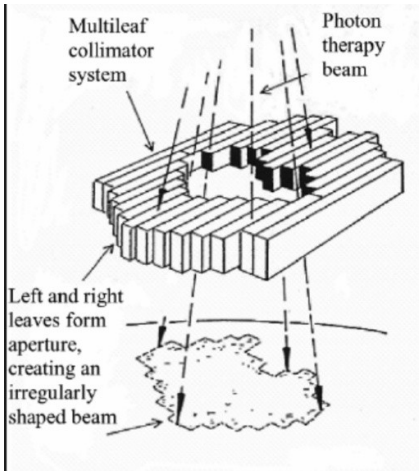
3.**Personalized medicine**: Advances in genomics and molecular profiling allow for treatments to be tailored to an individual patient's unique molecular profile, further increasing the effectiveness and precision of therapy.

iii) Radiation Therapy as Precision Destruction: How modern beams think like algorithms

Radiation beams are shaped and steered using advanced computer-controlled technology, primarily the multi-leaf collimator (MLC), to precisely match the tumour's 3D shape and minimize damage to surrounding healthy tissue.

- MLC is a component within the linear accelerator (LINAC) that consists of numerous independently moving 'leaves' made of a dense material, usually tungsten.
- The LINAC machine rotates around the patient, delivering radiation from multiple directions.
- Each individual beam is shaped by the MLC as it passes through the body. The convergence of all these precisely targeted beams delivers a **high, concentrated dose** where they intersect at the tumour site, which each individual beam passes through healthy tissue with minimal effect.

An advanced technique popularly used is proton therapy where, as the name suggests, it uses protons instead of X-rays, although it is highly expensive. Protons deposit most of their energy at a specific depth (known as **Bragg Peak**) and then stop, effectively delivering a high dose to the tumour with virtually no radiation deposited in healthy tissue past the tumour.



This move from external beam precision to biological targeting is best captured by 2 standout radionuclides: Lu-177 and Ra-223.

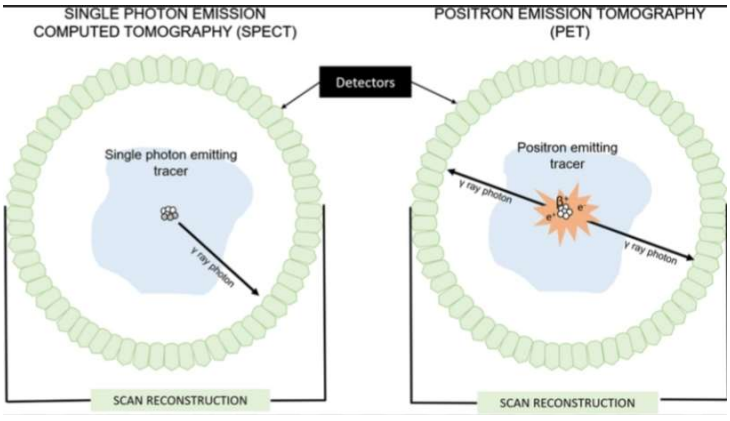
What makes Lu-177 so special? It all comes down to one thing: **precision**. Traditional chemotherapy often affects the entire body, leading to many side effects. However, Lu-177 primarily targets cancer cells. This is because Lu-177 is attached to a molecule that binds to specific characteristics of the cancer cells. This makes the treatment much more effective with fewer side effects. Since, each type of tumour has different characteristics, various molecules are used.

Radium-223 targets bone so accurately because it acts as calcium mimetic, chemically resembling calcium and being preferentially incorporated into areas of high bone turnover, which is a characteristic of bone metastasis, by specifically binding to hydroxyapatite, a major mineral component of actively forming new bone.

iv) <u>Functional Imaging: SPECT and PET as windows into real-time physiology</u>

Functional imaging marks the shift from seeing anatomy to seeing biology. SPECT and PET achieve this by tracking radiotracer distribution as a direct measure of cellular activity.

- When it comes to cardiovascular imaging, SPECT MPI cameras have the widest availability, are continuously improving and are the most flexible type of camera available.
- With SPECT, you can perform both stress and rest studies, and the modality allows you to physically stress the heart vs only relying on vasodilators. The extendable nature of it allows you to perform low dose imaging and when concerned with CT, allows for true attenuation correction and more.



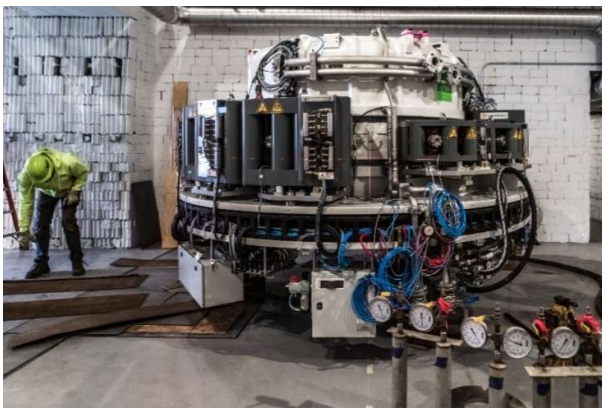
Where SPECT visualises organ perfusion and receptor activity, PET goes deeper by using tracers that imitate the body's own molecules. Cancer cells, with their heightened

metabolic demand unintentionally expose themselves through the intense uptake of these mimics.

- The most common radiotracers **[18F]-FDG**, is a glucose analog that cancer cells absorb at a high rate using their over-expressed glucose transporters(GLuT1 receptors).
- Once inside the cell, the FDG gets 'trapped' because it cannot be fully metabolised like normal glucose and causes the tumour to appear as a bright, concentrated spot on the PET scan image, revealing its location and metabolic activity.
- By mimicking natural substrates, the radiotracers are absorbed by cells using the same existing metabolic pathways or binding to specific receptors, allowing for the mapping of these biological activities within the body.

v) Manufacturing Atoms: How the world produces Medical Isotopes

The production of radioisotopes involves several interrelated activities, including the fabrication of targets; their irradiation, transportation of the irradiated targets to processing facilities, radiochemical processing or encapsulation in sealed sources, quality control and transportation to the users.



Radioisotope production in reactors is based on **neutron capture in a target material,** either by activation or generation of radioisotopes from fission of target material by bombardment with thermal neutrons. Research reactors and accelerators are also used to develop them for diagnostics and therapy in nuclear medicine, non-destructive testing and radiotracer industrial applications, as well as for radiotracer studies in scientific research.

- Accelerators have a number of advantages over nuclear reactors for radioisotope production, such as safety and cheaper operating and decommissioning costs.

- Since accelerators are powered by electricity rather than fission reactions, they produce *less than 10% of the waste of research reactors*.
- Furthermore, accelerator-produced waste is less hazardous than waste produced by a research reactor. They also don't pose a nuclear weapon proliferation risk.

vi) The Global Radioisotope Crisis: Why Medicine depends on Aging Reactors

When the world's largest medical isotope producer, National Research Universal (NRU) in Chalk River, Ontario, was shut down in May, 2009, due to high cost of maintenance, a global medical isotope shortage ensued, leaving hospitals with costlier and less effective procedures.

Faced with a **sudden 30% supply shortfall** in the wake of the reactor outage, doctors had no choice except to postpone vitally important diagnostic procedures.

Demand for medical procedures using isotopes is increasing, yet only 5 facilities ensure the vast majority of world's supply of critical needed radioisotope, Molybdenum-99.

Worryingly, this isotope supply gap is only the tip of iceberg of a much larger problem: global research reactor aging.

In the realm of medical Isotopes, new, dedicated reactors are unfortunately years away from operation and face economic, political and regulatory challenges.

Most nuclear medicine studies use $^{99}Tc^{m}$, which is the decay product of ^{99}Mo. The world supply of ^{99}Mo comes from only 5 nuclear research reactors and availability has been much reduced in recent times owing to problems at the largest reactors.

- In the short-term, there are limited actions that can be taken owing to capacity issues on alternative imaging modalities.
- In the long term, stability of ^{99}Mo supply will rely on a combination of replacing conventional reactors and developing new technologies.

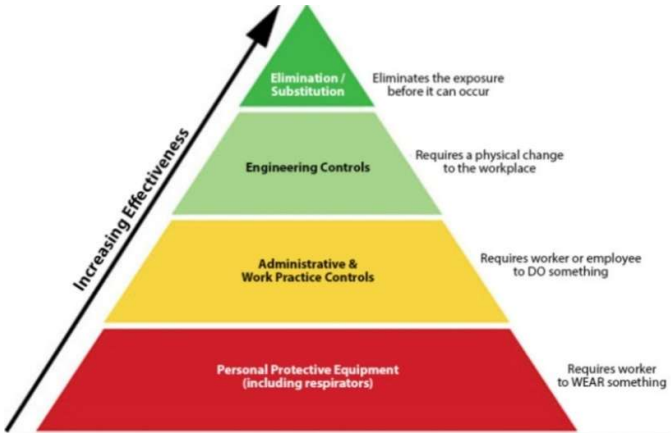
vii) Safety, Ethics and Public Perception: Why Radiation is feared more than it is understood

People tend to fear radiation more than surgery due to psychological factors and historical perceptions rather than an objective assessment of actual medical risks involved.

- The inability to see or feel the exposure makes it an 'unknown hazard' , which is inherently more frightening than a tangible procedure like surgery.
- Feelings of dread about potential outcomes strongly influence risk perception more than technical facts alone.
- Public fear of radiation has deep roots in historical events, such as the atomic bombings of Hiroshima and Nagasaki and Nuclear Power Plant accidents like Chernobyl and Fukushima.

In reality, modern medical radiation treatments and diagnostics are carefully controlled and targeted to maximize benefits while minimizing harm to healthy tissue.

Ethical guidelines for diagnostics in pregnancy prioritize essential procedures while minimizing foetal exposure and nuclear waste management focuses on containment and regulatory compliance to protect public health.



ix) The Future of Radiation Medicine: AI, Quantum Detectors and the New Atomic Age

Artificial intelligence is poised to become inseparable from medical imaging.

AI-assisted reconstruction algorithms can suppress noise, refine edges and enhance contrast, allowing diagnostically superior images to be generated from substantially lower radiation doses.

Machine learning systems will not only improve image quality but also streamline workflow, automate lesion detection and integrate multimodal imaging data to provide quantitative, reproducible assessments.

Advances in isotope production are equally transformative. Compact cyclotrons (small, efficient particle accelerators) are making it possible for regional hospitals to produce their own PET isotopes, reducing dependence on centralised production labs.

From Röntgen's accidental discovery to today's quantum detectors and targeted isotopes, radiation medicine is entering it's most transformative phase yet. As physics, AI and molecular engineering converge, the field moves beyond seeing disease toward predicting, guiding and curing it. The future of radiation science is not evolution, it's reinvention.