**Nuclear Medicine**

**Suman Khurana 1,2, Kavita Sangwan2 , Arun Mittal 1, Parveen Kumar Goyal2, , Rupali Sharma 1**

1. Amity Institute of Pharmacy, Amity University Haryana Amity Education Valley,

Manesar, Gurugram- 122413, Haryana. India.

1. Department of Pharmacy, Panipat Institute of Engineering and Technology (PIET) Samalkha, Panipat, Haryana-132102, India.

**Introduction**

Nuclear medicine (NM) is a field of medicine that uses ionizing radiation from unsealed sources to diagnose, treat, and study diseases. Radiopharmaceuticals are used in most treatments, mostly for diagnostic purposes (1).This is different from conventional radiology and radiotherapy methods, which typically apply radiation from an external source.Since its inception in the 1950s, nuclear medicine has grown to be relatively common, and most medium-sized and major hospitals include nuclear medicine departments (2).Targeting compounds that have been radiolabeled and given to patients are known as radiopharmaceuticals. They could be biologicals, chemicals, or particles (3).Therefore, it is crucial for operator and patient protection that radiopharmaceuticals be prepared and used in a safe and knowledgeable manner(4). For the creation of more effective medicinal or imaging radiopharmaceuticals, it is required to understand the processes through which the radioactive elements interact with the various compounds, medications, cells, and organs(5).Nuclear medicine is a cutting-edge diagnostic technology that requires the expertise of a well-educated and trained workforce from a variety of specialties, including engineers, technicians, pharmacists, doctors, and physicists. Its structure varies from nation to nation(6). The utilization of radiopharmaceuticals, or open sources of radioactivity, is the cornerstone of nuclear medicine imaging, which are typically delivered intravenously and virtually always systemically.With the aid of tools like gamma cameras, the ionising radiations that come along with the administered radioactivity's decay can be seen, measured, and imaged.In clinical practise, as well as in preclinical and clinical research, nuclear medicine imaging has a variety of significant benefits(7). Nuclear medicine techniques include single photon emission computed tomography (SPECT), positron emission tomography (PET), PET-CT, micro-PET (with ultra-high resolution), and micro computerized axial tomography (micro-CAT).These methods are employed to examine biochemical dysfunctions as early illness indicators, their causes, and connections to a range of disease states, including cancer, cardiovascular disease, and mental disorders(8,9). The pictures produced by positron emission tomography (PET) are entirely quantitative and parameterizable according to the quantity of activity present (for instance, in units of MBq/cm3)(10).Nuclear medicine imaging can have some disadvantages, though. The full-width half-maximum of the system's point or line spread function, which ranges from ;5 mm for PET to ;10 mm or more for single-photon emission computed tomography, is one illustration of coarse spatial resolution (SPECT)(11).Because radiation-based imaging is used in nuclear medicine, it exposes patients to low but not negligible radiation doses, with effective doses and maximum organ-absorbed doses per study typically being in the range of ten millisieverts (mSv) and several centigrays (cGy), respectively(12).Additionally, the limited anatomical information present in nuclear medicine pictures may make their analysis and interpretation more difficult. Due to the growing accessibility of multi-modality (i.e. PET-CT and SPECT-CT) technologies, nuclear medicine images showing in vivo function may be recorded and merged with anatomic images, basically circumventing this restriction(7,13,14). Gamma cameras have recently been combined with magnetic resonance imaging (MRI) or computed tomography (CT), creating hybrid devices that improve the accuracy of discovering lesions or functionally damaged tissues (15).The type of radiation employed determines the diagnostic and therapeutic applications.Technetium-99m is the most often utilized agent for gamma emitters in diagnostic procedures. The most common treatments employ beta radiation emitters like iodine-131 (15). For illnesses in oncology, cardiology, neurology, infectious and inflammatory diseases, nuclear medicine has diagnostic, prognostic, predictive, and intermediate endpoint biomarkers.The ability of PET systems to diagnose are being revolutionized at the same time by technological advancements like total-body and hybrid PET/MR imaging.Radiomics, machine learning, and artificial intelligence (AI) have all become popular buzzwords, but they have not yet reached their full potential for clinical decision-making.Theranostics, or using a single target for radionuclide imaging and treatment, was pioneered by radioiodine therapy. Later, the theranostic principle was successfully used in the treatment of paraganglioma, lymphoma, neuroendocrine tumors, neuroblastoma, and, most recently, prostate cancer (16).

**History**

**The Discovery of Radiation and Radioactivity**: On November 8, 1895, Wilhelm Roentgen was working with a cathode ray tube, also known as a Crooke's tube, he was investigating cathode rays by measuring the electrical discharge-induced light emissions in an evacuated glass Hittorf-Crookes tube (i.e. electrons) (shown in fig. 1). When he turned on the tube, which was itself covered in thick black paper, he discovered that a fluorescent, platino barium-coated cardboard screen would glow a distance away every time he did so (17). He correctly foresaw that the discovery was brought about by penetrating radiation released by the tube.Roentgen continued his research over the following seven weeks and discovered that various materials inhibited x-rays to varying degrees.The hand of his wife holding her wedding ring was one of the earliest medical images made possible by the varied attenuation by soft tissues and denser bones.In January 1896, he presented his research to the Wurzburg Physico-Medical Society, to predictably high praise (18). Reversibility of scientific events was still seen as an acceptable principle in the 1800s (19). Can exposure to intense visible light cause phosphorescent materials to produce x rays if x-rays caused them to glow (emit visible light) in the first place? Antoine Henri Becquerel conducted a test on this theory. In order to block visible light, he covered photographic plates in black paper in February 1986 and subjected uranium salts to intense sunshine. He then developed the plates afterwards.He mistakenly inferred from the salts' contour on the photographic plates that phosphorescence produced x-rays while sunlight was absorbed by uranium salts. On February 24, 1896, Becquerel presented his preliminary findings at a conference of the French Academy of Science (20,21,22). Becquerel stored the dark-paper-wrapped photographic plates, packs of uranium salts, and an attenuating Maltese cross medallion in a drawer for later use. He processed the photographic plates the next day even though they weren't supposed to have been exposed to uranium salts' probable x-ray emission. While some wonder why he did it, others claim that Becquerel was simply being thorough or

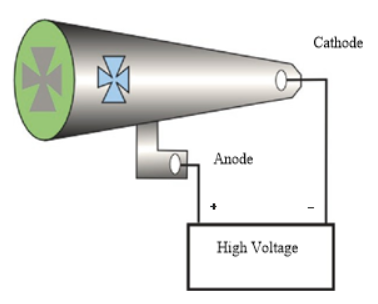


Fig.1. To examine cathode rays, a Hittorf-Crookes tube.

(Illustration by https://commons.wikimedia.org/wiki/ File:Crookes\_tube2\_diagram.svg).

lucky, which is serendipity similar to the discovery of penicillin (23). In an effort to develop color photography, French army captain Claude Félix Abel Niepce de Saint Victor experimented with uranium salts. He published his findings in a series of notes to the Comptes Rendus of the Académie des Sciences (24, 25).Edmond mentioned Niepce de Saint Victor's studies with things coated in uranium nitrate darkening photographic plates in a book he published in 1868 (26). The term "radioactivity" was coined by Marie and Pierre Curie, who also tried to chemically pinpoint the radiation's source. For failing to reference the earlier reports in his initial publications from 1896 to 1897, Becquerel came under fire (27). The Nobel Prize was shared by Becquerel and the Curies, not just for the discovery of radioactivity, but also for their joint groundbreaking work on describing radioactive compounds generally (27).

**The Discovery of the Neutron**: Early in the 20th century, Rutherford, Ernest created a primitive model of the atom that featured Protons with a positive charge and electrons with a negative charge. However, it was understood at the time that an element's atomic mass was concentrated in its nucleus and was roughly equal to twice its atomic number (or number of protons). The uncharged neutron, a significant missing component of the puzzle, was not included in Rutherford's model, thus numerous researchers went out to uncover the elusive particle. Rutherford later became the first to realize that one element might be artificially changed into a different element (28). He discovered that occasionally an alpha particle was halted and an extremely kinetic proton was produced after blasting nitrogen gas with alpha particles. The 14N (p,p)17O nuclear reaction was used for the first time to create oxygen-17. Herbert Becker and Walther Bothe demonstrated in 1930 that bombarding with alpha particles, Be, B, F, and Li released from polonium (Po) caused the emission of extremely invasive radiation. The daughter and son-in-law of Marie and Pierre, Irène and Frédéric Joliot-Curie, studied these reactions and hypothesized that the radiation generated was high intensity gamma rays. But when scientists allowed these "gamma rays" to strike a tiny slice of paraffin, it has several hydrogen atoms, the paraffin discharged hydrogen nuclei at a very high speed (29). Chadwick carried out the alpha particle bombardment experiment once more and discovered that the results supported the energy and momentum conservation in the production of 12C and a neutron (29).

**The Tracer Principle and the Discovery of Artificial Radioactivity**: Following in the footsteps of Pierre and Marie Curie, René and Frédéric Joliot-Curie created radioactive elements in 1934 by subjecting stable nuclides to alpha particle radiation. More specifically, the Joliot-Curies used alpha particles to attack a variety of elements, such as H, He, Li, B, Be, C, N, O, F, Na, Al, Ca, Mg, Ni, and Ag. Aluminum (Z = 13) was blasted by Polonium's alpha particles decay., resulting in the production of (Z = 15) Radioactive phosphorus and a neutron.

27*Al13* + 4*He2 →* 0*P15* + 1*n0*

*30P15 →* 30*Si14* + 0 *p1*

They were able to prove that In fact, they had formed artificially introducing a new element by condensing the radioisotope nitrogen-13, which emits positrons into a different vessel after a similar reaction with boron, which released radiation within a t1/2 of ten minutes. But they quickly managed to replicate and validate their finding of the creation of artificial radioactivity(30). The Nobel Prize in Chemistry was given to Irène and Frédéric Joliot-Curie in 1935 for their work in the production of new radioactive elements (31).Lawrence was using the cyclotron to produce fake radioactivity as well, but he was oblivious to these residual emissions because the lab's Geiger counter was controlled by the same switch as the cyclotron. In 1938 at Berkeley, Emilio Segre and Glenn Seaborg and John Livingood made the discoveries of technetium-99m and iodine-131 owing to the efforts of Lawrence's crew and the early 1930s with the Joliot-Curies. Additionally, it paved the door for the radionuclide production for SPECT and PET using cyclotron. The physics Nobel Prize was given to Ernest Lawrence in 1939 "for the invention and development of the cyclotron and for findings obtained with it, especially with reference to artificial radioactive elements" as a result of his hard work (32). The "father of nuclear medicine," George de Hevesy, initially proposed the radiotracer concept, which supports using radionuclides to examine the stable atoms and molecules' behavior (33). Bismuth-210 was employed in the first radiotracer experiment on animals to monitor the movement of Bi-containing antisyphilitic medicines in rabbits (34. 6, 22).De Hevesy and a colleague used the isotopic dilution technique for the first time in clinical sciences to calculate their bodily water content, which was 43 liters with a 50% turnover every nine days (35). Of course, these were the initial subjects, consuming progressively larger aliquots of water that had been tracer-injected with deuterium. One of the most significant investigations revealed that the skeleton could absorb and release phosphorus, demonstrating for the first time that the bone is an active organ like any other(36).

**The Use and Discovery of Iodine Radionuclides**: Only a few years after iodine's discovery in seaweed in 1811, the effects of iodine on the thyroid were first researched. Amazingly, it took only 8 years for iodine to be employed as a goiter treatment (37). Saul Hertz, a member (and eventually director) of the MGH Thyroid Clinic, questioned whether iodine could be turned radioactive during a colloquium at Harvard Medical School in 1936. Then-MGH President Karl Compton promised to look into it (Becker DV et al.1996). The outcome was a cooperative initiative between the Massachusetts Institute of Technology and the Massachusetts General Hospital that was designed to produce iodine -128 (t1/2 = 25 min) utilizing a neutron source and research its absorption in rabbits(38). They announced their findings in 1938 after using deuterons from the Berkeley cyclotron to bombard tellurium -128and produce Iodine-130 (t1/2: 12 hours) and Iodine-131 (t1/2: 8 days)(39). Iodine -131 studies in the future made it possible to trace the radionuclide in living things for extended periods of time (40).They discovered that the therapy of metastases required thyroid ablation, which lessened the thyroid's competition for iodine uptake(41, 42).These groundbreaking trials transformed thyroid carcinoma from a terminal illness to one with an approximate 85% overall survival rate (43).

**Studies using Carbon Radionuclides**: By blasting boron oxide with deuterons, late in the 1930s,Berkeley's Ernest Lawrence laboratory was regularly creating carbon-11 (C11; t1/2 = 20 min). Later, in the 1970, the Welch lab and Raichle and coworkers actively used the photosynthesis-based technique to produce 11C-labeled glucose (44, 45). The manufacture of carbon-14 was thereafter vigorously pursued by Kamen and Ruben. They could have built it based on calculations, but despite expecting it to have a longer half-life, they had no idea what it would be (46). On Berkeley's 60-inch cyclotron, Kamen created an iron target and attacked it with 5700 Amp Hours of 7 to 8 MeV deuterons in 1940. By precipitating CaCO3, Ruben examined the irradiated target and discovered persistent activity that may be attributed to carbon-14(47). The estimated half-life of carbon-14 by Kamen and Ruben was 4000 years, which was relatively close to the actual half-life, which was discovered many years later and is 5700 years (48).

**The 99Mo/99mTc Generator and Radiopharmaceuticals Labeled with 99mTc**: Segre and Perrier made the discovery of the element technetium in Palermo, Italy, in 1937(49). In order to examine the element's shorter-lived radionuclides, Segre went back to Berkeley and collaborated with Seaborg. This research resulted in the finding of technetium 99m (t1/2 6 h)(50). Technetium 99m is the perfect nuclear material for imaging molecular function in vivo because to its extensive chemistry, intermediate photon half-life, photon energy of 140 keV, and no particle emissions, Powell Richards vigorously pushed the use of technetium-99m as a result in the 1950s and 1960s(51, 52). Beck noted that In the 1960s, 150 keV was the appropriate detection energy for sodium iodide crystals (53). Iodine-132 rather than technetium 99m was the first generator system to be created (from tellurium-132)(54). The radioactive impurity in this tellurium-132, which was produced from fission products, was discovered by chance(54, 55). The tellurium-132 was subsequently shown to be followed by the impurity molybdenum-99 during the separation process, which was later used to create the Mo-99/Tc-99m generator (56, 51).

**Instrumentation for imaging development**: The next breakthrough was the creation of the rectilinear scanner, which from the 1950s through the early 1970s served as the primary tool for nuclear imaging and automated the positioning of the scanner. The time it took to photograph big organs was a major drawback of this technology. Hal Anger made a huge advancement in this area by creating a gamma camera with collimation to view the entire organ of interest at once and a number of photomultiplier tubes to increase the effectiveness of detection (57, 58.). In 1953, Brownell and Sweet developed a multidetector instrument using positron-emitting radionuclides to detect brain tumors (59, 60, 61).David Kuhl and Roy Edwards introduced the ideas of longitudinal and transaxial tomography and a nuclear medicine tomographic imaging apparatus in the 1960s (62). Transverse axial tomography was used by Godfrey Hounsfield to produce radiography, which he later used to create positron emission tomography (PET)(63).In 1975, Ter-Pogosian-filtered back projection, Phelps, and Hoffman were used to create a PET device (65, 66).The first camera that revolved around the patient wasn't invented until Keyes et al1977 .'s study at the University of Michigan (67). Larsson introduced the cantilever system in the 1980s as a result of this (68).

**Radionuclide Manufacturing**: After the cyclotron was built at Berkeley and Irene Curie and Frederic Joliet discovered how to create isotopes artificially, carbon-11 (t1/2 -20 min), nitrogen-13 (t1/2 -10 min), and fluorine-18 (t1/2120 min) were produced and used as biological radiotracers. Kamen investigated how plants absorb carbon dioxide that had been tagged with carbon-11 in the 1930s (69).Furthermore, Cramer and Kistiakowsky studied metabolic pathways using lactic acid tagged with carbon-11 in the 1, 2, and 3 locations(70).Tobias et al. employed carbon-11 for the first time in people to explore how carbon monoxide behaved in people after being labeled with 11C (71). Rueben et al's initial investigation using nitrogen-13 was aimed at investigating nitrogen fixing by non legume plants. Volker et al. studied the uptake of fluoride by bone and tooth enamel using fluorine-18 in the early 1940s. Nevertheless, despite these early developments, curiosity about these transient radionuclides decreased in the 1940s and 1950s(72). In order to measure the oxygen tension in malignant neoplasms, Powers and Ter-Pogossian created oxygen-15 (t1/2 = 2.0 min) in the physics department of Washington University's cyclotron in the 1950s. This innovation spurred an increase in evaluating cerebral metabolic studies and repertoire using radioactive gases (73, 74).

**The Discoveries and Uses of FDG**: 2-Deoxy-2-[18F] Fluoro-D-glucose, often known as [18F], Fig.2.shows that the hexokinase process is prevented by eliminating the hydroxyl in the 2-position.fluorine-18 atom replaces a hydroxyl group in the radiolabeled form of glucose known as FDG, sometimes known as just FDG. FDG was created specifically to track how much glucose is being used by the human brain. The hexokinase reaction is isolated when 2-deoxyglucose is used (75).Louis Sokoloff and Martin Reivich’s 1975 Science article proved to be a very useful resource in order to research glucose metabolism (76).

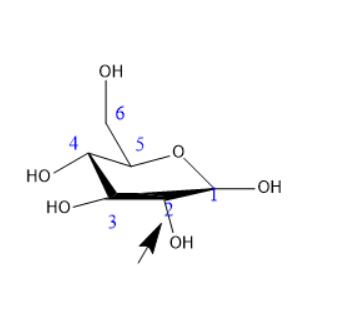


Fig .2: Shows that the hexokinase process is prevented by eliminating the hydroxyl in the 2-position.all carbons in the molecule of glucose are numbered; the black arrow points to the carbon that Sokoloff and Reivich have assigned the carbon-14 designation to.

To see the [18F]FDG in a human, it was essential to fly the substance to Philadelphia, which at the time had the nearest PET scanner. It should come as no surprise that the logistics were difficult. The [18F] FDG was made at Brookhaven, packaged by the health physics group, delivered to a local airport, loaded onto a small four-person plane, flown to Philadelphia airport, met by an ambulance from the hospital, and driven to the University of Pennsylvania so that it could be administered (77). Following this initial delivery, [18F] FDG's clinical application significantly increased. Preclinical research carried out in the late 1970s and early 1980s revealed that [18F]FDG, despite initially being created for brain imaging, may also be effective for monitoring heart metabolism and tumor metabolism (78). Kurt Hamacher made a big development by using [18F] fluoride to synthesize FDG in 1986(79) (Fig.3).

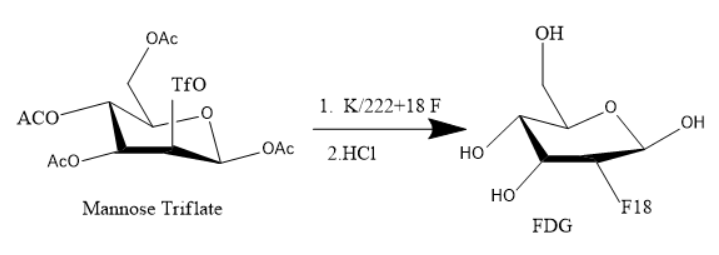


Fig 3. Synthesis of FDG

**A brief history of Indian nuclear medicine :** The "Father of Indian Nuclear Program," "Dr. Homi Jehangir Bhabha," must be mentioned in the historical context of the development of nuclear medicine in India. Dr. Homi Bhabha was given the responsibility of overseeing and developing India's bold nuclear energy programme after independence by Pandit Jawaharlal Nehru, the country's first prime minister (in 1948). Atomic Energy Establishment, Trombay (AEET) was constructed by Dr. Bhabha in 1954. a pioneering research reactor in Asia and India outside of the USSR and Russia, APSARA, reached criticality in 1956. In 1960, the site of AEET also saw the operationalization of the second reactor, CIRUS. This resulted in the domestic manufacture and availability of numerous radionuclides with medical applications (131I, 32P, and 51Cr). Particularly, radioiodine (131I) was becoming more and more relevant in clinical studies and practice. Since the early 1960s, the Bhabha Atomic Research Center, later known as the Isotope Division of AEET, has undertaken the enormous challenge of producing and commercially supplying radiopharmaceuticals to hospitals in India (80, 81). In 1956, with approval from the the late Pandit Jawahar Lal Nehru, an Indian Prime Minister, the multidisciplinary study group known as "Radiation Cell" was established within the purview of the Ministry of Defense with the goal of conducting biomedical research utilising radioisotopes and applying radiation to medicine. India began Allied Sciences and Nuclear Medicine Institute (INMAS) received approval from Delhi University in 1963 to offer the first programme of its kind in the world (82). The early 1960s contributions from the BARC Isotope Division and later the BRIT, the Board of Isotope and Radiation Technology (after 1989) served as the fundamental hub for the development and organization of India's current nuclear medicine culture (82). At KEM Hospital in Mumbai, In 1960, Dr. R. S. Satosker carried out the initial thyroid uptake measuring investigation. Later, at RMC, uptake measurements were standardized (83). The slow rectilinear scanner was purchased by RMC in 1965, and the fast rectilinear scanner took its place in 1969 (84). RMC began offering diploma programmes in radiation medicine and medical radioisotope techniques, both of which are approved by Mumbai University, in 1973. In 1982, the Indian government's National Board of Examination recognised nuclear medicine as a broad field of study and granted RMC accreditation for its Diplomate of National Board training programme. At the Sanjay Gandhi Postgraduate Institute in Lucknow, the MD programme began for the first time in Asia and India in 1990 (83, 85). With a total of 1425 nuclear medicine specialists as life members, the oldest and largest professional organization is the Society of Nuclear Medicine, India (SNMI). The inaugural Annual Conference of SNMI, which was founded in 1967, was held at RMC in Mumbai in 1968 (83). Since then, SNMI has been holding its Annual Conferences across the nation with the aim of fostering scholarly dialogue and increasing clinician awareness of the modality. RMC hosted the SNMI's first Conference in 1969(86). There have been 233 operational gamma cameras (Single-photon emission computed tomography [SPECT]/SPECT-computed tomography [CT] systems) in India since 1969, when the first gamma camera was commissioned at RMC. A revolution in molecular imaging had begun in India with the first PET (2002), first medical cyclotron (2002), and first PET-CT (2004; all of which were performed in Mumbai) (87, 88).Table.1 Nuclear medical facilities in India, categorized (Table data is driven by(89):

| Facility name | Quantity in numbers |
| --- | --- |
| Gamma cameras/SPECT | 163 |
| SPECT‑CT | 70 |
| PET‑CT | 222 |
| PET‑MRI | 3 |
| High dose radionuclide therapy ward | 92 |
| Cyclotron | 19 |

CT: Computed tomography, SPECT: Single‑photon emission CT, PET: Positron emission tomography, MRI: Magnetic resonance imaging Gamma cameras/SPECT.

The All India Institute of Medical Sciences in Delhi began offering a doctorate in therapeutic nuclear medicine in 2015. Nuclear medicine facilities in the nation have rapidly expanded as a result of the design and deployment of affordable generators (Having low specific activity and loaded 99Mo) using locally developed solvent extraction (Methyl Ethyl Ketone) technology. There are 293 nuclear medicine departments nationwide, according to the Atomic Energy Regulatory Board's list of facilities published in July 2018. The remaining 86 percent are privately held companies, of which 14% are owned by the government (89).

**Design of Radiopharmaceuticals**

**Radiopharmaceuticals**

Radiopharmaceuticals consist of two components i.e a radionuclide for permitting external scan, and non radioactive element for acting as a carrier for conducting the radionuclide to the particular organs (90). Radioactive elements are highly energetic unstable nuclides because of excess energy i.e stabilized by emission of electromagnetic radiation (𝛂, 𝜷 and 𝛄) during the decaying process of radioactive elements (91). For diagnostic applications, the radioactive element is utilized as an emitter of electromagnetic radiation (gamma or X-rays), whose detection allows to calculate the radiopharmaceutical's concentration. In contrast, the radioactive material can be applied therapeutically, where the ionizing radiation released by the radionuclide's decay is used to kill cells.

Single photon emission computed tomography (SPECT) and positron emission tomography (PET) are nuclear medicine procedures used for detection of radiations emitted from radionuclide distributed in the whole body or in the particular part of the body.

The image's contrast will be determined by the difference in radionuclide concentration between the target tissue and the surrounding tissue. Static imaging offers a picture of the radionuclide distribution at a particular period following the injection of the tracer, typically when the target/background ratio is at its best.

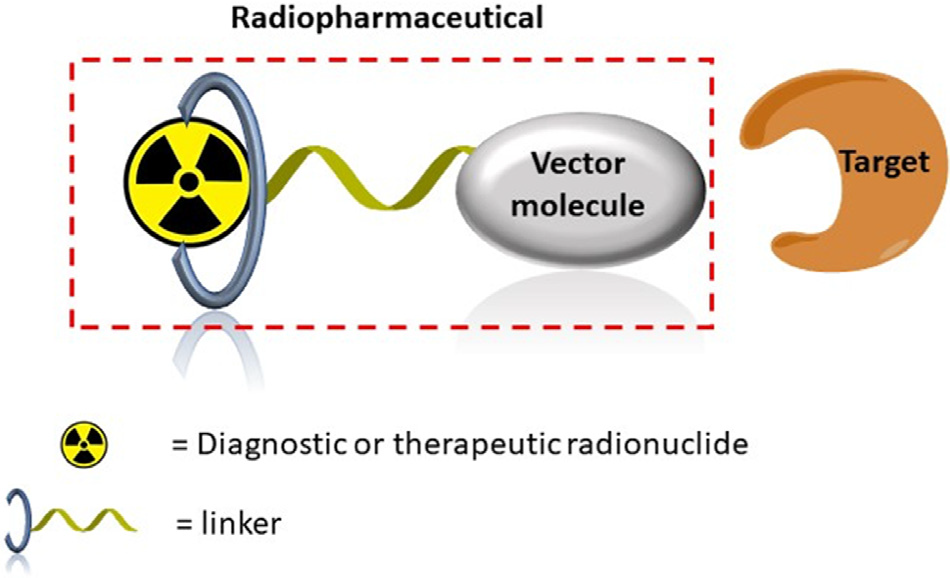
he radiopharmaceutical is made up of a linker between a radionuclide for medical or diagnostic use and a vector molecule, as illustrated in figure. ****

Figure: radiopharmaceutical design

The radionuclide emits radiation, and biomolecules expressed in tissues or cells are the target of the vector molecule with a specific intent to perform diagnostic and therapeutic procedures. The vector molecule may be a small molecule, a peptide, protein and nanoparticle. For the diagnostic and therapeutic purpose, the vector should have high specificity and selectivity when it is conjugated with radionuclide. When the radionuclide is in ionic form, such as [131I]I for the treatment of thyroid cancer or [89Sr]Sr2+ for the relief of bone pain, the radionuclide may also serve as a vector molecule.

The linker, which is the third component, aids in creating a secure bond between the vector molecule and the radionuclide. Bifunctional chelators are required for radiopharmaceuticals based on radiometals because they guarantee both a stable complex with radiometal nuclei and a covalent link with the vector.

Based on the decaying property of the radionuclide, it is determined that the radiopharmaceutical will be used for diagnostic or therapeutic purposes.

**Vector**

For the production of, radiopharmaceutical, vector is the main component as it is responsible for targeting the tissues for maintaining the higher concentration of radionuclide. As a result, therapeutic radiopharmaceuticals can selectively irradiate the target cells while still providing the picture contrast necessary for diagnostic imaging.

Small molecules, peptides and proteins and cells are used as vectors that are explained further.For intracellular targets, small molecules are used as vectors because of having specific characteristics such as membrane permeability and designing molecules within the cytoplasm and nucleus and can cross the blood brain barrier (BBB). Small molecules including Biochemicals Fatty acid, amino acids, nucleosides and xenobiotics are used as vectors.

Peptides are used as vectors because many peptides are present in tumor tissues as compared to normal tissue. Peptides contain less than 50 amino acids and diffusion is higher into the target tissues and long retention period in tumor cells. Peptides are synthesized easily and have favorable pharmacokinetic characteristics such as high concentration in target tissue, rapid clearance from blood pool and non targeted tissues. The receptors sich somatostatin, chemokine,

**Radionuclide**

Radionuclides are unstable and contain excess energy because of heavy nuclei or imbalance in ratio of proton and neutron. The electromagnetic radiations ( gamma rays) or particles ( alpha and beta particles) are released due to excess energy present in radionuclide. These can be produced artificially or spontaneously via cyclotrons, particle accelerators, or the radioactive decay of other radionuclides.

**Nuclear Medicine techniques**

In nuclear medicine, the camera will construct a picture taken at the radiation's emission points. The image is observed on the monitor and the anomalies are checked.(92). These methods include Positron Emission Tomography (PET) and Single Photon Emission Computerized Tomography (SPECT).

**Single Photon Emission Computerized Tomography (SPECT)**

Single-photon emission computed tomography (SPECT) is a most frequently used technique in diagnosis. It creates a 3-dimensional image of how a radioactive tracer is distributed throughout the body after being injected into the bloodstream and then absorbed by specific tissues(93). Utilizing specialised nuclear medicine cameras allows for this. So, using SPECT, a clinician can evaluate the perfusion and functionality of particular tissues. SPECT is based on the detection of single photons released upon a radionuclide's decay by spinning detectors, resulting in a 3D representation of the radionuclide's distribution in the body (94).Energy levels between 100 and 200 keV are necessary for effective imaging. Technetium (99mTc, T1/2 = 6 hours) in its metastable form is the radioisotope that is most frequently utilised in SPECT scans. In the clinic, the 99mTc-complexes are frequently used to assess cardiovascular illnesses, renal excretion, identify tumour lesions, and CNS disorders (95).

Table: Radionuclides frequently used in SPECT imaging (96)

| S No. | Radio Nuclei | Half Life (h) | Type of Emission | Photon emission Energy (MeV) |
| --- | --- | --- | --- | --- |
| 1 | 123I | 13.2 | Electron capture | 0.16 |
| 2 | 99mTc | 6 | Isomeric transition | 0.14 |
| 3 | 111In | 67.9 | Electron capture | 0.17/0.25 |
| 4 | 67Ga | 78.3 | Electron capture | 0.09/0.19/0.30 |
| 5 | 201Tl | 73.1 | Electron capture | 0.17 |

**PET**

PET works by detecting two photons with a combined energy of 511 keV that are emitted in opposite directions upon the annihilation of positronium, which is created when an electron and a positron from a neutron-deficient nuclei combine78

Table: Commonly used radionuclides for PET ( 97, 98, 99)

| S No. | Radio Nuclei | Half Life | Mode of decay | Decay Product | Energy (MeV) |
| --- | --- | --- | --- | --- | --- |
| 1 | 11C | 20.4 min | 𝛽+ | 11B | 0.960 |
| 2 | 13N | 10 min | 𝛽+ | 13C | 1.199 |
| 3 | 15O | 2.0min | 𝛽+ | 15N | 1.732 |
| 4 | 18F | 109.8 min | 𝛽+,  Electron Capture | 18O | 0.634 |
| 5 | 64Cu | 12.8h | 𝛽+,  Electron Capture | 64Ni  64Zn | 0.653  0.329-1.675 |
| 6 | 68Ga | 67.6 min | 𝛽+,  Electron Capture | 68 Zn | 1.899  0.227-2.821 |
| 7 | 76Br | 16 h | 𝛽+,  Electron Capture | 76Se | 3.382  0.599 |
| 8 | 82Rb | 1.3 min | 𝛽+, | 82 Kr | 3.378 |

**Applications of nuclear medicine:**

**Clinical Applications:**

**A)Renal and Urinary Tract Disorders:** 1**.**The renogram acquired with Diethylene triamine penta-acetic acid (DTPA) or 123I Hippuran-tagged 99mTccan be used to differentiate between urinary blockage and atonic dilatation; measurements of cortical transit and entire kidney, as well as responsiveness to furosemide, can also be obtained (100, 101, 102). 2.Detection and monitoring of vesicoureteric reflux utilising a direct cystogram with 99mTc pertechnetate or an indirect cystogram with 99mTc DTPA, both of which result in substantially lower gonadal irradiation than a radiological cystogram (103, 104, 105). 3.When determining creatinine clearance is not necessary, the overall clearance must be evaluated. A 99mTc DTPA or chromium-51 edetic acid intravenous injection is given between two and four hours later, two to three blood samples can be used to accurately measure glomerular filtration rate (51Cr EDTA). The latter method is more precise, simpler to use, does not involve collecting urine, and is helpful for renal illnesses that affect both kidneys equally(106). 4. Renal function evaluation of a person: this information is typically available during the initial stages of a 99mTc DTPA, 123I Hippuran Renogram, or 99mTc DMSA uptake. This is indicated in the study of uropathies and particular nephropathies, which may inflict unequal damage to the kidneys both before and after surgery(107, 108). 5.Accurate topographical description of kidney location, kidney morphology, and parenchymal damage using 99mTc DMSA static images (acute and chronic pyelonephritis, trauma) ( 109, 110).

Detectors used in kidney and urinary tract conditions (111)

| Detectors | Physiology |
| --- | --- |
| Diethylene triamine penta-acetic acid | only by the glomerular fraction |
| Technetium 99m-dimercaptosuccinic acid 99mTc | the tubular cells' uptake |
| Edetic acid-chromium 51 | Only glomerular filtration can eliminate; not suited for in vivo measurements |
| Hippuran 123I | 80 percent removed via tubular secretion and 20 percent through glomerular filtering |
| Pertechnetate technetium 99111 | bladder-filling and -voiding tracer |

**B)Pulmonary Diseases** : 1.To confirm or rule out the identification of local lung illness when chest x-ray pictures are normal or ambiguous (Small lungs, bronchiectasis, aspiration pneumonia, hyperlucent lungs, foreign body). When selecting patients who should have more invasive exams, For instance, the potential for developing bronchiectasis or receiving a foreign body is relatively low in the presence of a normal scan (bronchoscopy, bronchography).2. Before performing surgery to remove a lobe, to assess lung function (bronchiectasis, sequestration).3. prior to doing angiography, to identify intrapulmonary shunts and other vascular irregularities (a negative scintigraphy result could prevent angiography).4. to monitor severe disease, such as cystic fibrosis, bronchiectasis, or viral pneumonia after effects.5. The detection of primary arterial disease and pulmonary embolism requires coupled perfusion and ventilation investigations 6. in order to assess mucociliary removal (112, 113, 114, 115, 116)

| Tracers | Physiology | Comments |
| --- | --- | --- |
| Macroaggregates-technetium 99m or human albumin microspheres-technetium 99m | Regional perfusion | high-quality static graphics that are simple to create, affordable, and age-inclusive |
| Krypton gas 81m | Localized ventilation | Good cost and organizational requirements, static images of high quality when breathing normally with a mask, and low sensitivity for subsegmental abnormalities in infants younger than one year |
| Xenon gas 133 | Localized ventilation | Demands participation from the patient (patients must be over 6 years old), produces static, subpar photographs after a single breath, and is moderately priced. |
| Millimicrospheres aerosols-technitium 99m | Localized ventilation | Still needs more work standardization |

**C)Hepatosplenic Disorders**: 1) Jaundice to rule out in the child biliary atresia; to evaluate the biliary tree's post-surgical patency; to evaluatethe choledocal cysts' discharge; and to determine the existence of dilated ducts, for example, Caroli's sickness. 2.Detection and monitoring of liver lesions that take up space using other imaging methods (computed tomography, ultrasound). 3) To find anomalies of the spleen and congenital heart disease that are present at birth (asplenia, polysplenia). (4) To identify accessory spleens or splenic trauma (idiopathic thrombocytopenic purpura)(117).

| Tracers | Physiology |
| --- | --- |
| Colloid-technetium 99m | liver and spleen's reticuloendothelial systems uptake |
| Damaged red blood cells-technetium 99m | spleen's selective uptake |
| Iminodiacetic acid (N substituted)- technetium 99m | Early absorption by the parenchymal liver cell and excretion into the duodenum via the biliary ducts |

**D)Gastrointestinal Tract Disorders**:1. Gastroesophageal reflux disease diagnosis and monitoring (including the syndrome of near-miss sudden newborn death, recurrent lung infections, and chronic vomiting)( 118).2. Studying conditions including caustic stricture, peptic oesophagitis, achalasia, and impaired neurogenic peristalsis (119, 120). 3.Meckel's diverticulum containing stomach mucosa is diagnosed (121). 4. evaluation of the 24-hour stomach emptying (122).

Tracers used to diagnose digestive system issues:

| Colloid-technetium 99m | Static image activity is influenced by osteoblast activity and blood flow |
| --- | --- |
| Krypton 81 in glucose | because to the tracer's incredibly brief life, it disappears quickly. |
| Pertechnetate-technetium 99m | the stomach mucosa actively absorbs |

**E)Thyroid Disorders**:1. Aplasia, ectopia, and regularly occurring glands are defined.2. Analyzing nodules in the neck and their connections to thyroid tissues.3. (3) Identification of a foliated lesion as a potential hyperactive adenoma in hyperthyroidism (rare in children) (123). A trusted tracer for determining thyroid function is 131 Iodine. Due to the high radiation, youngsters should not use it (123).

**F)Heart Diseases**: 1) Evaluation of the left to right heart shunt with the help of 99MTc pertechnetate.2.Using 99mTc macroaggregates, the right to left cardiac shunt is evaluated (MAA).3. Red blood cells that have been 99mTc-labeled or iTc pertechnetate (first pass) can be used to measure the function of the left ventricle (equilibrium).4. Right ventricular function can be evaluated with an 81mKr infusion or 99mTc pertechnetate (first pass) (124,125).

| Tracers | Physiology |
| --- | --- |
| Krypton gas-181 m | As soon as it comes into contact with air, this isotope will leave the solution. If the 81mKr is administered continuously intravenously, the isotope will first enter the right heart before moving on to the pulmonary circulation. Since the isotope will freely pass through the alveolar barrier and be ejected, it won't normally enter the pulmonary veins or the left heart. Good right ventricular structural delineation can be attained without any left heart superposition, allowing for the assessment of right ventricular contractility. |
| Macroaggregates-technetium 99m | Following an intravenous injection, the isotope will frequently become caught in the first capillary plexus and stop moving completely across the pulmonary capillary bed. The isotope can be found in the tystemic circulation, such as the kidneys, when there is a right to left shunt present. |
| Pertechnetate-technetium 99m | The right heart will transport this isotope to the lungs, followed by the left heart and the systemic circulation. The left heart phase isotope will travel to the systemic vascular system as well as to the lungs again when there is a left to right shunt. The shunt has a measurable value. |
| Technetium 99m red blood cells | Red blood cells are linked to the isotope during this time, it is possible to collect mass pictures of the beating heart over time in order to evaluate ventricular function. Function changes are measurable (ejection fraction). |

**Diagnostic Applications:** The diagnosis of disease is more routinely performed using nuclear medicine.In this instance, the patient is administered a radioactive material, and then its dispersion in the body (2). Following the administration of a radiopharmaceutical, its biokinetics are observed, and the target organ or body system is functionally studied, or the lesion viability and the targeted biological process are characterized and evaluated (3).The tool being utilized determines the mode of observation:1)Imaging technology: shows the temporal distribution of radioactivity that is visible at specific times or over a predetermined period of time.Displays of images can be 2D (static/dynamic whole-body images), 3D (tomograms), or 4D (dynamic/temporal tomograms).2) Calculating tools: Externally, a probe system is utilized to examine in vivo body system and organ function (called radioassay).It is important to remember that radionuclides are administered in such dosages for research and diagnostics that there are no detectable biological side effects (3).To visualize the activities of many organs, including the kidney, lung, thyroid, and heart, as well as bone metabolism and blood circulation, radiopharmaceuticals are administered orally, intravenously, or by inhalation in the imaging modality(126).Although the applications of integrated diagnostic systems have expanded to include cardiology, neurology, and the imaging of inflammatory diseases, they have demonstrated their clinical worth most prominently in the field of oncology (127).

**A)Diagnostic application of nuclear medicine in oncology**: Imaging is essential for the early diagnosis of cancer, precise disease staging, and evaluation of treatment response. Contrarily, "conventional" nuclear medical imaging (planar and SPECT) and PET can provide important additional functional information, albeit with a reduced spatial resolution compared to radiological methods. CT and MRI provide significant anatomical information but do not offer significant functional information on the lesions detected. Furthermore, by accurately co-registering anatomical and functional data obtained through the use of hybrid SPECT/CT and PET/CT equipment, complementary information is obtained that, in the field of oncology, translates into greater sensitivity (better ability to localize lesions) and greater specificity (exclusion of false positives caused by the physiological accumulation of radio composed): approach makes it possible to accurately determine the functional significance of uncertain lesions (128).

**SPECT/function CT's in oncology**

**Imaging of Differentiated Thyroid Cance**r: The most frequent endocrine neoplasia, differentiated thyroid cancer (CDT), often has one favorable prognosis. The standard course of treatment entails a complete thyroidectomy and iodine-131 ablation of any remaining thyroid tissue. The thyroid gland values are measured as part of the CDT follow-up together with the neck's ultrasonography and, if necessary, Iodine-131 scintigraphy (WBS). Lack of anatomical and physiological references, as well as radioiodine accumulation in thyroid tissue remnants that can mimic metastasis, can make it challenging to interpret the WBS. By finding more lesions, enabling accurate localization of lesions, and excluding lesions in regions of normal radioiodine accumulation, hybrid SPECT/CT imaging improves both the sensitivity and the specificity of radioiodine scintigraphy in CDTs (128,129).

**B)Diagnostic application of nuclear medicine in urolog**y: Between 50% and 60% of kidney tumors have been reported to be detectable with 18F-FDG PET/CT as a first diagnosis. It has not been demonstrated to significantly improve on traditional imaging techniques like CT and MRI for this purpose. Although dual-phase delayed imaging and after forced diuresis imaging were undertaken to lessen the impact of physiological urine activity, neither strategy outperformed the standard imaging protocol. After the main tumour was surgically removed, Additionally, it was found that the uptake of 18F FDG and the amount of GLUT 1 expression were not correlated (130,131,132). Standard procedures and recommendations do not advocate the regular staging of kidney tumours with 18F-FDG PET/CT. The fundamental cause of this is that due to the intensive physiological urine activity, 18F-FDG has a significant rate of false negatives for the underlying tumour. However, it has been suggested that in patients who are at risk, it may be helpful in demonstrating extrarenal metastatic illness (133, 134).

**SPECT/CT Tc99m Myocardial Imaging of Perfusion Test**: In 14% of T1 kidney tumor operations (4 cm), benign and malignant differentiation cannot be accomplished by traditional procedures, and 20–30% of operated cases' pathology outcomes are described as benign. As a result, a SPECT agent may be helpful for preoperative characterisation of primary renal masses even though no PET agent can be demonstrated to do so. Tc-99m Traditional gamma cameras employ MIBI, a non-specific tumor agent, for imaging. It is kept in the mitochondria of the cell in benign and malignant tumors with enhanced metabolic rate (135). Oncocytomas have higher Tc-99m MIBI absorption than other forms of RCC because they include more mitochondria (136). Tc-99m MIBI was positive in almost all of the patients who were pathologically determined to have an oncocytoma and who underwent Tc-99m MIBI SPECT/CT evaluation in the run-up to surgery, according to the findings of the few research on this subject. There was no Tc-99m MIBI uptake in patients, who were determined to have other RCC subtypes. Oncocytoma sensitivity was shown to range from 83 to 100% (137).

18F-FDG PET/CT is helpful in RCC for staging high-risk illness and showing therapeutic response in patients with metastatic disease. However, more research on common use is required. High sensitivity and specificity are provided by Tc99m MIBI SPECT/CT for the malignant-benign distinction of ambiguous renal tumours.Testicular tumor staging, restaging, and follow-up are all aided by 18F-FDG PET/CT , while not being engaged in the metabolic characterisation of original scrotal masses, especially in the assessment of seminoma patients with a persistent retroperitoneal lesion larger than 3 cm following therapy. Ga68 PSMA PET/CT has good sensitivity in all stages of prostate cancer, Its use is expanding, particularly in individuals with biochemical recurrence (138).

**C)** **Diagnostic Application in Cardiology**: For measuring and evaluating the signs and symptoms of ischemic heart disease, the main method for functional cardiac imaging is radioactive myocardial perfusion scintigraphy (MPS). For examining IHD, a popular noninvasive nuclear image acquisition method is SPECT(single-photon emission tomography) of the heart . Currently, SPECT is suitable for detecting and controlling IHD in all its facets, consisting of diagnostic, risk assessment and classification, myocardial viability testing, and left ventricular function testing (139). More recently, individuals who may have coronary artery disease have been able to receive better diagnosis, risk assessment, and treatment planning thanks to hybrid images that integrate coronary angiography with computed tomography (CT) and SPECT functional imaging (140). Tl-201: The first radiopharmaceutical used extensively in clinical myocardial perfusion imaging was tl-201 chloride (141). Sestamibi and tetrofosmin, two technetium-based agents, are currently both commonly used. . I123 MetaiodobenzylGuanidine (MIBG): A guanethidine analogue with similar properties to norepinephrine, a transmitter of the adrenergic system in the heart, is named MIBG. The ratio of uptake in the mediastinum to the myocardium (heart) is used to semi-quantitatively measure sympathetic innervation of the myocardium (142). I123 15- (p-Iodophenyl) The beta-methyl fatty acid analogue 3-R, S-Methylpentadecanoic Acid (BMIPP) 15- (p-iodophenyl) S-Methyl-3-R, 3-Pentadecanoic Acid (BMIPP), Since the drug is retained in the myocardium for a while, SPECT imaging with a conventional gamma camera is more advantageous (143). Stress-only imaging was advised in a recent information statement from the American Society of Nuclear Cardiology (ASNC) when used on carefully chosen individuals (144). Major cardiac societies, including the American College of Cardiology and American Heart Association, as well as other imaging associations, have made proactive measures to limit the use of cardiac imaging over the past few years. To guarantee that doctors are, in the majority of cases, performing the right test on the right patient at the right time, for nuclear cardiology, acceptable use criteria have been created (145). This has brought about a number of quick advancements that have improved the hardware in nuclear cardiology scanners' photon sensitivity. Furthermore, software that uses innovative SPECT reconstruction techniques on established and specialized systems has retained or even enhanced SPECT image quality with reduced count statistics. To minimize radiation exposure while retaining diagnostic performance, MPI procedures should be improved. Use of radionuclides with shorter half-lives, such Tc-99m and PET tracers, stress-only imaging where possible, and weight-based dose are all significant parts of this advancement (142).

**D)Diagnostic Application in Thyroid Disease**: We are aware that the sodium-iodide symporter (NIS), which was first characterized by Kaminsky et al. in 1993, is responsible for Intake of iodine by the thyroid gland (146).Through the use of thyroid scintigraphy and radioiodine uptake tests, the thyroid cells' ability to absorb iodine is still frequently utilized to assess thyroid function (147). Thyroid scintigraphy shows the location of thyroid tissue that is actively producing thyroid hormones in addition to the morphological knowledge obtained by ultrasonography (148). The assessment of technetium-99m absorption in the thyroid is given much attention. 99mTc uptake ranges from 0.5-2.0% in euthyroidism with typical iodine intake. Similar to iodine intake, this proportion falls in hypothyroidism, iodine pollution, and iodine insufficiency, while rising in Graves' illness. This simple measurement is performed as an addition to thyroid scintigraphy by comparing the number of counts in the regions of interest above the thyroid with the number of counts above the syringe carrying the 99mTc-pertechnetate before injection (149, 150,151). Patients are photographed in a planar fashion when they are lying or sitting. 123I, 131I, and 99mTc. Technetium-99m (99mTc), obtained from a molybdenum-technetium generator, is delivered intravenously in the form of pertechnetate. An analogue of iodine, 99mTc-pertechnetate, is delivered to thyroid cells by NIS in a manner similar to that of iodine isotopes. It is important to keep in mind that 99mTc absorption is not just restricted to thyroid tissue when interpreting scintigraphic pictures acquired with the radioactive substance. Thyroid imaging is another procedure that makes use of the iodine isotopes 123I and 131I (148,150). The most often utilized radioactive isotope of iodine is 131I, sometimes known as radioiodine, with a half-life of 8.1 days, this nuclide emits both beta and gamma radiation. The energy of gamma rays is 364 keV and is employed in diagnostic procedures. Due to these limitations compared to 99mTc and 123I, 131I scintigraphy should only be used to monitor treatment in patients with differentiated thyroid cancer (148,150). Differentiated thyroid cancer can be diagnosed with PET using 18F-FDG. Although it is not advised to use PET to diagnose benign thyroid disease, there are clinical scenarios in which a thyroid issue is inadvertently found during a PET/CT scan. When a single pulmonary nodule is present, for example, a PET/CT scan employing 18F-FDG is performed to distinguish between benign and malignant tumors. Identifying the surgical indications in cases of a follicular neoplasm or an unclear biopsy is a difficulty that frequently arises in thyroid management. The positive predictive value (PPV) of an image of a metabolically active thyroid nodule ranged from 33 to 50% in different prospective investigations. Additionally, the standardized uptake value (SUV) for glucose metabolism in the focal lesion did not enhance the diagnostic accuracy of PET(151,152,153). If a thyroid nodule is accidentally discovered to be metabolically active, a biopsy should be performed to rule for thyroid cancer. TSH and thyroid antibodies (aTPO, aTg) tests should also be recommended if there is diffuse 18F-FDG absorption. The iodine isotope 124I, which emits positrons, is available in some facilities. Its 4.2-day half-life. Compared to conventional 131I scintigraphy, the PET/CT with 124I provides better accurate pictures with the benefit of having no influence on thyroid stunning(154). Only the diagnosis of differentiated thyroid cancer can be made with this technique (155).

**E)Diagnostic Application in Pulmonary Embolism**: If left untreated, PE has a significant fatality rate. The diagnosis cannot be made merely only on clinical findings or the results of straightforward tests like Blood chemistry, simple chest radiography, or ECG. Therefore, imaging studies are necessary to support or disprove a PE diagnosis. The following products are utilised for mapping regional ventilation: radiolabelled aerosols 99mTc-DTPA and 99mTc-labeled Technegas, inert gases 133Xe and 81mKr. Historically, the agent utilized for ventilation research was 133X e (156,157). By administering radioactive tracers to a vein in the arm, perfusion scintigraphy is carried out. The particles that are used in commerce are called MAA and are 99mTc-labeled (158). To reduce acquisition time and the possibility of patient movement during V/PSPECT, a dual or triple head gamma camera with a wide field of view is necessary. Palmer et al. thoroughly investigated the correlations between SPECT imaging activities, acquisition periods, collimators, and matrices (159). V/PSPECT is highly advised since it enables accurate PE detection even when pneumonia and diseases like COPD are present. In COPD patients, Technegas is preferable over DTPA.When offered, 81mKr is beneficial. In order to minimise the radiation exposure without clinically significant image degradation. This means that before the perfusion scan, which uses 100-120 MBq for both the V/ PPLANAR and V/PSPECT, the ventilation scan should use 30 MBq of 99mTc-aerosol. Only a perfusion scan is advised during pregnancy. Holistic interpretation should take the place of probability interpretation as it is no longer relevant.Mismatch in more than one subsegment is an essential PE criteria (160).

**Future of Nuclear Medicine**

Applications of radioisotopes in nuclear medicine include both diagnostic and therapeutic procedures as we have already discussed in this chapter.Actually, the key factors that led to the development of nuclear medicine as a distinct medical field were the accomplishments in using radioiodine to treat thyroid issues, both benign and cancerous.

**Oncology:**

Since 1990, the real number of cancer diagnoses has risen by 73%, despite the fact that In an age-standardized population, the incidence of invasive cancers has steadily decreased throughout the 1990s (161). This trend is caused by several factors, including an older population, higher incidence of cancer, and the detection of tumours through screening that would not have manifested as symptoms or resulted in death throughout the anticipated lifetime of a patient. From 469,000 in 1990 to 606,000 in 2020, 609,360 in2022 number of cancer-related fatalities in the US has climbed more gradually (161,162).As a result, a lot more patients are coping with a cancer diagnosis.In light of this, it is all but likely that cancer imaging will continue to be a key area of nuclear medicine practise in the years to come.Currently,oncologic imaging investigations' interpretation is almost entirely a manual, subjective procedure, including the scrolling through many stacks of images by nuclear medicine specialists or radiologists with appropriate training to find and define anomalies.Given how quickly machine learning-based approaches to picture classification are developing, it is likely that this procedure may soon be aided by or even replaced by computer systems (163).Because tumour and normal tissue generally contrast greatly, nuclear oncology imaging investigations appear to be especially well adapted for AI-based interpretation.With the employment of tracers in clinical settings, this is already the case, including 18F-FDG, somatostatin analogues, and PSMA ligand.Presently, patient staging and restaging before and after therapeutic intervention predominate oncologic imaging.Nuclear imaging has been used in oncologic research to evaluate the pharmacokinetics of therapeutic drugs for many years.Two significant challenges were the inability to radiolabel medications in time for clinical use and the limited sensitivity of PET scanners, which only allowed imaging investigations a few hours after drug administration. Significant advancements made in recent years may help to get beyond both constraints. New total body systems exhibit previously unheard-of sensitivity and expand the time window for pharmaceutical research(164).Oncologic research will benefit greatly from the combination of radiolabeled antibodies and more sensitive PET devices (165).Initial efforts like pre-targeting and cutting-edge antibody labeling techniques show potential for minimizing radiation exposure and lowering the time between antibody injection and imaging (166).In oncologic molecular imaging, PET imaging of the dynamic TME following immune modulation therapy has emerged as the next frontier.It has been shown that using CD8-positive T cells and antibodies against programmed death ligand 1 labeled with 89Zr for PET imaging improves the precision of predicting the results of immunotherapy and is superior to biopsy and immunohistochemistry (167). The targeting of immune cell markers using 89Zr-labeled antibodies is the only restriction on their use.FAP inhibitors, which target the tumour stroma, can be used alone (168); they can be used in conjunction with cell-based therapies that target PSMA, such as CAR-T cells, that have reporter genes transfected into them, which can target both prostate cancer tumour cells and the PSMA-expressing tumour neovasculature, or they can be added to pretargeted strategies (like bispecific antibodies or bioorthogonal click chemistry) (169).Through the development of hybrid imaging methods like SPECT/CT, PET/CT, and PET/MRI, as well as the advent of PET, nuclear medicine technology has evolved during the past 20 years (170,171.The development and commercialization of PSMA-targeted theranostics were spurred on by the success of peptide receptor radionuclide treatment. Major clinical guidelines for the detection of biochemical recurrence now include PSMA-directed PET imaging as a key component(172).The FDA just received a new medication application for 68Ga-PSMA11, and approval is anticipated soon. The 18F-labeled PSMA ligand registration studies are still ongoing(171).

**Neurology:**

In the years to come, it is anticipated that a number of current research applications in the field of molecular brain imaging will become common therapeutic tools. This shift encompasses both technological and radiotracer developments. Additionally, innovative and interesting research methodologies will develop.It is reasonable to suppose that brain PET tracers in the future would be available to imaging the majority of neurodegenerative diseases, if not all of them. This would be an example of effective research translation from the bench to the bedside.This progression began with the known b-amyloid PET tracers' acceptance some time ago and continued with the first authorized tau PET tracer(173). As the clinical use of molecular brain imaging significantly develops, the criteria and diagnostic methods now used for neurodegenerative illnesses are expected to be scrutinised.This alteration in perspective is primarily driven by the inability to offer disease-modifying therapies for any of these conditions up to this point given the way they are currently diagnosed.It was recently proposed to begin with AD and replace the disease's current classification as a syndromal construct with a biologic definition that includes running diagnostic tests for neurodegeneration, tau, and amyloid (the so-called ATN concept) (174).Growing evidence indicates that the role of PET imaging in the context of treatment stratification and therapy monitoring will increase, which is consistent with the anticipated paradigm change on how to identify neurodegenerative illnesses. There is optimism that the most innovative disease-modifying treatment approach for neurodegeneration, aducanumab, a human monoclonal antibody, will be granted a licence for clinical usage in anti-amyloid drugs for AD (175).Experts believe that in order to justify drug administration, a positive PET scan for amyloid demonstrating the actual existence of therapeutic target will be necessary because such medications will be highly expensive and may have important adverse effects. Based on the knowledge gained from drug testing trials conducted on individuals with a suspected AD clinical diagnosis, such an application seems reasonable.About 20% of these individuals had baseline amyloid PET results that were negative despite standard evaluation by experienced doctors(176).In terms of technical developments, In the years to come, there will surely be additional research addressing the critical question of the clinical use of the use of AI and hybrid PET/MRI in molecular brain imaging (despite the value proved in research).Many experts anticipate that once disease-modifying medicines are available, AD will be the first clinical application for hybrid PET/MRI. For example, there is optimism that AI will be able to distinguish between different illness subtypes, which will improve differential diagnosis and treatment choices.Both in terms of academic study and therapeutic application, the future of molecular brain imaging appears promising (16).

**Cardiology:**

Nuclear medicine has been utilized in cardiovascular applications to measure ischemic heart disease's myocardial perfusion, function, and viability, as well as to guide revascularization operations.True molecularly focused imaging has not yet made an impact on clinical cardiovascular care comparable to oncology or neurology, despite continual advancements in imaging technology.This discrepancy is best explained by the fact that targeted molecular imaging—which is most effective when combined with targeted molecular therapies—has not always been required in cardiology, where mechanical interventional techniques and widely applicable, generalizable pharmacological therapies have generally predominated.However, molecular imaging will be the key to the development of cardiovascular nuclear medicine. This will be closely related to the advancement of cardiovascular medicine in the future, when molecularly focused approaches will become increasingly important (177).One excellent example of how molecular imaging will become clinically relevant when targeted medicines define a particular need is the recent radionuclide imaging's success in detecting cardiac amyloidosis (178).Nuclear imaging makes it simple to see chemokine receptors like CXCR4, also known as CC-motif chemokine receptor 2, is a kind of chemokine receptor (CCR2) and profibrotic proteins like FAP.The heart is the focal point of the circulatory system, but it also has an impact on a number of other systems, including the immunological and neurohumoral systems, therefore systems-based, holistic methods will increasingly dictate cardiovascular therapy. A systemic, targeted solution should take into account all of the impacts on the intended area and surrounding tissues because cardiovascular disorders are closely linked to disease of other organs and tissues.As a whole-body method, radionuclide-based molecular imaging is ideally suited to find such systemic networks. One current illustration is the connection between inflammation and the kidneys, the brain, the hematopoietic system, the arterial wall, and the heart (179).Another instance is the recent focus on cardio oncology, which focuses on assessing how tumors affect the body and tumor therapies on the circulatory system (180).Therefore, new, targeted imaging methods that are created to guide particular molecular therapies in cardiovascular target tissues as well as the concurrent condition of networking distant organs and tissues will influence the future of cardiovascular nuclear medicine.

**Radiopharmaceutical chemistry**

In order to best select molecular targets for radiopharmaceutical development, biologists from all disease fields must work closely with doctors to determine and prioritize clinical needs and open questions. This will be accurate for the creation of PET imaging with fresh radiotracers and theranostics (in oncology, cardiology, neurology, infection, and other domains).The use of radiometals, most notably 64Cu and 89Zr, has likely had the greatest expansion in terms of fundamental, translational, and clinical studies over the past few decades, despite the emergence of novel techniques for labeling molecules with 11C and 18F.Despite the substantial advancements previously made in the 68Ga field, this should be a focus in the upcoming years.Given the promising clinical outcomes with 225Ac-PSMA, future advances may focus on the usage of a-emitters (181).It is also possible to employ a well-designed tracer to non-invasively check on the efficacy of therapeutic medications that are used after the drug target. One instance of this is the use of human epidermal growth factor receptor 2 imaging for medicines that target tyrosine kinase and inhibit human epidermal growth factor receptor 2 (182).

**Instrumentation and Analysis:**

From simple, single-channel, position-sensitive probes with rectilinear scanning to complex detectors with great energy, spatial, and time resolution, nuclear imaging detectors have advanced. Imaging technology has advanced from planar cameras to tomographs that can generate high-quality 3- and 4-dimensional data. In order to offer precisely matched anatomic information to supplement the functional and molecular information provided by nuclear imaging, CT and later MRI were linked with equipment for PET and SPECT.parallel developments in mathematics and computing for the reconstruction and analysis of PET and SPECT images accompanied these improvements in hardware.A new era of picture quality was ushered in by iterative image reconstruction techniques based on statistical and physical models, which are now the industry standard for both PET and SPECT. With the development of novel data analysis methods that can quantify intricate molecular processes like enzymatic activity and receptor binding as well as sophisticated image analysis methods like pharmacokinetic models, our ability to measure regional tracer concentration has significantly improved, first for PET and more recently for SPECT (16).Faster, more compact, and more precise detectors are now possible thanks to developments in material science and electronics (183).The development of imaging equipment and image generating algorithms has produced a setting with a wealth of biological and clinical data for the construction of molecular imaging biomarkers (184).The aim of published criteria like PERCIST for Cancer and 18F-FDG PET and of organizations specializing in quantitative imaging in the US and Europe has been to establish standards for quantitative molecular imaging (185).

**Artificial Intelligence**:

Among the many research and development fields that AI is currently reshaping are nuclear medicine and molecular imaging.Early in the 1990s, proof-of-concept publications in the fields of cardiac and brain imaging demonstrated the potential of AI and neural network-based technologies for image processing and pattern recognition (186,187,188,189).Total-body PET scanner data that we begin to gather regarding physiologic and pathologic pathways may potentially be advantageous for training AI-based reconstruction algorithms.Thus, these methods could produce total-body PET-like images obtained with contemporary scanners without ultralong axial field of view, AI might play a significant role in maximizing the impact of technological investments in nuclear medicine clinical practise (the same would be true for ultrafast PET detectors).If true, the modest spatial and temporal resolution that has always been regarded as a drawback of PET and SPECT imaging would be resolved, and readily available scanners would soon be able to provide an unmatched sensitivity combined with great spatial and temporal resolution.AI is also changing the analysis and interpretation of nuclear medicine pictures (16).

At the beginning of the 2000s, a number of doctors legitimately questioned whether PET/CT systems were clinically necessary (190). However, SPECT/PET systems were thought to be a potential strategy for expanding access to clinical PET imaging (191).Until recently, it was thought that imaging radiolabeled PSMA for prostate cancer inhibitors was not possible(192).There were also convincing arguments that creating novel imaging agents is typically too expensive to be profitable(193).Radioisotopes are frequently used in nuclear medicine to diagnose and treat human illnesses. However, the relative relevance of nuclear medicine's diagnostic and therapeutic applications has fluctuated throughout time. Internal medicine gave rise to nuclear medicine, which was initially used in clinical settings primarily for investigations of the pathophysiology of various diseases and the treatment of thyroid disorders(194,195).In the early 2010s, the American Board of Nuclear Medicine promoted the elimination of nuclear medicine as a distinct medical specialty since clinical nuclear medicine resembled radiology so much (196).The majority of people believed that the only financially viable task for nuclear medicine doctors was the accurate reading of 18F-FDG PET/CT scans. On the basis of this premise, it seemed obvious that nuclear medicine should be added to the list of radiology's subspecialties(197).Recent developments suggest that this choice was sound.

In the interim, the FDA has approved a number of additional imaging products, consequently, it is doubtful that nuclear medicine will only be able to read 18 F-FDG PET/CT readouts in the future. The FDA's clearance of the theranostic pair 68Ga-DOTATATE and 177Lu-DOTATATE for use in imaging and treating neuroendocrine tumors, as well as the extremely encouraging outcomes from the use of radiolabeled PSMA ligands in imaging and treating prostate cancer, are even more significant.Therefore, it is very possible that therapeutic uses of radioisotopes will become increasingly important in clinical nuclear medicine in the years to come. In other words, nuclear radiology will retake nuclear medicine's place in the profession (191).

**Conclusion**

An essential instrument for a comprehensive approach to medical radiation science is provided by nuclear medicine. It is established historically and in the evolution of contemporary best practise that nuclear medicine and both radiography and radiation treatment complement one another. Clinical practitioners in all branches of the medical radiation sciences benefit from knowledge of the technical and clinical elements of integrated modalities. To enhance the skills of radiographers, radiation therapists, and other healthcare professionals working in the diagnostic imaging sector, this article offers a fundamental understanding of nuclear medicine. Since the area of nuclear medicine has been so inventive and quick to adapt to new scientific discoveries and clinical requirements, its development has been unexpected. Nuclear medicine will surely have a promising future if this success is sustained.

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