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Board of Radiation & Isotope Technology

Application of Radioisotope in Healthcare – An Overview

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The application of radioisotopes in healthcare is one of the prominent peaceful applications of atomic energy. Natural radioactivity was discovered by Henri Becquerel in 1896 and subsequently radioactive elements radium and polonium were discovered by Madam Curie in 1898. The value of treatment of cancerous conditions by radioactivity of radium was first demonstrated in 1901. Henri Alexandre Danlos and Eugene Bloch attempted treatment of tuberculosis skin lesions by placing radium in contact in the same year. In 1913 Frederick Proescher published the first study on the intravenous injection of radium for therapy of various diseases. Herrman Blumgart and Soma Weiss performed the first application of radioactive tracers in medical research in a study of the velocity of circulating blood in 1925. But the effective use of radioactivity in healthcare application had to wait the invention of artificial radioactivity by J.F Joliot-Curie and Irene Joliot-Curie in Paris in 1934 and production of radioisotopes by cyclotron invented by Ernest O. Lawrence in Berkeley in 1930 and by nuclear reactor demonstrated by Enrico Fermi and co-workers in Rome in 1942. Since then radioisotopes have been playing a vital role in the growth and development of life science and medicine right from the understanding of the chemistry of the photosynthesis (by Melvin Calvin's Berkeley team using

^{14}C) to the development of molecular biology. Today, radioisotope labelled tracers are one of the fundamental tools of biological and medical science. Realizing this importance of the radioisotopes in healthcare and biology, the Rockefeller Foundation funded the first cyclotron dedicated for biomedical radioisotope production at Washington University in St. Louis, USA as early as 1940. Later the production of radioisotope and labeled compound became an industry and became available commercially. The availability of radioisotope and labeled compound in turn encouraged the scientists to develop many useful applications in medicine and other branches of science. It is beyond the scope of this article to touch upon all the applications of radioisotopes in healthcare.

In medicine the application of radioisotope and labelled compounds as tracer lead to the development of a new branch of medicine called nuclear medicine capable of imaging and providing functional status of organs in the body. The early history of the application of radioisotope in healthcare is in fact tied to the development of nuclear medicine. The most fundamental principle of nuclear medicine is the tracer principle, whose inventor George de Hevesy received the Nobel Prize in Medicine in 1944. In 1924 Georg de Hevesy, J.A. Christiansen and Sven Lomholt performed the first radiotracer (^{210}Pb and ^{210}Bi) experiment in animals and in 1935 Hevesy and O. Chieivitz administered ^{32}P as phosphate to rats and demonstrated the renewal of the mineral constituents of bone.

The discovery of the artificial element ^{99m}Tc by Emilio Segre and Glenn Seaborg in 1938, the advent of the ^{99m}Tc generator (^{99}Mo-^{99m}Tc generator was developed at the Brookhaven National Laboratory in 1957) based on the principle of radioactive equilibrium and the design of the scintillation camera by Hal O. Anger in the 1950's were important events leading to the growth in

nuclear medicine. Further the growth of nuclear medicine was progressed by the introduction of the gamma camera and the commercial availability of ^{99m}Tc generator in 1964. This was followed by the rapid development in ^{99m}Tc radiopharmaceuticals for investigation of all vital organs such as brain, thyroid, lung, heart, stomach, liver, kidney, pancreas, gall bladder etc. ^{99m}Tc generator also underwent modifications to attain user friendliness. The cumbersome solvent extraction generator is now mostly replaced by user-friendly column generator. From a possible population of more than 2300 radioisotopes, ^{99m}Tc is pre-eminent, being used in more than 80% of the estimated 100,000 or more patient studies that are performed worldwide each day. ^{99m}Tc has thus become the "workhorse in nuclear medicine". This is because ^{99m}Tc has unique radiation properties near ideal for diagnostic application that demands short lived pure gamma ray emitting radioisotope with good chemistry for incorporating into chemical compounds permitting specific physiological process. Some of the physiological processes that govern the distribution of the radiopharmaceuticals are passive transport in brain and heart, active transport, phagocytosis in liver, cell sequestration in pancreases, capillary blockage in lungs, receptor binding, antigen binding etc. ^{99m}Tc is a pure gamma emitter of energy of 140 kev with a 6 hours half life. The energy of the gamma ray is ideally suited for efficient detection by gamma camera. Being a radio-transition metal, ^{99m}Tc can be complexed with a host of ligands. The early development of radiopharmaceuticals was in fact mostly based on trial and error methods. However, the current trend is based on either structure-distribution (perfusion imaging) relationship or structure- activity relationship as in the case of modern drug discovery process.

After ^{99m}Tc the radioisotopes, which made major contributions in healthcare particularly in the area of therapeutics, are ^{131}I and ^{60}Co. These radioisotopes were discovered by John Livingood and Glenn Seaborg in 1938. ^{131}I based radiopharamceuticals as internal radiation source for radiotherapy and ^{60}Co as external radiation source for radiationtherapy form the major radioisotopic products for the treatment. ^{131}I is also used in diagnosis of diseases such as thyroid disorders, endocrine tumors etc. The use of this radioisotope in 1940 for the diagnosis of hyperthyroidism can be listed as one of the earlier applications of radioisotope in diagnosis. Treatment of thyroid cancer patients with ^{131}I, by Samuel M. Seidlin, Leo D. Marinelli and Eleanor Oshry in 1946 and use of ^{131}I labeled di-iodofluorescein to probe the brain for tumors at surgery by George Moore in 1947 were few of the memorable in-vivo experiments using ^{131}I. ^{131}I is now commonly used to treat thyroid cancer, probably the most successful kind of cancer treatment. It is also used to treat non-malignant thyroid disorders. Currently large quantity of this radioisotope is produced world wide in reactors. But Seaborg and his team discovered this versatile isotope by irradiation of tellurium metal with deuterons in a cyclotron.

After these radioisotopes, a series of cyclotron produced radioisotopes, such as ^{201}Tl, ^{67}Ga, ^{111}In and ^{123}I, are the next most popular in the list of medical radioisotopes. These are for diagnostic purpose. A different group of radioisotopes are popular for therapeutic use. Well-established examples are ^{131}I, ^{32}P and ^{90}Y, ^{89}Sr; but several others are being investigated for possible therapeutic applications. ^{153}Sm, ^{186}Re, ^{188}Re, ^{165}Dy, ^{166}Ho are the examples. The beta emitter ^{169}Er, beta/gamma emitters ^{67}Cu electron-emitters ^{80m}Br and ^{125}I and alpha emitter ^{212}Bi are under investigation in various laboratories for the therapeutic applications

During the past decade, the perspectives of application of radioisotope have been totally transformed. This field is no longer only an imaging specialty that provides some functional information; but is progressively acquiring a central role in the understanding of many physiological and pathological processes, both in research and in routine clinical practice. The radioisotopes in combination with progress in molecular biology, immunology and biochemistry have now enabled the medical science to probe the molecular basis of diseases and a new branch of medicine called molecular nuclear medicine has evolved. This branch of medicine is further strengthened by the availability of well-designed radiolabelled compounds. Genetic engineering, genomic and proteomics are expected to bring in more radioactive probes based on radiolabelling of biomolecules such as antibodies, oligonucleotides, peptides etc. This field of nuclear medicine is also described as “tomographic physiological chemistry”. Nobel Prize wining hybridoma technology invented by Milstein Cesar and Kohler in 1975**,** in concert with advances in the field of nuclear medicine already offered the prospect of utilizing monoclonal antibodies against tumor antigens labeled with gamma-emitting radionuclide for imaging of tumor sites in a noninvasive fashion. This mode of immunologically based diagnosis was first demonstrated by David Goldenberg in 1978 using polyclonal antibodies to carcino embryonic antigen (CEA). This immunological procedure is termed as radioimmunoscintigraphy (RIS).

In addition to imaging, another important application of radioimmunoscintigraphy is in the study of distribution of an antibody as a prelude to treatment with the same antibody. Monoclonal antibodies directed against human cancer-associated antigens also have been used to selectively deliver cytotoxic radionuclide to malignant cell populations for therapy

(radioimmunotherapy). Here the tumor specific antibody act as a carrier for the tagged radionuclide. Unlike conventional external beam radiation therapy, radioimmunotherapy (RIT) offers the possibility of selectively targeting radiation, from the radioisotope tagged to the antibody, to malignant cell populations, while minimizing destruction of neighbouring normal cells, which are antigen negative. ^{131}I was the first radionuclide used for radiolablled antibody imaging. Advantages of ^{131}I includes its low cost, the ready availability and ease of protein radio-iodination methodology. ^{111}In, ^{123}I and ^{99m}Tc have found place in radiolabelling of the antibody. The progress in the chemistry of radiolabelling of proteins has greatly contributed in the preparation of in-vivo stable radiolabelled antibodies. With the emergence of positron emission tomography (PET) as a clinical imaging modality, a number of laboratories have been investigating the potential utility of antibodies and antibody fragments labelled with positron-emitting radionuclide The feasibility of so called immuno-PET has already been demonstrated in a patient with neuroblastoma injected with ^{124}I-labeled antibody.

Medical cyclotron has provided us with very useful radioisotopes of basic elements such as ^{11}C, ^{13}N and ^{15}O and thus enabling the preparation of radiotracers without tampering their biological properties and structural integrity. All these positron-emitting radioisotopes are very short lived and their half life is only of few minutes. However the development of ‘fast chemistry’ and automated modules for radiochemical synthesis have lead to the development of many useful radiotracers that can be prepared at hospital site. The availability of these tracers has opened up another radioisotope based medical application called positron emission tomography (PET). The radioisotope ^{18}F is produced in cyclotron and one of the ^{18}F labelled compounds, ^{18}F-Fluro deoxy

glucose popularly know as FDG has received the recognition of "Molecule of the Millenniums". The use of FDG revealed the biochemistry of brain and other vital organs and already established as a dependable tool for oncological investigations for visualizing the metastasis. Cyclotron produced ^{201}Tl is one of the important and unique radioisotopes that strengthened the development of nuclear cardiology. PET offers possibilities to study physiology, molecular biology, energy metabolism, drug-receptor and drug-enzyme interactions in-vivo. Cyclotron produced radioisotope and PET are also expected to contribute in the new pharmaceuticals development. The progress in the knowledge of the receptor system and the ability of PET to image the receptors tempted many pharmaceutical companies to interact with PET centers in attempt to better understanding of pharmacology of new therapeutic drugs. Now more than 200 PET cameras are operating world wide. The technology has progressed so much that highest resolution that can be obtained in the PET imaging is now about 2.6 mm. In fact the history of PET has been one of continuous improvements in resolution and sensitivity. New emerging procedures combining PET with CT scans to give co-registration of the two images will enable more insight into the body system. Another area that deserves the mention is tat PET in combination with neuro-receptor binding radiopharmaceuticals enables us to understand the relation between brain chemistry and behavior in health and neurological (Parkinson's and Alzheimer's disease) and psychiatric diseases (schizophherenia and depression). Also it has paved the way for assessing activity of neurotransmitters such as serotonin , dopamine etc.

The interventional studies in nuclear medicine technique is yet another exciting approach to enhance disease specific diagnosis through drugs or technical

intervention during the procedure. The intervention is aimed at a particular organ function which alters during the disease process. Dimox brain SPECT, nitrate augmented ^{201}Tl scan and captopril renogram are some of the established procedure in this regard. This approach is growing with nuclear medicine and even entering in the surgical procedures. Currently this subset of medical procedure is termed as interventional nuclear medicine.

The next generation nuclear imaging is expected to be that based on the concept of dual-imaging (fusion imaging). The principle of dual-modality imaging technology is to combine a functional. imaging device (SPECT or PET) with an anatomical imaging instrument (CT or MRI) to acquire co registered images with a single integrated system. This is a hardware approach instead of software based, where manual or automated image registration technique is used to align images acquired separately on two different instruments. This development is an emerging research field encouraged by the need for effective diagnostic methodology in clinical oncology. Here the PET or SPECT data is fundamentally aligned with the anatomical information from CT scan. The PET/CT fusion image is already established its value in better anatomic localization of abnormal tissue metabolism. SPECT/CT and PET/CT fusion tomographs were now developed for diagnosis in clinical oncology and such integrated systems are now commercially available.

With all these advances in radioisotope and development of radiotracers, the science and technology of nuclear medicine can also of help in solving problems related genetic disorders. Radioisotope is best suited for translating the advances in genetics and molecular biology into the benefit of the diseased. In-situ radiotracers can serve as biomarkers for the single gene and

multigencic disorders as well as for evaluation of the efficacy of gene therapy and status of apoptosis (programmed cell death) in radiation therapy of cancer. Use of radiotracer of biomolecules as the imaging agent for cellular receptors will enable the study of brain chemistry and optimize the drug dosage in individual basis and the study of basic molecular process affected by drugs.

Applications of radioisotope as tracer is only one side of the story. Radioisotopes as a source of ionizing radiation also contribute immensely to the health care. Radiation is used for sterilization of medical products, development of biomedical materials, treatment of cancer and destruction of abnormally proliferating cells, preservation of tissues in tissue banks, production of vaccines, blood irradiation to prevent graft-versus-host disease (GVHD) etc.

Therapy using radiation from radioisotopes such as ^{192}Ir, ^{137}Cs, ^{60}Co etc is used to fight many types of cancer. In this treatment modality, gamma radiation is directed to tumor either from an external source of ^{60}Co (teletherapy) or from radioactive sources as wires, needles and seeds implanted in the diseased part of the body generally through body cavity (brachytherapy). The type of cancer and location and degree of cancer decide the mode of radiation therapy. Prostate cancer, uterine cancer, breast cancer and retinal cancer are treated by brachytherapy. The birth of the brachytherapy was in 1903 when small radium tubes were inserted into tumors. During this period major brachytherapy work was done at the Curie Institute in Paris. Robert Abbe, a surgeon at New York, placed tubes into tumor beds after resection, and later inserted removable radium sources thus introducing the ‘after loading technique’ as early as 1905. The availability of various radioisotopes and progress in remote after-loading techniques’ have brought renewed interest in brachytherapy in the last two

decades. The imaging modalities such as CT scan, magnetic resonance imaging (MRI), transrectal ultrasound and sophisticated computerized treatment planning has further enhanced positional accuracy and optimized dose distribution in brachytherapy. While brachytherapy was initially used only for treatment of cancer, it has now been found to be useful in non-malignant diseases (for example, heart stents in the prevention of vascular restenosis-blockage in the blood vessels) as well. Brachytherapy is the optimum way of delivering conformal radiotherapy tailored to the shape of the tumor while sparing surrounding normal tissues. Radiation teletherapy is also one of the most effective and commonly adopted forms of treatment currently available. In 1951, ^{60}Co teletherapy was first put to clinical use in Ontario, Canada. Thereafter it was adopted with tremendous enthusiasm in the treatment of malignant disease.

Often radiation therapy is used to shrink the toumor as much as possible before surgery to remove the cancer. Radiation can also be given after surgery to prevent the recurrence of cancer. Radiation treatment may also be used to provide temporary relief of symptoms, or to treat malignancies (cancers) that cannot be removed with surgery. Even when curing cancer is not possible, radiation therapy is used to shrink tumors and reduce pressure, bleeding, pain or other symptoms associated with cancer. This is called palliative treatment. About half of all people with cancer are treated with radiation, and the number of cancer patients who have been cured is rising every day. For many patients, radiation is the only kind of treatment needed.

Beams of neutrons and protons and heavy ions are also used for the treatment of diseases. The accelerators made possible the use of beams of these nuclear particles. Researchers first investigated the use of neutron beams for cancer

radiation therapy in the 1940s. Helium ions and proton beams first began to be used in the 1950s. Later, in the 1980s, medical researchers investigated the use of heavy ion beams to treat cancerous tumors as well as a deadly brain disorder known as arteriovenous malformations (AVMs). This brain disorder is a disease manifested by abnormal growth of blood vessels in the brain. Heavy ion beams can be precisely focused to obliterate these growths which, unless treated, can cause lethal or disabling brain hemorrhages and seizures. Charged particle patient treatment facilities are functional in Japan and Germany.

Many therapeutic procedures are palliative, usually to relieve pain. For instance, ^{89}Sr and increasingly ^{153}Sm are used for the relief of cancer-induced bone pain. ^{186}Re is a new addition to this product list. Radiation synovectomy is one of such radioisotope based palliative treatments. It is in fact an attractive alternative to chemical and surgical synovectomy for the treatment of inflammatory synovial disease of joints including rheumatoid arthritis as well as some extent osteoarthritis. The procedure entails a single injection directly into the synovium of the joints to control and ablate inflammation. Beta emitting radio-colloids of ^{90}Y, ^{198}Au, ^{165}Dy, ^{186}Re, ^{169} Er etc are used for this purpose.

The beneficial effect of use of ionizing radiation from radioisotopes such as ^{60}Co or ^{137}Cs for irradiation of blood and blood components is increasingly gaining attention of medical professionals. The irradiation prevents graft-versus-host disease (GVHD) by decreasing the number of viable T lymphocytes in blood and blood components. GVHD occurs when viable T lymphocytes in transfused blood or blood components engraft, multiply, and react against the tissues of the recipient. GVHD may be frequently seen when blood components are transfused to immunocompromised recipients, such as bone marrow transplant

patients, patients with malignancies receiving aggressive chemotherapy and persons with congenital immune deficiency syndromes.

The radioanalytical techniques such as neutron activation analysis (NAA) and radioimmunoassay (RIA) have also contributed immensely in healthcare area. The invention of radioimmunoassay by Solomon Berson and Rosalyn Yalow in 1959 in USA based on a novel analytical concept and the subsequent development of related techniques (such as immunoradiomeric assays) including the non-radioactive counter part have revolutionized the way we look at the hormones and hormone actions. Not only endocrinology but many other fields of medicine such as oncology, cardiology, gasteroenetrology, microbiology and infectious diseases and veterinary medicine are being benefited by these in-vitro techniques. The uniqueness of this technique is superior sensitivity achievable to the order of pico and femto mole level and molecular specificity. Currently 60% of the clinical laboratory investigations in hospital and clinical laboratories are carried out by RIA and related techniques, thanks to the commercial availability of ready to use RIA kits. RIA is the first line of investigation in suspected thyroid disorders and infertility. The neutron activation analysis (NAA) is another very sensitive technique to determine the trace elements in body fluids and tissues. The trace elements are very essential to maintain the normal physiology. Zn, Se, Cu are all trace elements needed for health. Deficiency of trace elements can cause disease and excess can lead to toxicity. This technique is used also in the research on nutritional epidemiology. Several studies using NAA have been reported. Some of them are nutritional epidemiology study on diet and cancer risk, and study on nutritional epidemiology of thyroid cancer etc.

This article describes is only a limited area of applications of radioisotopes in healthcare. Radioisotope and radiation will continue to contribute in healthcare and in improving the quality of life. In India research and development effort in the area of application of radioisotope in healthcare was initiated as early as 1958. Number of important radiopharmaceuticals such as radioiodine, radiochromium, radiophosphate, radio labelled vitamin B_{12}, radioiodinated thyroxin were developed in 1960s. The first radioimmunoassay kits were introduced in the Indian market from BARC in 1970s, which is not much later than that of the first global appearance of radioimmunoassay kit. Immunoradiometric assay kit was introduced in the market from Board of Radiation and Isotope Technology (BRIT) in 1980s. Presently know-how for the production of over 100 radiopharmaceuticals and labelled compounds for medical use are established. This includes ^{99m}Tc generator, cold kits for the preparation of ^{99m}Tc- radiopharmaceuticals and radioimmunoassay kits. The formation of Board of Radiation and Isotope Technology (BRIT), a Unit of Department of Atomic Energy in 1989 was a further thrust in the programme of healthcare application of radioisotope. BRIT and BARC have been responsible for the production of radioisotopes and processing them into medical products and service. The radioisotopes of medical interest used for the nuclear medicine are from Druva and Cirus reactors and these are chemically processed at radiological laboratories at Trombay and converted into various medical products in BRIT`s Vashi Complex laboratories. The production of these radioisotope based medical products are carried out in radiologically and pharmaceutically safe laboratories under GMP conditions. In India, currently there are 120 nuclear medicine centers and more than 400 RIA laboratories are deriving the benefit from the indigenous products. This benefits more than 10 lakh patients in a year. Various type of ^{60}Co tubes and needles

and other radiation sources for teletherapy and branchytherapy are indigenously produced. The sources are tested to the appropriate international standard. These sources are estimated to provide the benefit for more than 10 lakh patients in a year. BARC has successfully developed a teletherapy unit indigenously. Cost effective blood irradiator is yet another contribution of BRIT for healthcare applications of radioisotope. Isomed radiation plant of BRIT which has been rendering service for the last 30 years for the radiation sterilization of medical products is yet another achievement. There are four radiation plants are functioning and few are expected to be commissioned in the private sector in India to augment the use of radiation in various healthcare related areas. Thus India has achieved significant level of self reliance in the healthcare application of artificially produced radioisotopes. The vision of Dr Homi Bhabha and effort of the Indian scientists, engineers and the medial doctors are the sole support for this achievement.

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