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Radiopharmaceuticals—Pattern of Development and Utilisation in India

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ABSTRACT

The availability of research reactors at an early stage of our Atomic Energy Programme led to developmental efforts in the field of radiopharmaceuticals. Starting with temporary laboratories for this work, a sophisticated and dedicated Radiopharmaceutical Laboratory is now installed at Vashi in New Bombay.

The use of several ^{125}I-labelled compounds like Rose-Bengal, hippuran, etc. for imaging has been replaced over the years by ^{99m}Tc compounds; the final formulations are prepared at the hospital using generators and cold kits supplied by the Board of Radioisotope Technology. Parallel with the development of short-lived generators in radiopharmaceuticals came advances in imaging and instrumentation techniques, the scanners being replaced by sophisticated gamma cameras, with capabilities for tomography and computerisation. About 40 centres in India have the modem instrumentation and equipment needed for carrying out nuclear medicine procedures. Further growth of nuclear medicine eentres in the country has, however, been limited by the need to import such advanced high cost instrumentation not currently available from indigenous sources. Regarding *in-vitro*

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radiopharmaceuticals, some RIA and IRMA kits and procedures have been developed. These include assay of T_3, T_4 and TSH in the thyroid group of hormones. Kits for several other important procedures are still being imported by some large medical centres. There are over a hundred and fifty medical laboratories carrying out RIA procedures.

1. INTRODUCTION

The development of atomic energy in India owes much to the leadership provided by many dedicated Indian scientists and technologists. It was indeed fortuitous for India that Dr. Homi Bhabha came on the scientific scene in the fifties, at the time when Pandit Nehru, himself an ardent believer in science, was the Prime Minister of India. As a consequence of the mutual trust and admiration they had for each other, the Atomic Energy Programme (AEP) obtained the right priority and got off with an early start. The commissioning of the 1 MW swimming pool reactor, APSARA in 1957 and the 40 MW research reactor CIRUS in 1960 gave a great impetus to the development of nuclear science and technology in India.

The applications of radioisotopes in diverse fields were recognised by the Govt. of India to be one of the important objectives of the AEP, second only to the production of the nuclear power. Radioisotopes were already in use 'for medical applications in many advanced countries--in particular, ^{131}I was the single most frequently used isotope, and was found to be of great benefit in the diagnosis and treatment of thyroid disorders. Around 1957, I (V.K. Iya) was given the responsibility to build a self-reliant production and applications programme for isotopes. Our first task was to set up a temporary isotope production laboratory in an old and dust-laden textile shed, leased out from Bombay Dyeing, off Cadell Road in the central part of the Bombay.

It was my (Iya) privilege to come into contact with the young Col. Mazumdar right in the early stages of the radioisotope programme around 1960, when he was still at the Safdarjang Hospital. We had just established the production of ^{131}I (0.5 to 1 curie per batch), of Colloidal ^{198}Au, and, of ^{32}P, at the Cadell Road Laboratory. Though the laboratories were ventilated with filtered air and airconditioned, the surrounding areas were filthy and far from ideal. Entering as we were in a new field of producing radioactive materials which were to be administered into human beings for medical use, we were naturally hesitant and somewhat diffident about supplying our products. Mazumdar sensed this and gave me and my colleagues his advice as well as his unstinted support. He expressed his full confidence in the quality of our scientific efforts.

In 1960 the Atomic Energy Commission had set up a pavilion in the World Agricultural Fair. Dr. Homi Bhabha had put me (Iya) in-charge of setting up the Atomic Energy Exhibit, which included, inter alia, live isotope production laboratory. This was fitted with glove boxes and lead-shielded remotely operated production boxes, inside a glass-fronted laboratory so that the public could view the handling of radioactive materials. The idea was to produce isotopes in a TRIGA reactor, which was on display in the US pavilion of exhibition, process them in the isotope laboratory of the atomic energy pavilion and supply short-lived isotopes to hospitals in Delhi.

The young Col. Mazumdar was enthused by this idea and gave us his full support. He took me to Safdarjang Hospital to Col. Rao and Col. Iyer, the big medical names of that period, who immediately agreed to support our efforts to introduce nuclear medicine. at the Safdarjang Hospital.

Col. Mazumdar and Dr. Venkatasubramanian (of the Pate1 Chest Institute) saw our production processes, and, after satisfying themselves about the quality of our products, used some of these isotopes for clinical applications. In fact Col. Mazumdar was the first doctor to use colloidal ^{198}Au in India, He was truly a pioneer in nuclear medicine in India.

The end of the exhibition saw the dismantling of the atomic energy pavilion. I (Iya) took the liberty of transferring some of the materials like lead bricks, fume hoods and tong-and glove-boxes to the Safdarjang Hospital. Col. Mazumdar hired some carpenters to put up partitions and we were thus able to set up a functioning isotope laboratory for nuclear medicine at the Safdarjang Hospital in a few days time. This 'radiation cell' was the first such isotope laboratory for nuclear medicine in the country. I did not seek any formal government clearances from any authorities. But Col. Mazumdar and I were partners in a project for the public good and those were the days when scientists like Bhabha were tall, and bureaucrats did not dare question them or put any obstacles. We knew that Homi Bhabha would support us fully if any questions were raised.

A few years later, the Institute of Nuclear Medicine and Allied Sciences (INMAS) was set up at Probyn Road, Delhi by Col. Mazumdar with the full support of Dr. Kothari, the then Scientific Adviser to the Defence Minister. This important project was a pioneering effort and a remarkable achievement set up in record time. Our scientific collaboration increased and so did our friendship. Mazumdar was a warm-hearted human. He often invited me (Iya) to Delhi officially to visit his Institute, and to have discussions with him and his colleagues. None of these visits passed without my visiting his house in Lytton Lane in the evenings. I often look back with nostalgic memories at those wonderful evenings, enjoying the hospitality provided by Mrs. Mazumdar. We relaxed long over our drinks and poured out to each other our problems and frustrations. These we had in plenty, making for us one more common bond. Mazumdar was a lovable and generous person. At many scientific meetings, he was fulsome in his praise of the work of the Isotope Group of BARC. He often emphasised the pioneering nature of the work of the scientists in the Isotope Group in establishing a self-reliant programme so early in the country's developmental efforts.' All this was possible because we could always depend for advice and support of many specialists like Col. Mazumdar.

The growth of nuclear medicine in India has been influenced by several factors. These include the availability of trained manpower, the indigenous development and production of radiopharmaceuticals, and, of the electronic instrumentation for imaging, and finally, the availability of the necessary supporting infrastructure in hospitals. Over the years, the indigenous production of radiopharmaceuticals, with some exceptions, has generally kept pace with the technological developments elsewhere.

2. DEVELOPMENT OF RADIOPHARMACEUTICALS IN INDIA

2.1 Reactors

Commissioned in 1957, the 1 MW APSARA reactor helped us in the early research work for isotope development. The CIRUS, a 40 MW research reactor, was commissioned in 1960 and has good facilities for the production of most of the isotopes required in nuclear medicine. This reactor has proved invaluable for the production of radiopharmaceuticals in the country, and has indeed been the mainstay of the isotope production and applications programme. Neutron fluxes of upto about 5×10^{13} ncm^{-2}s^{-1} are available and is adequate to achieve the specific activity required for most isotopes. With the increased facilities available from DHRUVA, the 100 MW research reactor, commissioned in the mid-eighties, neutron flux facilities may be considered as sufficient to meet the country's requirement of reactor-produced isotopes needed for radiopharmaceuticals production.

2.2 Hot Laboratories

Matching with these reactor facilities and also with the progress in the use of radiopharmaceuticals, increasingly sophisticated laboratories were set up for radiopharmaceutical production. Starting with the Cadell Road Laboratories initially, production facilities were transferred in the mid-sixties to the intermediate laboratories in the South Site at Trombay. At the same time, detailed planning of more advanced facilities for large scale production was taken up, and as a consequence, the Radiological Laboratories were commissioned in the early seventies. Full scale production cells were set up in these laboratories for each of products required, alohg with a quality control laboratory for establishing the chemical and radio-chemical purity of the radiopharmaceuticals. With the setting up of a well equipped animal house in the Modular Laboratory at Trombay, the Radiopharmaceutical Division of the Isotope Group was now self-sufficient to carry dut all the biological tests necessary for ensuringthe quality of the radiopharmaceuticals supplied. One major disadvantage of the Radiological Laboratories, however, was that these laboratories also housed a number of other activities, involving the handling of various toxic materials, including some industrial isotopes, fission products, plutonium and trans-uranium elements. Taking this into account,' and' considering the need for expansion of the radiopharmaceutical programme', it was decided to set up more streamlined facilities to keep pace with advancing concepts in pharmaceutical practices. A new, modern and dedicated Radiopharmaceutical Laboratory was set up and commissioned in 1985. This new laboratory, named Isopharm (isotopes for pharmaceuticals) is located at Vashi, New Bombay, about 15 kms from BARC, Trombay. The laboratory has an area of about 4000 sq m and is equipped with modem facilities for the handling and storage of adequate levels of radioactive isotopes on the one hand, and for fulfilling the requirements of good manufacturing practices necessary for production of pharmaceutical products, on the other. The hot laboratories and processing plants are designed to take up the processing of a wide spectrum of isotope products for medical use, including short-lived generators and their cold kits, without cross-contamination from other isotopes.

The Isopharm Laboratory also has a facility for the production and quality control of radioimmunoassay (RIA) kits, storage of thermolabile antigens, radiolabelling of multiple batches of different antigens at a time, and freeze drying of RIA reagents.

The routine production and supply of all radiopharmaceutical products including in *vivo* products (orals and injectables), generators and kits, RIA kits, and reagents are made from Isopharm today. A second phase expansion of Isopharm has been envisaged bearing in mind the need for newer reagents and RIA products and a Hybridoma Laboratory for the production of monoclonal antibodies. With a view to providing a nucleus for the growth of applications in different regions of the country, the Radiopharmaceutical Division also set up two regional centres for radiopharmaceuticals, one located at the Kidwai Memorial Institute of Oncology, Bangalore, and the other at INMAS, Delhi. Apart from these, the Division operates a regional RIA centre at Dibrugarh and a small radiopharmaceutical laboratory at Calcutta.

The radiopharmaceutical programme itself now forms a constituent of the Board of the Radiation and Isotope Technology (BRIT) which was constituted as a separate unit in the Department of Atomic Energy in March 1988, so that the production and commercial aspects of the radioisotope programme could be developed to its full potential.

2.3 Development and Utilisation Pattern of *In Vivo* Products

The production of several primary isotopes in multicurie quantities, (for example, ^{131}I and ^{32}P radiopharmaceutical formulations) is currently carried out in the Radiological Laboratories located in Trombay. Many of the isotopes produced in the early years of our programme, viz., ^{24}Na, ^{42}K, ^{51}Cr etc., for investigations of trace elements in physiology and haematology have now gone into gradual disuse. The use of colloidal ^{198}Au for cancer therapy, of ^{203}Hg labelled neohydrin for kidney and brain scanning, and the use of many ^{131}I labelled compounds like Rose-Bengal, hippuran, human serum albumin and other compounds for the scintigraphy of different organs and the study of different systems, progressively came down. The routine production of some of these was halted in the late seventies and early eighties, while others came in the 'limited production' list. Their role has largely been taken over by various labelled compounds of ^{99m}Tc which has now become the workhorse of nuclear medicine. *Pari passu* with these developments in the radiopharmaceuticals field, there were significant developments in imaging technology. The advent of sophisticated gamma cameras, on the international scene, capable of imaging different organs, using the short-lived ^{99m}Tc-labelled compounds, led to a rapid decline in the use of scanners.

The emphasis in nuclear medicine has thus veered to the use of ^{99m}Tc-labelled compounds based on structure-activity relation. These labelled compounds are generally prepared at the hospital itself using ^{99}Mo-^{99m}Tc generator systems supplied along with 'cold' kits containing the reagents for preparing the required labelled formulations. The current technetium compounds most commonly used in the country include *Tc*-pertechnetate (thyroid), Tc-MDP (methylene disphosphonate) for skeleton and bone imaging, *Tc*-DTPA (kidney function) and *Tc*-phytate and *TcS*-colloid (liver imaging). Current efforts are directed towards the development of ^{99m}Tc alkyl

isonitriles for cardiac studies. This would obviate the need to import ^{201}Tl (a cyclotron-produced isotope) for myocardial perfusion studies. The development of ^{99m}Tc-HMPOA will provide nuclear medicine centres with a suitable agent for brain perfusion studies.

2.4 In Vitro Products

The two main categories of radiopharmaceutical in *vitro* products are based on RIA and the related immuno-radiometrie assay (IRMA) techniques. Both are highly sensitive and specific analytical techniques, enabling the quantitative measurement of molecules like hormones, drugs, metabolites, etc., in body fluids and biological samples. The techniques based on an antibody-antigen reaction-derive their specificity from the use of antibodies, while the sensitivity is mainly due to the use of a radioisotope (usually ^{125}I iodine-125) as tracer.

A number of RIA kits and procedures have been developed by BARC/BRIT scientists, and are in regular use in over a hundred centres in the country. These include kits for the assay of the thyroid group of hormones, T_3, T_4 and TSH, and some others like HCG, insulin, etc. Apart from these, a number of other RIA procedures, using imported kits, are in regular use in some of the larger and more advanced medical laboratories.

A number of tumour markers like CEA, AFP, PAP, CA125, CA 19-9, etc. are currently available in the international market and are being increasingly used for the early detection and follow-up in the diagnosis and treatment of different types of cancer. The use of monoclonal antibodies combined with a wide range of new separation and detection procedures have led to the increasing use of in vitro RIA, IRMA and ELISA techniques. Development efforts in India will need to be directed on a time-targeted basis towards these recent advances, if we are to catch up with this technology in the country.

2.5 Manpower Development

A large number of useful training programmes have been instituted by BARC and other institutions. These include specialised training in nuclear. medicine, radioisotope technology, medical physics, hospital pharmacy and RIA techniques. Regarding RIA, however, there is need to consider the formulation of a more indepth and comprehensive training programme comparable with those in western countries so that the use of *in* vitro techniques may grow on the right lines and be used more effectively for medical diagnosis in India.

3. CONCLUSION

In conclusion, we may note that the dedicated work of scientists in BARC/BRIT in close cooperation with eminent specialists and pioneers in other nuclear medicine centres over the years has led to the early development of nuclear medicine in the country. This growth has however been limited, owing to several factors, especially the inadequate infrastructural support provided by the government and hospitals, and the lack of advanced gamma cameras for imaging. There are only about 40 gamma cameras in the whole country, compared to about 300 in France and 8000 in USA. Finally a time targeted programme for the development of RIA kits would be of great support to the growth of nuclear medicine in the country.