Radiopharmacy: New techniques spur growth

by Hernan Vera-Ruiz

Radiopharmacy has experienced dramatic growth in the past decade, during which time newer scientific concepts and innovative approaches have been introduced to design radiopharmaceuticals with improved characteristics for diagnostic nuclear medicine.

Recent developments in the field were reviewed last October at the IAEA Conference on Radiopharmaceuticals and Labelled Compounds, which was jointly organized with the Japan Radioisotope Association and held in Tokyo at the invitation of the Government of Japan. The conference succeeded a similar meeting jointly organized with the World Health Organization and held in Copenhagen in 1973. At the 1984 meeting, 156 participants attended, representing 34 IAEA Member States and one international organization.

Following is a brief report on subject areas addressed:

Production of radionuclides

It is now a fact that most useful radionuclides are always available when needed in developed countries in the quality and quantity necessary for use in nuclear medicine studies — particularly those of nuclear reactor origin such as technetium-99m, Iodine-131, and others, which are available from well-established commercial sources. In most of the developing world, the situation is less than desirable mainly due to a lack of suitable neutron fluxes in the existing nuclear reactors, and due to a chronic shortage of foreign exchange to import them.

Most reported progress during the past few years took place in the area of cyclotron production of radionuclides. Many cyclotron facilities with active radioisotope programmes have become operational. Ultra-compact cyclotrons have been developed for automated in-house production of positron emitters, such as carbon-11, nitrogen-13, oxygen-15, and fluorine-18. The required nuclear data for their production is well known and the radiochemistry for the preparation of simple compounds is well established. "Black boxes" — automated computer driven mini-organic-synthesis factories utilizing positron emitters — are expected to become increasingly important in routine production of labelled compounds.

Radionuclide generators

These have played an important role in the widespread use of nuclear medicine procedures by providing reliable sources of short-lived radionuclides.

The most prominent of these generators now in use is the so-called "chromatographic" or "column" generator based on the molybdenum-99/technetium-99m system, prepared almost exclusively from fission-produced molybdenum-99 of high specific radioactivity in large production centres in the industrialized world. Because of the high technology involved and the large investments required to prepare suitable chromatography generators based on the process, the developing countries had sought to solve the supply problem by producing "instant technetium-99m" by the solvent extraction method, with methyl ethyl ketone, or by the sublimation method.

Major advances were reported at the conference by Hungarian and Australian scientists on the preparation of molybdenum-99/technetium-99m generators that overcome the difficulty of using fission-produced molybdenum-99 of high specific activity by using only inexpensive, non-polluting molybdenum-99. The former group reported on the development of a new, transportable sublimation generator capable of using low specific activity molybdenum-99 produced in low-power research reactors, and the latter group reported the development of a gel generator. These developments are undoubtedly of great significance for developing countries because most of the operational research reactors have low thermal neutron fluxes.

Research in radiopharmaceuticals

Over the past few years, a more systematic rationale has been applied to synthesize newer technetium-99m agents with improved characteristics for *in vivo* diagnostic imaging. The use of better analytical tools such as High Performance Liquid Chromatogrphy (HPLC), mass spectrometry, X-ray crystallography and others, together with fresher concepts on chemical structure-biological distribution relationships, a deeper insight and perspectives are being rapidly developed in radiopharmaceutical research. In particular, it helps to understand to some extent the chemistry of carrier-added and no carrier-added technetium-99 and technetium-99m. Promising results were reported on the research in technetium monovalent atomic complexes for myocardial imaging agents such as dimethylphosphate ethane (DMPE), as well as lipophilic complexes for brain blood flow imaging agents, such as amino-oxine, bis-aminoethanethiol and glucose-derivative complexes.

Another interesting new family of radiopharmaceuticals also is developing. These hold good potential in diagnostic nuclear medicine to unravel physiologic, pharmacologic, and/or biochemical processes occurring in normal/diseased states and are based in bifunctional radiopharmaceuticals. The radiopharmaceuticals contain a biological active molecule, together with a moiety having a functional group capable of chelating radiometallic nuclides such as gallium-67, gallium-68, indium-111, indium-113m, and technetium-99m. Many types of macromolecules such as monoclonol antibodies, enzymes, proteins, and so on have been used to tag bifunctional agents.

Recently, several molecules such as glucose, fatty acids, amino derivatives, and phthalein-based derivatives have

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been used to design agents they may selectively localize in brain, heart, or hepatobiliary systems. Nitridotechnetium complexes of the nitrate group instead of the oxide group show interesting biological behaviour that may render them interesting as radiopharmaceuticals.

Clinically useful compounds labelled with carbon-11 and other elements of life have already demonstrated their bright future in probing human biochemistry in a quantitative way. It was pointed out that many ideas now in the research phase were close to, or actually undergoing, initial evaluation in the clinic and some would soon begin to initiate a new growth phase in the routine practice of nuclear medicine. Excellent accounts were presented on the research into the visualization of neuroreceptor distribution, both in health and disease, as well as the use of positron-emitting agents for the study of dementia, Alzheimer's disease, epilepsy and cerebral tumours.

Monoclonal antibodies

The use of different antibodies for radio-immunoassay (RIA) detection of colorectal cancer, gastric cancer, melanoma, neuroblastroma, ovarian cancer, and cardiac myosin have been demonstrated. Recent results show that administered antibodies to tumour antigen localize on tumour cells and could be detected by external photoscanning.

Experiments in animal models with several monoclonal antibodies are promising. At this time, this field is undergoing clinical trials in various laboratories. Only time can tell the ultimate usefulness of monoclonal antibodies for *in vivo* diagnosis.

In ample supply at hospitals in industrialized countries, radiopharmaceuticals for valuable nuclear medicine studies often are not on hand when needed by doctors in many developing countries. Fortunately, the supply outlook is improving. (Credit: Atomic Industrial Forum, Inc.)