Impact of Radiopharmaceutical Innovations on Nuclear Medicine Technology

The year 1970 found nuclear medicine technology limited to the use of a few radiopharmaceuticals such as I-131 and Tc-99m. Major developments in the next few years altered the manner in which the Tc-99m radiopharmaceutical would be prepared and increased the scope of imaging procedures through the availability of new radiotracers.

It is noteworthy that the day after the first business meeting of the Technologist Section, Dr. Gopal Subramanian described a Tc-99m bone imaging agent. This presentation signified a giant step forward for two reasons. First, Tc-99m bone scintigraphy had soon become a mainstay of nuclear imaging because of its exquisite sensitivity for changes in osteogenic activity. Second, the introduction of the stannous-acid labeling system revolutionized the manner in which Tc-99m is tagged to a variety of ligands.

To appreciate the significance of the stannous reduction approach, it is necessary to recall that a limitation of technetium chemistry is its relatively nonreaction nature. Traditionally, Tc-99m was radiolabeled by reducing pertechnetate to a reactive intermediate in dilute acid and reacting it with a specific ligand; this was usually followed by neutralization. This approach required multiple manipulations and reactants. The benefit of stannous-acid reduction is that this two-step reaction usually requires only one manipulation. In its simplest form, current Tc-99m labeling is achieved by adding a sufficient amount of [^{99m}Tc]pertechnetate to a vial containing a lyophilized, balanced mixture of a stannous ion and the desired ligand. Presently, most organ systems may be studied by a Tc-99m soluble complex or insoluble form wherein the preparation is mediated by stannous reduction.

The Tc-99m generator experienced considerable improvement in the 1970s. Although the basic operational principal for the Mo-99/Tc-99m generator system has not changed since its introduction in 1957 by Powell Richards, manufacturers have greatly improved the quality of the eluate and total performance of the system. Early generators were often fraught with poor yield, Mo-99 breakthrough, alumina contamination, and low specific concentrations of Tc-99m. By 1974, separation technology had developed to the extent that fission-product Mo-99 was available with sufficient radionuclide purity to replace neutron-irradiation produced Mo-99. This switch permitted use of a more compact column and greatly increased the specific concentration of eluted Tc-99m. Thus, the useable life of a generator was extended, and more importantly, dynamic imaging techniques were enhanced.

The quality of the eluate was improved by numerous modifications. More effective activation of alumina controlled troublesome Mo-99 breakthrough. Alumina contamination was resolved by decanting away minute alumina particles prior to column loading, and by incorporating a membrane filter into the system. Microbiological purity was enhanced by redesigning generators so that elution was made through a disposable needle that could be changed before each elution. Generator yield was improved by taking steps to assure that technetium was maintained on the column in its highest oxidation state. Generators became more convenient by building in a saline supply. Finally, the need for greater Tc-99m activity was met by shielding the highly penetrating photons of Mo-99 with depleted uranium, a more dense material than lead. Consequently, the new shielding permitted Mo-99 generator loads up to 15 Ci.

The advent of plentiful supplies of accelerator-produced radiotracers heralded the next growth period in nuclear medicine. Gallium-67 as citrate was investigated as a bone imaging agent, but was found to have applications for imaging occult infections and certain malignancies. Iodine-123 became the radioiodine of choice for diagnostic thyroid studies because of its optimal photon energy and radiation dosimetry; however, its short half-life limits its usefulness to locations served by overnight shipments. Indium-111 brought renewed interest in extemporaneous labeling procedures as methods were developed for labeling formed elements of the blood (i.e., erythrocytes, platelets, and white cells). One pitfall is that ionic indium, which is insoluble at physiological pH, required complexation as an intermediate labeling step. Oxine is one of several interesting lipid-soluble complexing agents that effectively transports radioindium across cell membranes.

The emergence of nuclear cardiology, however, prompted the greatest changes in our technology. It required the development of novel instrumentation, collimation devices, and computer software. Consequently, these innovations required the technologist to develop an in-depth understanding of the cardiovascular system and to acquire computer-related skills. The serendipitous finding that stannous ion could mediate the reduction and incorporation of Tc-99m into the red cell provided a noninvasive convenient means for studying cardiac function. Although the role of Tl-201 was clouded for years, it has become an effective tool for assessing the perfusion and vitality of myocardium.

Radiopharmaceutical distribution patterns changed markedly to meet increased demands as nuclear medicine spread to all hospitals in the early 1970s. Manufacturers coordinated air and ground transportation systems so that long-lived radiopharmaceuticals could be supplied overnight to over 90% of hospi-

tals in the continental states. Nuclear pharmacies emerged as intermediate suppliers as they demonstrated proficiency in dispensing ready-to-use unit or multiple dose radiopharmaceuticals. By centralizing Tc-99m generators and long-lived inventories, pharmacies were able to provide complete services competitively.

Not all developments have favored nuclear medicine. Organs such as the brain and pancreas are better studied by other imaging modalities. Such erosion in nuclear medicine may continue unless new radiotracers are designed that provide unique quantitative and functional information about physiologic phenomena. Although therapeutic applications did not keep pace with diagnostic studies, the future is now bright with the development of radiolabeled monoclonal antibodies for certain neoplasms.

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A Review of Instrumentation 1970–1985

"Change, that is the only thing in the Universe which is Unchanging." **—Helmuth Wilhelm (1905–)**

The past decade and a half has witnessed some profound changes in the technology of nuclear medicine—particularly the instrumentation. Admittedly, this time span does not include the announcement of the Anger scintillation camera (*1*), the introduction of Tc-99m (*2*), or the earliest applications of computers to nuclear medicine (*3*). Nevertheless, those three items—scintillation cameras, Tc-99m tagged radiopharmaceuticals, and computers—have all undergone considerable development and their impact on the practice of nuclear medicine since 1970 accounts for the important role presently played by nuclear medicine in medical diagnosis.

In 1970, a very large proportion of nuclear medicine imaging was performed using rectilinear scanners, and there was considerable debate concerning the merits of scanners versus cameras if one was budgeting for new equipment. This debate was justified by the fact that scintillation cameras did not exhibit spatial resolution much better than good scanners and the uniformity of the field of view was only marginally acceptable.

Unquestionably, the most significant development outside of nuclear medicine that has affected the instrumentation has been the development of large scale integrated circuits or "chips" and "micro-chips." Electronic circuits have become much more powerful, cheaper, and considerably more stable. It is this factor that has enabled manufacturers to progress: from 19 photomultipliers to scintillation cameras with as many as 90 tubes; from scintillation cameras that exhibited poor differential linearity and uniformity to those which have energy and linearity correction built into the detector heads; from scintillation cameras that could accept only 50,000–70,000 cps to those which can respond to 400,000 cps; and from scintillation cameras that gave an analog output on Polaroid film to those which have computers as an integral component of the camera.

The technology of scintillation crystal manufacturing has advanced so that a scintillation camera can have a 16-in diameter, ¼-in-thick crystal compared to 12-in diameter by ½-in-thick. At the same time, more sensitive and stable photomultipliers have been introduced in a variety of shapes and sizes that have provided far better light gathering properties. On the other side of the crystal, the technology of collimator manufacturing has changed considerably and the spatial resolution of collimators can now be made to match the much improved intrinsic resolution of scintillation cameras.

The performance specifications of scintillation cameras improved steadily during the 1960s and 1970s (Fig. 1), but are probably close to theoretical limits now. With sodium iodide

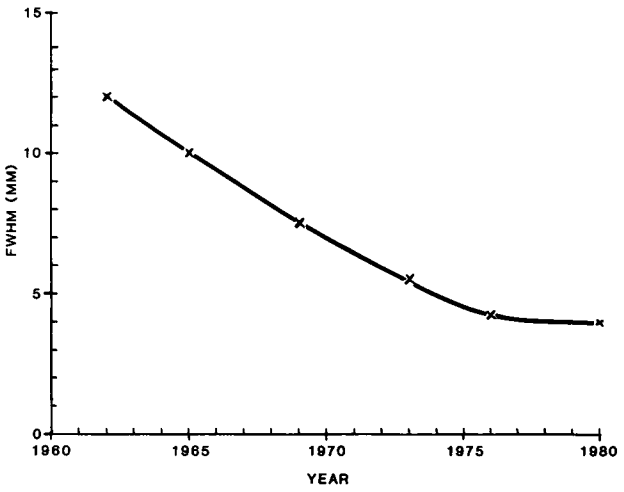

FIG. 1. Intrinsic spatial resolution of scintillation cameras improved dramatically during the 1960s and early 1970s—values are approximate for commercial cameras. It has not improved remarkably since 1980 though intrinsic uniformity has continued to improve with the development of sophisticated linearity correction circuits.