# **Fifty Years of Radiopharmaceuticals**

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To celebrate the 50th anniversary of the founding of the SNMMI Technologist Section in 1970, the Radiopharmaceutical Sciences Council board of directors is pleased to contribute to this celebratory supplement of the Journal of Nuclear Medicine Technology with a perspective highlighting major developments in the radiopharmaceutical sciences that have occurred in the last 50 years.

Key Words: radiopharmaceuticals; history; nuclear medicine practice

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he practice of nuclear medicine incorporates both diagnostic imaging and radiotherapeutics to image and treat a wide range of clinical questions and disorders. It is estimated that about 20 million diagnostic nuclear medicine procedures are performed annually in the United States (1,2). Of these, more than 90% are SPECT scans, and the remainder are PET scans. Radiotherapeutic studies occur in addition to these diagnostic imaging procedures. Diagnostic nuclear medicine is able to provide unique physiologic temporal and spatial information from the biodistribution of radiopharmaceuticals, which can be visualized by traditional planar imaging or high-resolution cross-sectional studies using either SPECT or PET cameras. Modern SPECT and PET studies fuse the physiologic data from SPECT or PET with the anatomic information

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from high-resolution CT or MRI. The clinical information that can thus be obtained is of particular benefit in oncology to determine the extent of cancer and the success of therapy; however, many other different clinical disciplines (e.g., cardiology, endocrinology, infectious diseases, dementia research, and pain management) use diagnostic nuclear medicine studies to provide biodynamic information that cannot be obtained through other radiographic or diagnostic studies. Nuclear medicine radiotherapeutics incorporate similar physiologic processes to deliver targeted radiation on radiopharmaceuticals attached to an  $\alpha$ - or  $\beta$ -emitting isotope. Radiotherapeutic applications are used to treat various malignancies, as well as hyperthyroidism and myeloproliferative diseases. Growth in the use of both diagnostic nuclear medicine and radiotherapeutics has

"During my term of office it was a relatively quiet time. Dr. Dworkin and I would call each other on Mondavs and discuss our weekends. Near the end of my term there was concern regarding technologist finances with the Society. That was resolved over a few beverages. It was a pleasure working with everyone, with special thanks to Virginia Pappas, Jim Wirrell, Marcia Boyd."



Wayne J. Wcislo, CNMT, FSNMMI-TS SNMMI-TS President. 1986-1987

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been dependent on the development of, and access to, an arsenal of radiopharmaceuticals.

Radiopharmaceuticals are bioactive molecules (or compounds) tagged with a radionuclide. The radionuclide is selected for the application at hand (diagnosis or therapy), and the physiologic processes in the body deliver the bioactive core (along with the radionuclide) to the desired biologic target. Radiopharmaceuticals had their genesis in the 1920s and 1930s. The first use of a radiotracer for a diagnostic procedure was a study by Blumgart and Weiss, who used what was known at the time as radium C (subsequently identified as <sup>214</sup>Bi) to measure the arm-to-arm transit time of blood (3). Subsequently, the discovery of 99mTc was reported by Perrier and Segrè (4) while de Hevesy was investigating the distribution and metabolism of <sup>32</sup>P-labeled compounds with Chiewitz at Biels Bohr's Institute in Copenhagen (5). Concurrently, Hamilton and Stone were conducting human research with <sup>24</sup>NaCl (6), whereas Compton (Massachusetts Institute of Technology), as well as Hamilton and Soley (University of California at San Francisco and Berkeley), were investigating the diagnosis and treatment of thyroid disease, and their initial work clearly showed that radioiodine was taken up by the thyroid gland (7-9). All of this early work paved the way for development of the radiopharmaceutical sciences, an exciting and multidisciplinary field that incorporates aspects of chemistry, biology, and physics and is heavily integrated with nuclear medicine.

To celebrate the 50th anniversary of the founding of the SNMMI Technologist Section in 1970, we on the Radiopharmaceutical Sciences Council board of directors are pleased to contribute to this celebratory supplement of the *Journal of Nuclear Medicine Technology* with a perspective highlighting major developments in the radiopharmaceutical sciences that have occurred in the last 50 years. We highlight key milestones that have occurred, but a comprehensive discussion of the field is beyond the scope of this perspective. However, when we were reviewing content for this article, it became apparent that such a history is probably warranted.

### **THE 1970S**

As far back as the 1970s, the field of radiopharmaceuticals has involved both innovations in chemistry and adaptation to regulatory reform. In 1970, the U.S. Food and Drug Administration (FDA) announced its plans to withdraw exemptions granted to radiopharmaceuticals and begin regulating them as drugs. This process was completed in 1977, after which time new-drug applications were required to market new and existing radiopharmaceuticals. From a chemistry perspective, this decade included key developments in the use of <sup>201</sup>Tl for myocardial perfusion imaging (*10*), as well as <sup>89</sup>Sr to reduce the pain associated with metastatic bone disease (*11*). Interestingly, early attempts to use labeled antibodies for tumor imaging were also pioneered by Primus et al. (*12*). However, the 1970s are likely remembered best for milestones in <sup>99m</sup>Tc chemistry and <sup>18</sup>F-FDG. After the introduction of the <sup>99m</sup>Tc generator in the 1950s (*13*), and the realization by Richards that <sup>99m</sup>Tc has medical utility (*14*), the 1970s saw significant efforts to develop new <sup>99m</sup>Tc-based radiopharmaceuticals. For example, Loberg and Fields discovered the substituted iminodiacetic acid analogs for hepatobiliary imaging (*15*). The development of these compounds, radiolabeled with <sup>99m</sup>Tc, was an early example of the concept of bifunctional chelators, that is, ligands that are designed to both chelate and target biodistribution of the <sup>99m</sup>Tc complex. The 1970s also saw the introduction of the <sup>99m</sup>Tc-diethylenetriaminepentaacetic acid instant kit for renal imaging by Eckelman and Richards (*16*).

Ido and colleagues, at Brookhaven National Laboratory, were the first to describe the synthesis of <sup>18</sup>F-FDG (*17*). The first clinical PET scan with <sup>18</sup>F-FDG, in 1976, was likely the most important milestone of this decade. <sup>18</sup>F-FDG remains the mainstay of clinical PET imaging to this day and makes up most clinical PET scans that are performed in the United States each year. The <sup>18</sup>F-FDG was manufactured at Brookhaven National Laboratory in August 1976 and then flown to Philadelphia, where it was first administered by Alavi at the University of Pennsylvania to 2 healthy human volunteers (*18*). At the time, the interest was in neuroscience applications, and images obtained with an ordinary nuclear scanner showed uptake of <sup>18</sup>F-FDG in the brain.

## **THE 1980S**

<sup>99m</sup>Tc chemistry grew further during the 1980s, and in 1985, Ell reported the first instance of cerebral blood flow imaging using <sup>99m</sup>Tc-exametazime, developed by Amersham (19). By 1988, the FDA had approved this for diagnosis of stroke. At the University of Michigan in the early 1980s, Kline et al. developed *meta*-iodobenzylguanidine for imaging and treatment of neuroblastoma and other adrenergic tumors in the body, as well as myocardial imaging (20,21). In oncology, <sup>123</sup>I-*meta*-iodobenzylguanidine was used to stage disease, and it was found that <sup>131</sup>I-*meta*iodobenzylguanidine could be used for both imaging and



therapy. By the late 1980s, <sup>131</sup>I-*meta*-iodobenzylguanidine was being used for the detection and treatment of malignant pheochromocytomas and neuroblastomas, as well as myocardial imaging.

The 1980s were also an active decade for PET research. For example, 1989 saw the FDA approval of <sup>82</sup>Rb for PET myocardial perfusion imaging (22), and the discovery that <sup>18</sup>F-FDG accumulates in tumors began the evolution of PET as a major clinical tool in cancer diagnosis that continues to this day (23). Brodack et al. were also developing  $^{18}$ F-labeled ligands for estrogen receptors (24), while Jerabek and colleagues reported <sup>18</sup>F-fluoromisonidazole for tumor hypoxia imaging (25). The 1980s in many ways also represented the golden age of PET in neuroscience. Henry Wagner reported the first imaging of neuroreceptors in humans. Using himself as the subject, Wagner, along with his coworkers, imaged dopamine receptors using 3-N-11Cmethylspiperone (26). At about the same time, Crawley et al. was using <sup>77</sup>Br-*p*-bromospiperone to image dopamine receptors in the U.K. (27). Concurrent with efforts to image dopamine receptors, Garnett et al., who were working at McMaster University in Canada, described the first distribution of dopamine in the basal ganglia using <sup>18</sup>F-6-fluoro-DOPA (28). As a side note, Eckelman and Reba also carried out the first example of SPECT neuroreceptor imaging using <sup>123</sup>I-3-quinuclidinyl-4-iodobenzilate to image muscarinic acetylcholine receptors in Alzheimer disease (29). All of this work established the use of functional imaging in neuroscience applications and stimulated development of many new radiopharmaceuticals for brain imaging. For example, the 1980s would see Fowler et al. introduce <sup>11</sup>Cdeprenyl for imaging of monoamine oxidase (30), Herscovitch et al. measure cerebral blood flow with <sup>15</sup>O-water and <sup>11</sup>C-butanol (31), and Dannals et al. at Johns Hopkins image  $\mu$ -opioid receptors with <sup>11</sup>C-carfentanil (32). It is interesting to look back and recognize that the desire to develop new radiopharmaceuticals in this period was also driving innovation in synthesis and radiochemistry and that even

"My relationship with the Tech Section was very pleasant and cordial. My co-president was to be Paul Cole, but his unfortunate death meant that his vice-president, Art Hall, was my colleague. Art is a man with a big smile. We enjoyed working together."



Barbara Y. Croft, PhD SNMMI President, 1988–1989 Southeastern Chapter in the 1980s, radiochemists were thinking about new precursors for radiochemistry (33), automation (34) and strategies for simplified purification of radiopharmaceuticals (35).

### THE 1990S

The 1990s saw FDA approval of <sup>99m</sup>Tc-sestamibi as the first <sup>99m</sup>Tc myocardial agent. <sup>99m</sup>Tc-Sestamibi is still widely used today, mainly for myocardial imaging but also to identify parathyroid adenomas, for radioguided surgery of the parathyroid, and in breast cancer imaging (*36*). Other developments in SPECT imaging included the first FDA-approved monoclonal antibody for tumor imaging, <sup>111</sup>In-satumomab pendetide (*37*).

This decade was also a turning point for PET imaging, as approval of <sup>18</sup>F-FDG by the U.S. FDA was seen, as well as subsequent reimbursement by the Centers for Medicare and Medicaid Services. Automated-synthesis modules were introduced for its production, and pharmacy networks were established for commercial distribution to satellite PET centers without a cyclotron. Use of <sup>18</sup>F-FDG grew substantially, and new applications emerged, such as the prediction and assessment of tumor response to therapy. Since that time, the use of <sup>18</sup>F-FDG PET for imaging applications in oncology, neurology, and cardiology has grown steadily, and reflecting this growth, the estimated number of <sup>18</sup>F-FDG PET studies that occurred in the United States in 2017 was more than 1.9 million.

#### THE 2000S

The 2000s saw a number of substantive changes in the field, from the development of hybrid PET/CT scanners in 2000 (the Siemens Biograph was Time Magazine's Invention of the Year in 2000) (38) to the introduction of goodmanufacturing-practice regulations for radiopharmaceuticals (title 21 of Code of Federal Regulations, part 212) by the U.S. FDA in 2009 (39). The 2000s were also an important time for PET imaging. The pioneering work of Klunk et al. in developing <sup>11</sup>C-Pittsburgh compound B for imaging amyloid plaques in dementia patients came to fruition, and they reported the first human studies in 2004 (40). This work sparked the widespread use of PET imaging as a tool in dementia research and led to the more recent establishment of multiple-site clinical studies (e.g., the Alzheimer's Disease Neuroimaging Initiative (41)) and the use of PET to support therapeutic trials (42). Besides use in clinical trials, the use of PET as a serious tool to support drug discovery efforts began with, for example, work from Bergström et al. at Merck using PET to inform go/no-go decisions on therapeutic assets such as aprepitant (Emend; Merck) (43).

The emerging role for radiotherapeutics in general clinical care also began during the 2000s. The FDA approved Zevalin (ibritumomab tiuxetan [Acrotech Biopharma], a monoclonal antibody radioimmunotherapy treatment for relapsed or refractory, low-grade or transformed B-cell non-Hodgkin's lymphoma) and Bexxar (unlabeled tositumomab combined with <sup>131</sup>I-labeled tositumomab, approved for treatment of relapsed or chemotherapy/rituxan-refractory non-Hodgkin lymphoma [GlaxoSmithKline]).

## THE 2010S

The 2010s were an extremely exciting time for the radiopharmaceutical sciences and nuclear medicine, as both disciplines matured from research techniques to underpin powerful standards of care. For example, <sup>123</sup>I-DaTscan (<sup>123</sup>I-ioflupane [GE Healthcare]), under development since the 1990s, was approved by the FDA in 2011 to help differentiate essential tremor from tremor due to Parkinsonian syndromes (44).

Title 21 of Code of Federal Regulations, part 212, mandated that anyone marketing PET drugs in the United States was required to obtain FDA approval by filing new-drug applications or abbreviated new-drug applications (39). This change moved PET radiopharmaceutical production from the practice of pharmacy to FDA-regulated drug manufacture and saw commercial nuclear pharmacies and academic medical centers alike obtain FDA approval for established radiopharmaceuticals such as <sup>18</sup>F-FDG (oncology, neurology, and cardiology), <sup>18</sup>F-NaF (bone imaging), and <sup>13</sup>N-ammonia (myocardial perfusion imaging). In many ways, title 21 of Code of Federal Regulations, part 212, clarified the path forward for obtaining regulatory approval and marketing authorization for new PET drugs as well. Reflecting this clarity, the 2000s witnessed FDA approval of numerous new PET radiopharmaceuticals for imaging. For example, in the neuroimaging space, Amyvid (florbetapir, 2012 [Eli Lilly]), Vizamyl (flutemetamol, 2013 [GE Healthcare]), and Neuraceq (florbetaben, 2014 [Life Molecular Imaging]) were all approved for PET imaging of the brain to estimate  $\beta$ -amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer disease and other causes of cognitive decline.

In oncology, the Mayo Clinic obtained FDA approval for <sup>11</sup>C-choline, and Blue Earth Diagnostics received approval for Axumin (<sup>18</sup>F-fluciclovine), both to image patients with suspected prostate cancer recurrence. This decade also saw a paradigm shift in radiotherapy and theranostics. In 2013, Bayer obtained FDA approval of Xofigo (223RaCl<sub>2</sub>) for the treatment of patients with castration-resistant prostate cancer (and symptomatic bone metastases) and, perhaps for the first time, demonstrated that a big pharmaceutical company could successfully market a radiotherapeutic. Later in the decade, FDA approval of Netspot (68Ga-DOTATATE) and Lutathera (177Lu-DOTATATE) was obtained by Advanced Accelerator Applications (which was subsequently purchased by Novartis), and FDA approval for <sup>68</sup>Ga-DOTATOC was granted to the University of Iowa (45). Netspot and DOTA-TOC are indicated for localization of somatostatin receptorpositive neuroendocrine tumors with PET imaging, whereas Lutathera is a radiolabeled somatostatin analog indicated for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors. These agents have ushered nuclear medicine into a new era of theranostics (46), and analogous agents targeting the prostate-specific membrane antigen and labeled with diagnostic (<sup>18</sup>F, <sup>68</sup>Ga) or therapeutic (<sup>225</sup>Ac, <sup>177</sup>Lu) radionuclides are currently in advanced clinical trials all over the world for diagnosis and treatment of prostate cancer.

#### 2020 AND BEYOND

The growth in the radiopharmaceutical sciences and nuclear medicine in the last 50 years has been impressive. However, as we turn our gaze to the future, it is possible that the best is yet to come. New diagnostic and therapeutic radiopharmaceuticals are being approved by the FDA, heralding in the age of theranostics, and we expect this trend to continue. Advances in the production and availability of new isotopes such as <sup>89</sup>Zr, <sup>52g</sup>Mn, <sup>86</sup>Y, <sup>43,47</sup>Sc, <sup>55</sup>Co, and many others are expanding the chemistry toolbox for the synthesis of new radiopharmaceuticals. At the same time, advances in

"My term as President began early with the untimely death of the newly installed President Paul Cole. Paul David Cole was a dedicated technologist and upon his death I assumed the presidency and with the support of the executive members decided to continue with the course of action that Paul had laid out for his year as President. Upon my assuming my elected year as President the following memorable events occurred. Since the shortage of Nuclear Medicine Technologists was serious I sought out funding for a Recruitment Video. Once funding was received from ACNP, technologists from around the nation began the process of completing the task to develop the recruitment video and literature. Brad Pounds and Mickey Williams were instrumental in making this happen. Additionally, recruitment material from many of the vendors was developed in an effort to curtail the technologist shortage. A Paul Cole Scholarship was started and administered by the Education and Research Foundation. Marcia Boyd and I worked extensively with legislative individuals on the Hill to ensure adequate funding for educational programs for the Nuclear Medicine profession. In addition, I worked with other Radiology Groups, Summit on Manpower, ASRT and others, to share in solutions to address the technologist shortage and educational challenges facing the medical imaging community. As a result of Paul's untimely death, Paul Hansen worked exclusively to revise the bylaws to ensure a smooth transition of leadership should a similar event occur in the future. My years as President were challenging but extremely rewarding thanks to all of the support from our organization, vendors, and working technologists from around the world. As a final note: Virginia Pappas, your support was extraordinary."



Author (Art) J. Hall, CNMT, FSNMMI-TS SNMMI-TS President, 1988–1990 technology (e.g. mini cyclotrons, new synthesis module paradigms, and miniaturized equipment for automated quality control testing) are facilitating wider access to radiopharmaceuticals, particularly in developing nations. These developments, in conjunction with potentially disruptive new technologies such as total-body PET (47), could change the radiopharmaceutical paradigm. In addition to the impact on clinical scanning, total-body PET may have implications for the traditional commercial distribution model for radiopharmaceuticals. For example, the increased sensitivity of these new scanners allows the use of smaller amounts of injected activity. This change could permit a longer-range distribution of established radionuclides such as <sup>18</sup>F while also potentially enabling routine distribution of shorter-lived radionuclides such as <sup>11</sup>C and <sup>68</sup>Ga for the first time. All these developments make this an extremely exciting and rewarding time to be in the field of radiopharmaceutical sciences, and we at the Radiopharmaceutical Sciences Council are passionate about our mission to provide a forum for discussion and dissemination of information on the radiopharmaceutical sciences, to promote and encourage basic research and applied technology in the radiopharmaceutical sciences, and to provide the SNMMI with information on the radiopharmaceutical sciences. We are also actively engaged in supporting and training the next generation of radiopharmaceutical scientists and committed to working with the SNMMI and SNMMI-TS to ensure a bright future for our field. We congratulate the SNMMI Technologist Section on its 50th anniversary, and we look forward to the new developments that occur in the next 50 years.

#### DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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"My presidency year, 1990–91, coincided with Brad Pounds' Technologist section presidency and I enjoyed working with Brad on a variety of issues. Virginia Pappas was the Administrator for the Technologist section at that time and both she and Brad worked vigorously to advance the Technologist section in the Society."



Naomi Alazraki, MD SNMMI President, 1990–1991 Southeastern Chapter

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"My fondest memories during my term as President, SNMMI-TS, included creating many lasting friendships within the NM community and addressing challenges facing our industry. A significant amount of effort was invested to deal with the technologist manpower shortage, which resulted in more NMT training programs and subsequently more qualified applicants nationwide."



Bradley K. Pounds, CNMT, FSNMMI-TS SNMMI-TS President, 1990–1991 "My fondest memory the year I was president was having the opportunity to work with some of the best and brightest technologists from all over the country. We were all focused on a common goal of enhancing nuclear medicine technology as a profession as we helped develop and guide the technologist leaders of the future."



Paul C. Hanson, CNMT, FSNMMI-TS SNMMI-TS President, 1992–1993