Jason S. Lewis
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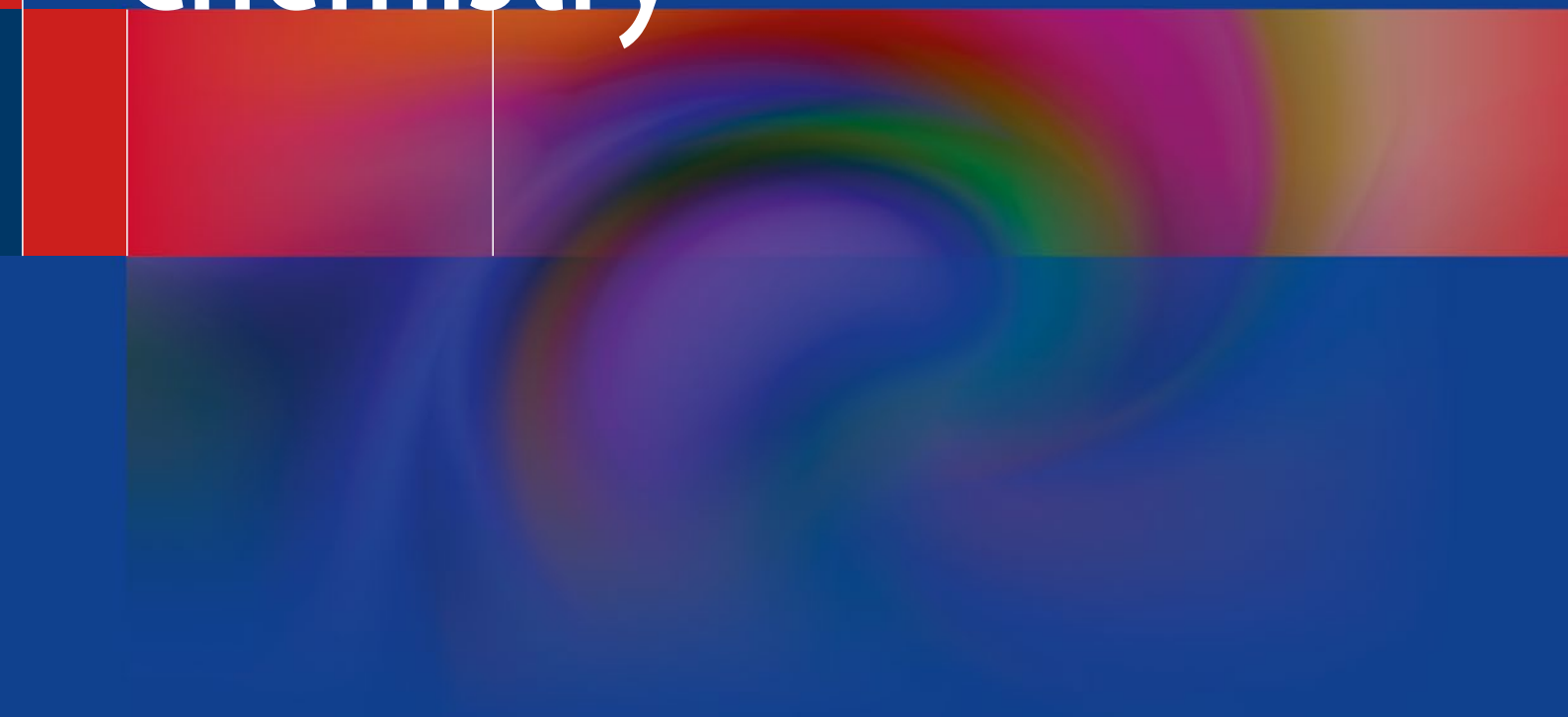
Editors

Radiopharmaceutical Chemistry



Springer

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Foreword

In the second volume of his journals, Ralph Waldo Emerson wrote, "Chemistry began by saying it would change the baser metals into gold. By not doing that, it has done much greater things." As I sat down to write this Foreword, Emerson's words came to mind for two reasons. First, perhaps more than any other branch of science, radiopharmaceutical chemistry depends on the transmutation of one element into another. And second, while Emerson was, of course, talking about chemistry as a whole, it is hard to deny that the remarkable story of radiopharmaceutical chemistry over the last half century provides a particularly fine example of the "greater things" of which he speaks.

The clinical efficacy of radiopharmaceuticals – particularly radiopharmaceuticals for imaging – is predicated on the *tracer principle*, the notion that radiolabeled compounds are administered in such small molar amounts that they do not significantly perturb the biological systems with which they interact. This is critical both with respect to the integrity of the biological assays they provide and in the context of side effects for patients. To illustrate the latter, there have been ~50 million clinical PET imaging studies without a reported complication from the radiotracer. The benefits of the tracer principle are clear. However, working with such small amounts of radionuclides creates both opportunities and a challenging scenario for radiochemists: many of the principles of stoichiometry and mass action in chemical reactions are not applicable at the "tracer scale." Yet this is not the only way in which radiopharmaceutical chemistry is unique. The short-lived nature of many radionuclides means that time is of the essence during the synthesis of radiopharmaceuticals, an issue that prioritizes the incorporation of radionuclides at late stages in the synthesis of a tracer. This, in turn, has led to the advent of novel automated systems for radiosynthetic processes and, because of the minute masses involved, has more recently fueled the development of small microsynthesizers as well. Ultimately, while radiopharmaceutical chemistry is based on many general principles of chemistry, these key differences have forced the field to undergo an evolution all its own.

In this textbook, Professors Lewis, Windhorst, and Zeglis have – arguably for the first time – created a comprehensive educational framework for radiopharmaceutical chemistry. Each chapter has been thoughtfully crafted by leading experts from around the world, and the trio of editors has merged these contributions into a cohesive and accessible book that will undoubtedly become an indispensable guide for students and radiochemists at all levels of education and experience. The interdisciplinary and specialized nature of radiopharmaceutical chemistry has had two important implications for the training of radiochemists. First, radiochemistry and radiopharmaceutical chemistry are seldom taught during the undergraduate years. And second, aspiring radiochemists often come to the field after years of training in other disciplines, including organic, medicinal, inorganic, and materials chemistry. While the latter has provided a pipeline of diverse talent, it has also created an educational gap: for years, aspiring radiochemists – whether undergraduates, graduate students, postdoctoral fellows, or experienced chemists – have not had the benefit of a single, authoritative resource to help them transition into the field of radiopharmaceutical chemistry. This is even more important now due to the ever-growing importance of molecular imaging in transferring knowledge from the *in vitro* biological sciences to *in vivo* animal models of disease and to clinical research and practice, along with the integration of molecular imaging diagnostics with molecular and

cell-based therapies. This textbook *emphatically* closes that gap and, in doing so, will play a critical role in the education of the next generations of radiopharmaceutical chemists worldwide.

I have had the good fortune to be involved in one branch of radiopharmaceutical chemistry – PET imaging – since the very beginning, starting with my invention of the PET scanner with my postdoctoral fellow at the time, Dr. Edward Hoffman. This journey has given me an acute appreciation for the interdisciplinary nature of the field of nuclear imaging. Indeed, the origin and advancement of nuclear medicine have their foundation in the collaboration and cooperation of physicists, engineers, physicians, and (of course) radiochemists. The three parts of this textbook – First Principles, Radiochemistry, and Special Topics – reflect this interdisciplinary approach. An extraordinarily wide array of topics is covered, ranging from the fundamentals of the production and decay of radionuclides to electrophilic radiofluorinations and the coordination of radiometals. The book also addresses the integration of radiotracers with therapy in theranostics as well as the translation of radiopharmaceuticals to clinical practice to improve the care of patients.

Finally, on a personal note, I have spent my entire professional career working with a wide array of radiochemists, many of whom are contributors to this book. Over the years, they have displayed an inspiring passion for this field, and it has been a pleasure spending so much time as teachers and students of each other and – most importantly – building lifelong friendships with them.

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Preface

From the naming of "radioactivity" in 1897 by Marie Curie to the first intravenous injection of radium in 1913 to the installation of the first PET/MRI in 2008, the use of radiolabeled compounds has become fully integrated into medical care. The stunning clinical successes of nuclear imaging and targeted radiotherapy have resulted in rapid growth in the field of radiopharmaceutical chemistry. Without question, this growth will ultimately prove extremely beneficial to the field (and, by extension, nuclear medicine). However, at this point, interest in the field outpaces the academic and educational infrastructure needed to train new radiopharmaceutical chemists. The aim of this book is to help bridge this educational gap at a time when an increasing number of young scientists are interested in radiopharmaceutical chemistry.

When conceiving and developing this book (over a number of beers), we requested that the authors of each chapter regard their contribution not as a review but rather as a piece of a larger educational framework meant for undergraduate students, postgraduate students, and postdocs. We also asked that the chapters include "tricks of the trade," methods that are vital for success but are often not discussed in the primary literature. Ultimately, we hope that this book can fill an important niche in the educational landscape of radiochemistry and thus prove vital to the training of the next generation of radiopharmaceutical chemists.

The book is divided into three overarching parts: First Principles, Radiochemistry, and Special Topics. The first ten chapters seek to offer "bird's-eye view" discussions that cover fundamental and broad issues in the field. The second part is the "meat" of the book and delves much deeper, covering both well-established and state-of-the-art techniques in radiopharmaceutical chemistry. This part has been divided according to radionuclide and includes chapters on radiolabeling methods using both common and emerging medical isotopes. Finally, the third part of the book is dedicated to chapters that – frankly – do not fit elsewhere in the work yet still contain important information for young radiochemists.

The three of us have dedicated our careers to radiochemistry, and this book is the manifestation of our desire to grow the field we love. This work would not have been possible without extraordinary contributions – following occasional arm-twisting on our part – from our dear friends and colleagues. Their efforts and work are very much appreciated. We would also like to thank Katherine Kreilkamp (Developmental Editor, Springer Nature) for her incredible hard work, persistence, and ability to keep us on our toes, as well as Margaret Moore (Editor, Clinical Medicine, Springer) for signing on to this idea at the very beginning. Finally, we would like to thank our better halves, Mikel Ross, Monique Bolland, and Emily Zeglis, for their patience and understanding while this work developed and, in particular, for wrangling some very active 2-year-olds (Elliott Zeglis, Grace Lewis, and Evan Lewis).

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Part I

First Principles

Why Nuclear Imaging and Radiotherapy?

David Mankoff

Fundamentals

What Is Nuclear Medicine?

Nuclear medicine is classically defined as the application of radionuclides to medicine [1]. Nuclear medicine takes advantage of the unique properties of radioactive elements, which have significantly different physical properties compared to stable elements but identical chemical behavior. More specifically, radionuclides decay at a characteristic rate (*i.e.* half-life) via the emission of particles or electromagnetic radiation (*e.g.* positrons, gamma rays, *etc.*). These emissions can be harnessed to facilitate the imaging or therapy of disease. Radiolabeled molecules, termed "radiopharmaceuticals," are an essential element in the medical subspecialty of nuclear medicine [2]. As such, radiopharmaceutical chemistry—the branch of chemistry dedicated to the synthesis, characterization, and evaluation of radiopharmaceuticals—is a fundamental and critical component of nuclear medicine.

Why Nuclear Imaging?

Nuclear imaging is predicated on the fact that essentially none of the biomolecules within the body are radioactive. As a result, radiopharmaceuticals can be distinguished easily from native molecules, providing nearly infinite contrast for imaging. This represents a dramatic departure from other imaging modalities—such as computer tomography (CT)—in which *all* tissues produce a signal and differences in the intensity of the signal between different tissues provide image contrast. In principle, every molecule of a diagnostic radiopharmaceutical can be detected over its lifetime, providing extraordinary sensitivity for imaging [3, 4]. In practice, however, several factors—including the limits of detection devices, the absorption of emissions before they leave the body (attenuation), and the need to limit radiation exposure to patients—all impose limits on imaging the emissions from a radiopharmaceutical. That said, it is possible to generate high-quality images using radioactivity doses as low as 30–600 MBq, values which correspond to as little as nanomoles of the compound or less, depending upon the half-life of the radionuclide [5–7] (see Table 1 for a representative calculation). This unique property allows radiopharmaceuticals to behave as true molecular tracers without perturbing the native biochemistry of the system, following the tracer principle of De Hevesy [2].

Why Nuclear Radiotherapy?

Nuclear radiotherapy (also called radionuclide therapy) is predicated on the use of radiopharmaceuticals to deliver therapeutic radiation to a target within the body [8–10]. For example, diphosphonates—which are commonly labeled with the gamma-emitting radionuclide ^{99m}Tc to enable the imaging of bone mineralization——can also be labeled with a beta particle-emitting radionuclide such as ^{153}Sm to deliver therapeutic radiation to sites of new bone formation, most typically for the treatment of cancer metastases [11]. Nuclear radiotherapy offers some significant advantages over traditional systemic therapy with nonradioactive drugs (*e.g.* chemotherapy) and external beam radiotherapy. Unlike traditional chemotherapeutics, radiopharmaceuticals can deliver potent therapeutic doses that are not limited by the biochemical action of the drug on the target. Radiopharmaceuticals are administered at low molecular doses and therefore do not generate the nonspecific off-target biochemical effects that can be seen at higher doses of chemotherapeutics. Compared to external beam radiotherapy, molecularly targeted radiopharmaceuticals are typically able to deliver radiation to tissues more selectively than

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Table 1 Example of the nuclear medicine tracer principle based on radiopharmaceutical radioactivity dose and theoretical mass limits

The following illustrates the tracer principle of nuclear imaging in the case of the radiopharmaceutical [^{18}F]fluoroestradiol (FES), an analog of estradiol used for the visualization of the regional expression of the estrogen receptor (ER) in breast cancer [5, 6]
Calculation of the molecular quantity of FES needed to image regional ER expression
Radioactivity needed to generate an image, balancing radiation dose and imaging quality: 185 MBq (5 mCi)
Typical specific activity of FES at the time of injection: 37 GBq/μmol (1 Ci/μmole)
The molar dose associated with this dose of radioactivity: 5 nmol
Expected peak concentration after the infusion of FES for a typical 5 L distribution volume: 1 nM
Physiologic range for the concentration of circulating estradiol: as low as 1 nM in menopausal patients
Thus—at transient peak concentrations—the molecular concentration of FES is at or below the lower limits of physiologic concentrations of estradiol, permitting PET imaging of FES-ER binding without perturbing the biology of native estrogen

spatially-targeted external beam radiotherapy. For example, nuclear radiotherapy of thyroid cancer with Na^{131}I can deliver up to 10–15 Gy to thyroid cancer cells without disturbing most adjacent neck tissues. In contrast, only 5–7 Gy can be deposited in the thyroid cancer cells during external beam radiotherapy due to concerns surrounding the toxicity to normal tissues [12]. Yet nuclear radiotherapy is not perfect, of course. Indeed, nuclear radiotherapy is limited by the specificity of the probe for the targeted disease—typically cancer or endocrine disorders—and by the toxicity to organs involved in the absorption, transport, and clearance of the radiopharmaceuticals.

Why Nuclear Medicine Vis-a-Vis Alternatives?

Nuclear imaging and radiotherapy gain their principal advantages over competing approaches from the "tracer principle." The essence of "tracer principle" is that radiopharmaceuticals are administered at such low molar masses that they can create high-contrast images or deliver therapeutic doses without perturbing native biochemistry whatsoever. As such, nuclear medicine approaches hold their greatest advantages over other forms of imaging and therapy in molecularly sensitive processes—*i.e.* those that are most readily affected by low doses of exogenous molecules—including metabolism, receptor binding, and cellular transport [2, 13, 14]. More specifically, glucose metabolism [13, 15], binding to neuroendocrine and steroid receptors [5], and amino acid transport [16, 17] are three clinically important examples of biologic processes that are well served by radiopharmaceutical-based strategies. Nonetheless, nuclear medicine approaches inevitably have some disadvantages compared to other imaging and therapeutic modalities:

- Nuclear medicine offers limited spatial resolution compared to modalities such as X-ray or CT.
- Nuclear medicine involves exposure to radiation, unlike modalities such as MRI or ultrasound.
- Nuclear medicine requires patient-specific radiation safety precautions for treatments, unlike chemotherapy and external beam radiotherapy.

Ultimately, the advantages of nuclear approaches outweigh their disadvantages when applied to diseases associated with molecular targets that can be targeted by diagnostic or therapeutic radiopharmaceuticals. This has led to the considerable use of radiopharmaceuticals in both clinical practice and clinical research for oncology, endocrinology, neuropsychiatry, cardiology, and several other diseases, as outlined later in the chapter.

Details

Clinical Applications for Nuclear Imaging

Nuclear imaging is a key tool for clinical diagnosis that is used thousands of time each day around the world. It is most commonly used to detect and quantify organ function and/or abnormal physiology and molecular biochemistry in a variety of disorders [1]. The need to trace a particular physiologic process or molecular pathway is a common trait of many current clinical applications. Below is a non-exhaustive list of common clinical situations in which nuclear imaging is applied, in rough order of frequency. One or more examples of radiopharmaceuticals used for each application are provided as well.

- *To detect cancer and/or document its spread:*
  - By imaging aberrant glucose metabolism using [^{18}F]fluorodeoxyglucose (FDG) [15] (Fig. 1)
  - By imaging abnormal amino acid transport using [^{18}F]fluciclovine [16, 17] (FACBC)
  - By imaging the expression of cancer-specific biomarkers using ^{18}F- and ^{68}Ga-labeled small-molecule ligands that target prostate-specific membrane antigen [18]
  - By imaging new bone formation associated with cancer metastases using [^{99m}Tc]methylene diphosphonate (MDP) or [^{18}F]NaF [19] (Fig. 2)
- *To identify and quantify endocrine disorders:*
  - By characterizing and quantifying the basis of hyperthyroidism indicated by the uptake and retention of iodine using [^{123}I]NaI [20]
  - By localizing abnormal catecholamine-producing tumors such as pheochromocytomas and neuroblastomas using [^{123}I]metaiodobenzylguanidine (mIBG) [21]

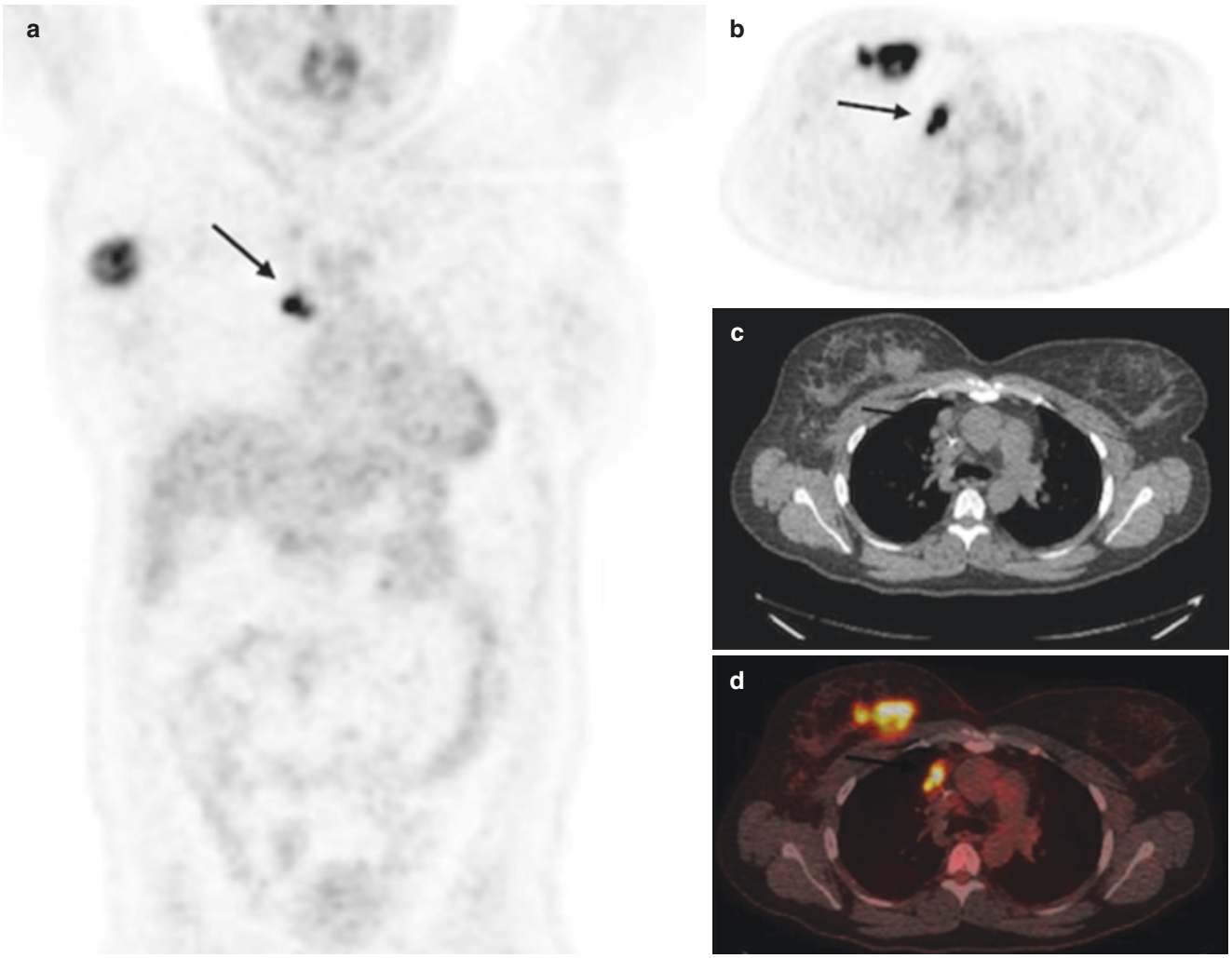

Fig. 1 [^{18}F]fluorodeoxyglucose ([^{18}F]FDG) PET/CT of breast cancer demonstrates the spread of the disease to small mediastinal nodes that are not detected by CT (*arrows*). Image **a** is a coronal PET image of the regional retention of FDG; on the right, axial PET images (**b**) have been combined with CT in the images (**c**) to yield fused images overlaying PET and CT images (**d**)

  - By localizing neuroendocrine tumors on the basis of somatostatin receptor expression using [^{111}In]pentetreotide or [^{68}Ga]-DOTATATE [21] (Fig. 3)
- *To detect and monitor cardiovascular disease:*
  - By identifying significant coronary artery disease on the basis of the delivery of perfusion agents retained in myocardium using [^{99m}Tc]sestamibi or [^{82}Rb]RbCl [22, 23]
  - By measuring aberrant presynaptic cardiac innervation in heart failure and arrhythmias using [^{123}I]mIBG [24]
- *To identify patterns associated with specific neurologic and psychiatric diseases:*
  - By identifying seizure foci on the basis of aberrant perfusion and/or glucose metabolism using [^{99m}Tc]ECD or [^{18}F]FDG, respectively [25]
  - By diagnosing Alzheimer's dementia on the basis of the deposition of amyloid in neural plaques using [^{11}C] Pittsburgh compound B (PIB) or ^{18}F-labeled analogs [26] (Fig. 4)
- *To document normal and abnormal function of excretory organs:*
  - By determining the causes of renal dysfunction by tracing the clearance of renal substrates using [^{99m}Tc] MAG3 [27]
  - By documenting cholecystitis and biliary dyskinesia by tracking biliary excretion using [^{99m}Tc]mebrofenin [28]
- *To identify regional tissue damage due to infection, trauma, etc.:*
  - By localizing bone trauma and infection on the basis reactive new bone formation using [^{99m}Tc]MDP [19]
  - By localizing infection using white blood cells (WBCs) labeled using [^{111}In]oxime [29]

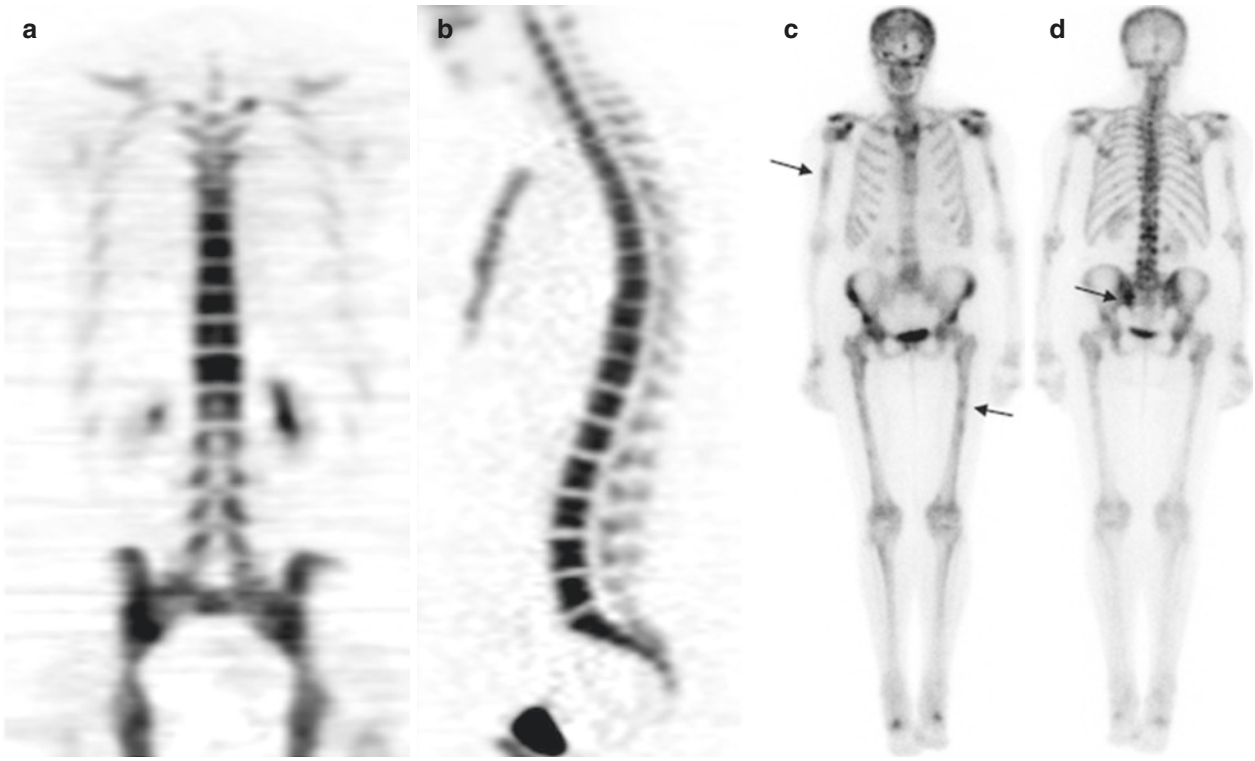

Fig. 2 Bone imaging using [^{18}F]NaF (PET imaging, **a** and **b**) [^{99m}Tc] methylene diphosphonate (MDP, single-photon imaging, **c** and **d**). The FDG PET scan shows the normal distribution of the tracer from the skull base to the pelvis in coronal (**a**) and sagittal tomographic views (**b**). The MDP bone scan shows anterior (**c**) and posterior (**d**) planar images that demonstrate multiple bone metastases, including sites in the left femur, right humerus, and left sacrum (*arrows*)

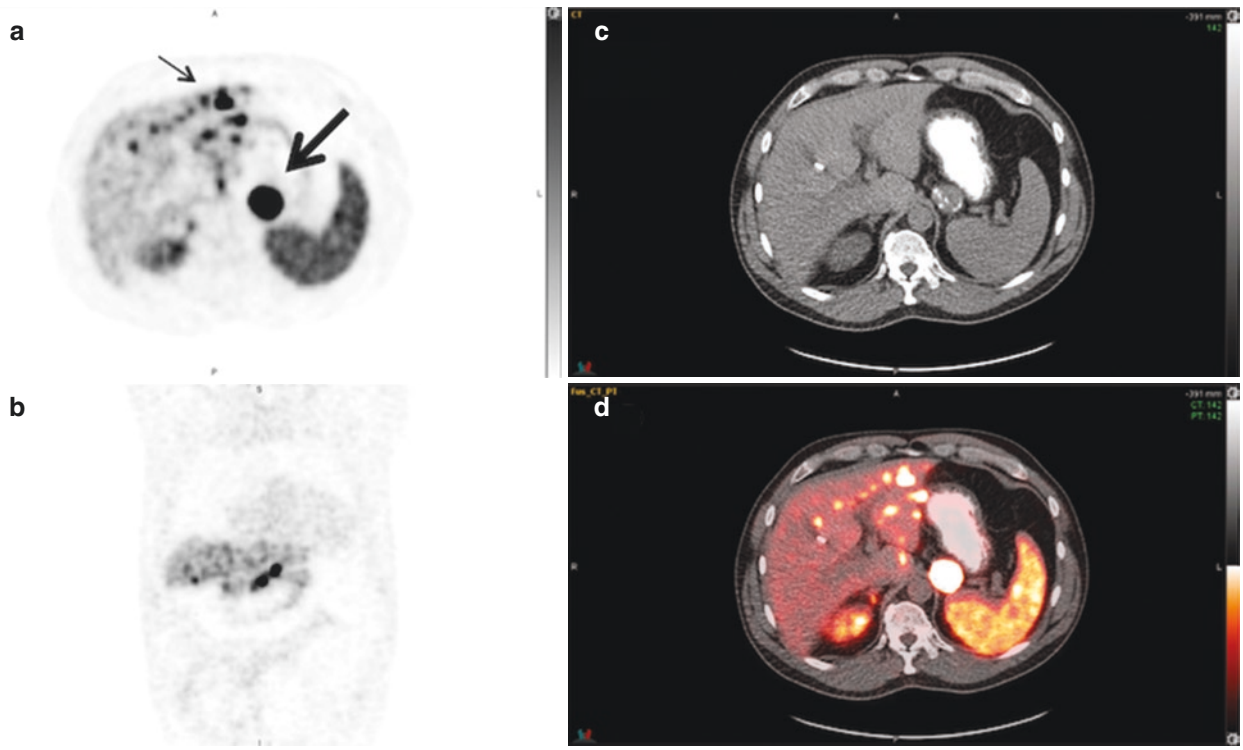

Fig. 3 The staging of neuroendocrine tumors using [^{68}Ga]DOTATE PET/CT. These images demonstrate the feasibility of imaging somatostatin receptor-expressing carcinoid tumor deposits on the emission PET scans (axial view, **a**, coronal view, **b**) and relate the localization of sites of radiopharmaceutical uptake to anatomic sites indicated by the accompanying CT (**c**) and depicted on fused PET and CT images (**d**). Images depict a low-grade neuroendocrine tumor presenting as a perigastric mass (thick arrow) with numerous liver metastases (*thin arrow*)

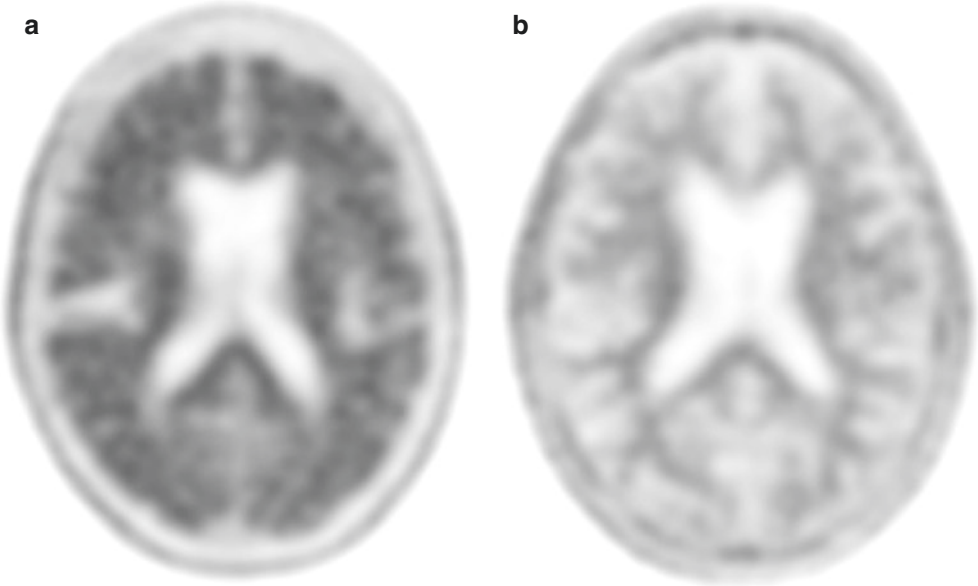

Fig. 4 Imaging amyloid deposition in Alzheimer's dementia neural plaques using [^{18}F]florbetapir. [^{18}F] florbetapir PET images from an Alzheimer's disease patient (**a**) and a normal control subject (**b**) are shown. The prominent cortical tracer binding in (**a**) indicates the presence of moderate amyloid plaques, as compared to absence of cortical binding in a negative scan (**b**). Nonspecific white matter binding is present in both the positive and negative [^{18}F] florbetapir scans

A common thread that runs through all of these applications is the need to localize and measure specific physiologic and molecular processes associated with either normal organ function or tissue dysfunction. In recent years, fundamental research in biology has led to the identification of new targets, and radiopharmaceutical chemists have leveraged this information for the creation of novel radiopharmaceuticals. This has increased the specificity of clinical diagnostic tasks through the use of imaging agents based on receptor-targeted ligands, substrates for specific transporters, and metabolic substrates specific to certain disease and tissue repair processes [14, 30, 31].

Clinical Applications of Nuclear Radiotherapy

Nuclear radiotherapy, while certainly an important clinical tool, is somewhat less commonly used than nuclear imaging. The first—and still most common—use of nuclear radiotherapy is the treatment of hyperthyroidism caused by Graves' disease and toxic nodular goiter. In this approach, modest doses of [^{131}I]NaI provide a safe and highly effective therapeutic alternative to more risky and/or toxic alternatives such as surgery or antithyroid medications. Specifically, in Graves' disease and toxic nodular goiter—in which a large fraction of ingested iodine (typically, well in excess of 30%) goes to the thyroid—thyroid tissue can be ablated by targeted radiotherapy with minimal radiation exposure to the rest of the body [32, 33].

The remaining applications of nuclear therapy largely focus on treating cancer, in which the small risk of modest radiation exposure to some normal tissues is offset by the potential for considerable therapeutic efficacy in otherwise often refractory disorders [8, 34]. The established therapeutic radiopharmaceuticals rely upon targeting either transport phenomena, metabolic pathways, or characteristic tumor biomarkers. Some examples of the established roles of nuclear radiotherapy in the treatment of cancer include:

- Thyroid cancer, using [^{131}I]NaI (typically higher doses than those needed in hyperthyroid treatments) [12] (Fig. 5)
- Painful bone metastases, using bone-targeting agents such as [^{89}Sr]$SrCl_2$, [^{223}Ra]$RaCl_2$, and [^{153}Sm]EDMP [11]
- Catecholamine-producing cancers (*i.e.* neuroblastoma and malignant pheochromocytoma), using the catecholamine transporter substrate [^{131}I]mIBG [21, 35]
- Neuroendocrine tumors, using ^{177}Lu or ^{90}Y-labeled analogs of somatostatin receptor-targeted peptides [21]

An additional type of nuclear radiotherapy is termed "radioimmunotherapy" and takes advantage of the specificity and affinity of monoclonal antibodies for molecular markers of disease. Radioimmunotherapy is predicated on the use of therapeutic radioimmunoconjugates, most commonly labeled with beta particle-emitting radionuclides such as ^{131}I or ^{90}Y [36, 37]. The application of radioimmunotherapy to B-cell lymphoma generated considerable excitement and resulted in two FDA-approved agents—Bexxar and Zevalin—which are based on anti-CD20 antibodies labeled with ^{131}I and ^{90}Y, respectively [37]. Though these were popular at the time of their introduction, advances in the application of non-labeled anti-CD20 antibodies (*e.g.* rituximab) and other drugs limited the more widespread use of these agents.

There has been considerable recent excitement over the future of nuclear radiotherapy [34]. This optimism has been driven by two recent trends in radiopharmaceutical research:

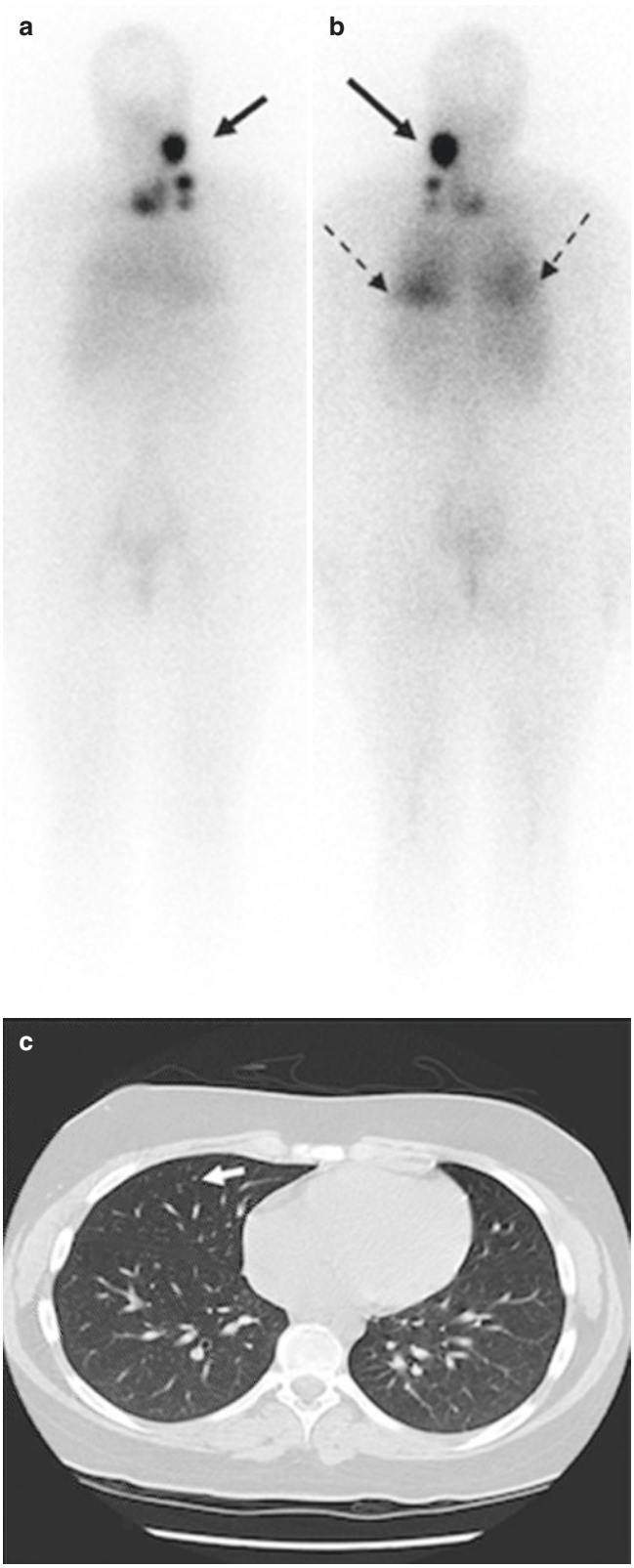

Fig. 5 Imaging with [^{123}I]NaI or low-dose [^{131}I]NaI provides a highly sensitive and specific way to detect the metastatic spread of thyroid cancer to sites of disease outside of the neck. In this case, anterior (**a**) and posterior (**b**) planar whole-body images taken 7 days after a therapeutic dose of [^{131}I]NaI demonstrate regional lymph node metastases in the neck (*solid arrow*) and distant metastatic spread to the small nodules in the lung bases (*dashed arrows*). Lung metastases were not as easily seen by CT (**c**, arrow indicates a single small nodule) but were readily apparent in the radioiodine images

1. The increased success in generating highly targeted small molecules and peptides that have high uptake and retention in cancerous tissues (*e.g.* PSMA-targeted therapeutics for prostate cancer) [18].
2. The increased potency and efficacy for therapeutic radiopharmaceuticals labeled with alpha-emitting radionuclides. For example, the recent approval of the alpha-emitting radiotherapeutic [^{223}Ra]$RaCl_2$ was heralded in clinical trials for demonstrating both highly effective pain palliation and improved survival [9]. This represents a notable departure from many years of experience with beta-emitting therapeutics which provided effective pain palliation but did not improve survival [11].

Tricks of the Trade

What Tools Do We Need?

The current and future success of nuclear imaging and therapy depends on several key technical issues:

- *Imaging instrumentation*: Over 50 years ago, the specialty of nuclear medicine was brought into the mainstream by the advent of the gamma camera, which enabled the practical collection of high-quality single-photon emitting radiopharmaceutical images in the clinic. In the 1990s and early 2000s, the advent of clinically practical positron emission tomography (PET) and PET/CT enabled clinical PET imaging to become an important and rapidly advancing part of nuclear medicine. Advances in the design of detectors and imaging systems have played a large role in the advancement of nuclear medicine [38] and have enabled the acquisition of high-quality, quantitative images with lower and lower doses of radiopharmaceuticals. Further advances in the design of hybrid imaging platforms and novel imaging devices will likely add significantly to our current capabilities [3, 4].
- *Image computing and analytics*: Advances in computational capability—enabled by advances in computing hardware and algorithms—have led to improved imaging quality at low tracer doses though sophisticated image reconstruction and post-reconstruction processing [39]. Further advances in image analysis and advanced analytics (such as machine learning-based feature extraction) will continue to maximize our ability to draw meaningful diagnostic information from nuclear imaging and guide the safer and more effective dosing in nuclear radiotherapy.

However, while instrumentation and analytics have set the pace of discovery and advancement in nuclear medicine for many years, the future of the specialty will increasingly be determined by radiopharmaceutical research and development.

Rapid advances in our understanding of the molecular biology of health and disease underlie an increasing trend toward precision medicine using treatments guided by molecular diagnostics [14, 30, 31, 40]. As such, advances in nuclear medicine will increasingly be driven by the development of new and improved radiopharmaceuticals to guide precision medicine. The creation of paired nuclear diagnostic and therapeutic agents—known as "theranostics"—will be particularly important, as theranostics provide unparalleled opportunities with regard to the selection of patients for treatment as well as the monitoring of ongoing therapies [34]. There is therefore much reason to believe that radiopharmaceutical chemistry will increase in importance as a discipline in nuclear medicine specifically and biomedical research in general.

Controversial Issues

Will Other Imaging and Therapeutic Approaches Replace Nuclear Approaches?

The need to administer radioisotopes—and the inherent practical difficulties and need for radiation exposure—has been seen as a disadvantage of nuclear medicine since its creation. This has led many to predict the demise of the specialty over the years, especially in light of the advent of new imaging modalities such as CT and MRI. In addition, the recent development of nonnuclear probes with molecular capability—*e.g.* agents for ultrasound, optical imaging, and hyperpolarized MR—has created concerns about incremental threats to the field. Some of these concerns have been realized. For example, the use of CT to detect liver metastases replaced the nuclear liver spleen scan in the 1980s.

However, nuclear imaging procedures continue to retain significant advantages over other approaches, especially when the application is focused upon the molecular basis of the disease. For example, the aberrant glycolysis of malignant tissues compared to normal tissues reintroduced nuclear imaging as a key component of the detection of liver metastasis using [^{18}F]FDG PET/CT and now PET/MR [41]. The ongoing discovery of disease-specific biomarkers will provide an increasing basis for the use of molecular tracers for the diagnosis and treatment of disease [40]. As a result, the ongoing application of nuclear medicine for diagnosis and treatment will depend critically on radiochemistry.

The Future

What Does the Future of Nuclear Medicine Look Like?

The future of nuclear medicine will continue to exploit the unique properties of radiopharmaceuticals to exploit the tracer principle for diagnosis and treatment. Several issues within the field of radiochemistry will help drive the future of nuclear medicine [14, 30, 31]:

- *The development of precision diagnostics for precision medicine*
- *The creation of improved targeted therapeutics for cancer and other diseases*
- *The advent of paired diagnostics and therapeutics*, with nuclear imaging paired with both nuclear and non-nuclear therapeutics

The Bottom Line

- Nuclear medicine is the application of radioactive elements to medicine.
- Radiopharmaceuticals operate on the "tracer principle," namely, that radioactive tracers are administered at such low molar doses that they do not perturb the native biology of the system into which they are introduced.
- Nuclear imaging radiopharmaceuticals provide high sensitivity and molecular specificity.
- Radionuclide therapy provides a highly targeted treatment modality based upon the physical impact of radiation. It is similar to external beam radiotherapy but much more targeted.
- Radiopharmaceuticals provide a key link between basic biology and clinical practice. The future of nuclear medicine depends upon the ability of radiopharmaceutical chemists to leverage advances in molecular biology into new approaches to clinical imaging and therapy.

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A Short History of Nuclear Medicine

Carolyn J. Anderson, Xiaoxi Ling, David J. Schlyer, and Cathy S. Cutler

The Discovery of Radiation and Radioactivity

Diagnostic *in vivo* imaging was born with the discovery of x-rays in 1895 by Wilhelm Conrad Roentgen, a German physics professor working in Wurzburg (Fig. 1a). On November 8, 1895, he was studying light emissions generated by electrical discharges in an evacuated glass Hittorf-Crookes tube that he was using to investigate cathode rays (*i.e.* electrons) (Fig. 1b). The tubes were covered in black paper and the room was dark, but he noticed that a screen across the room was glowing. Remarkably, when he blocked the beam with his hand, he could see the bones in his hand projected on the screen. Roentgen spent several weeks experimenting with the new rays, and on December 28, 1895, he gave a report entitled "*On the Use of the New Rays*" to a local physics society, during which he presented a 30-min exposure of his wife's hand on a photographic plate (Fig. 1c). By 1896, x-rays were becoming an established tool in medicine, and in 1901, Roentgen won the Nobel Prize in Physics.

Radioactivity was discovered by Antoine Henri Becquerel in Paris in 1896. Upon learning of Roentgen's discovery of x-rays, Becquerel chose to study the "mysterious rays" created when he exposed $K_2UO_2(SO_4)_2 \bullet H_2O$ to sunlight and placed it on photographic plates wrapped in black paper. When developed, the plates showed an image of the uranium crystals, and he initially believed that the sun's energy was absorbed by the uranium, which then emitted x-rays (see Fig. 2). The uranium-covered plates were returned to a drawer, and although Becquerel expected only faint images, they remained strong and clear. He later demonstrated that the radiation emitted by uranium shared certain characteristics with x-rays but—unlike x-rays—could be deflected by a magnetic field and, therefore, must consist of charged particles.

Although Becquerel was awarded the 1903 Nobel Prize in Physics for his discovery of radioactivity, the term itself was coined by Marie Sklodowska Curie. In 1897, she was looking for a topic for her doctoral thesis research. She was fascinated by the work of Becquerel and decided to systematically investigate the uranium "rays" using an electrometer based on the piezoelectric effect that was constructed by her husband Pierre and his brother Jacques. Madame Curie discovered that thorium emitted the same rays as uranium and that the strength of the rays did not depend on the chemical composition, only on the amount of uranium or thorium in the sample. She concluded that the radiation did not depend on the arrangement of the atoms in the molecule but was linked to the interior of the atoms themselves. This was a revolutionary finding that completely changed the field of physics. Madame Curie then obtained natural ore samples containing uranium and thorium from geological museums and found that pitchblende had 4–5 times the amount of radioactivity that was expected based on the amount of uranium. From this finding, she determined that the ore samples contained a new element that was more "active" than uranium. Marie and her husband Pierre (Fig. 3) then extracted the uranium from the ore and found that the residual material was indeed more "active" than the pure uranium. In addition to uranium, the ore contained the radioactive elements polonium (named for Marie's native country, Poland) and radium (from the fact that it radiated very strongly). The unit of radioactivity "Curie (Ci)" is equivalent to 1 g of radium and was named in Madame Curie's honor.

The Curies were awarded the Nobel Prize in Physics in 1903 for their work on radioactivity. Pierre Curie died sud-

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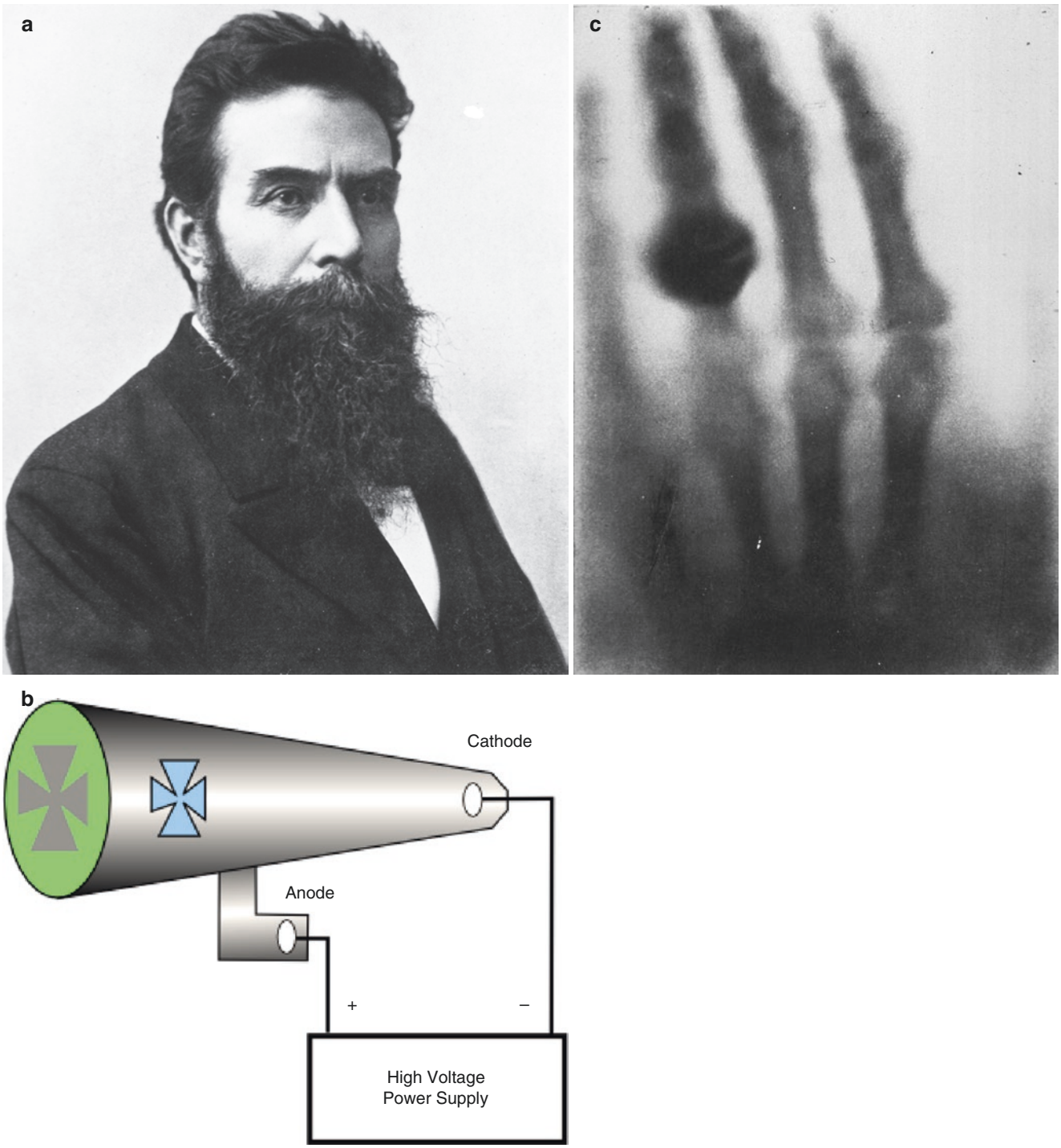

Fig. 1 (**a**) Wilhelm Conrad Roentgen (1845–1923) who discovered x-rays when working with a (**b**) Hittorf-Crookes tube to study cathode rays. (**c**) X-ray taken by Roentgen of his wife's hand and presented to the local physics society on December 28, 1895. (Images courtesy of the National Library of Medicine; Wikimedia, Public domain: by Chetvorno, rebuilt by Drondent, https://commons.wikimedia.org/wiki/File:Crookes_tube2_diagram.svg and the National Library of Medicine, respectively)

denly on April 19, 1906, when he slipped in the rain and fell under a heavy horse-drawn cart. Marie continued their work, even taking over Pierre's teaching position and thus becoming the Sorbonne's first female professor. Madame Curie was later awarded a *second* Nobel Prize in Chemistry in 1911 "in recognition of her services to the advancement of chemistry by the discovery of the elements radium and polonium, by the isolation of radium and the study of the nature and compounds of this remarkable element." She was the first person—male or female—to be awarded two Nobel Prizes.

The Discovery of the Neutron

Ernest Rutherford developed a crude model of the atom in the early twentieth century that included positively charged protons and negatively charged electrons. However, it was known at this time that the atomic mass of an element was approximately twice the atomic number (or number of protons) *and* that the mass was concentrated in the nucleus. The missing piece of the puzzle—the uncharged neutron—was not part of Rutherford's model, and many scientists set out to find the elusive particle. Rutherford went on to be the first to recognize that an element could be transformed into a different element by artificial means [1]. After bombarding nitrogen gas with alpha particles, he noticed that sometimes the alpha particle was stopped and a proton with high kinetic energy was released. This was the first production of oxygen-17 via the $^{14}N(\alpha,p)^{17}O$ nuclear reaction. In 1930, Walther Bothe and Herbert Becker bombarded Be, B, F, and Li with alpha particles emitted from polonium (Po) and showed that these reactions resulted in the emission of highly penetrating radiation. Irène and Frédéric Joliot-Curie—Marie and Pierre's daughter and son-in-law—investigated these reactions and postulated that the radiation produced was high-energy gamma rays. However, when they allowed these "gamma rays" to hit a thin piece of paraffin (rich in hydrogen atoms), very fast hydrogen nuclei were ejected from the paraffin [2]. They stuck by their original conclusion, even though gamma rays have no mass and therefore could not have ejected the hydrogen nuclei from the paraffin. James Chadwick at the Cavendish Laboratory in Cambridge also studied the reactions performed by Bothe and Becker. Chadwick repeated the experiment of bombarding ^{9}Be with alpha particles, and he found that the results were compatible with the energy and momentum conservation of the production of ^{12}C and a neutron [2]. This discovery of the neutron—with no net electric charge and a mass slightly larger than the

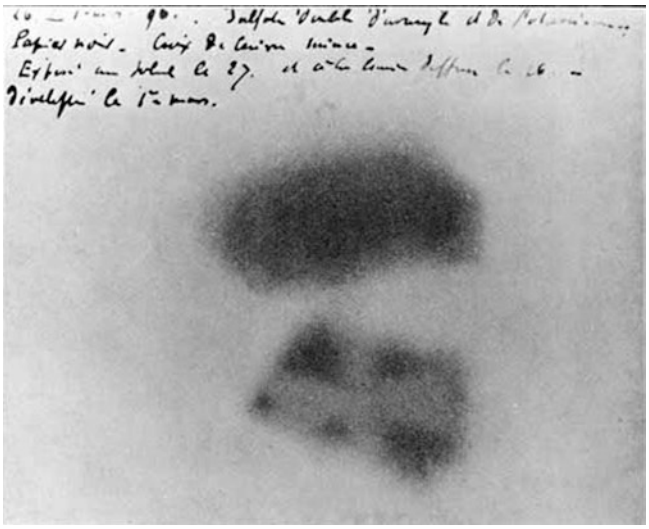

Fig. 2 A photographic plate made by Henri Becquerel illustrating the effects of exposure to radioactivity. A metal maltese cross placed between the plate and the radioactive uranium salt left a clearly visible shadow on the plate. (Wikimedia: This work is in the public domain in its country of origin and other countries and areas, where the copyright term is the author's life plus 100 years or less [70 years in the USA] https://commons.wikimedia.org/wiki/File:Becquerel_plate.jpg)

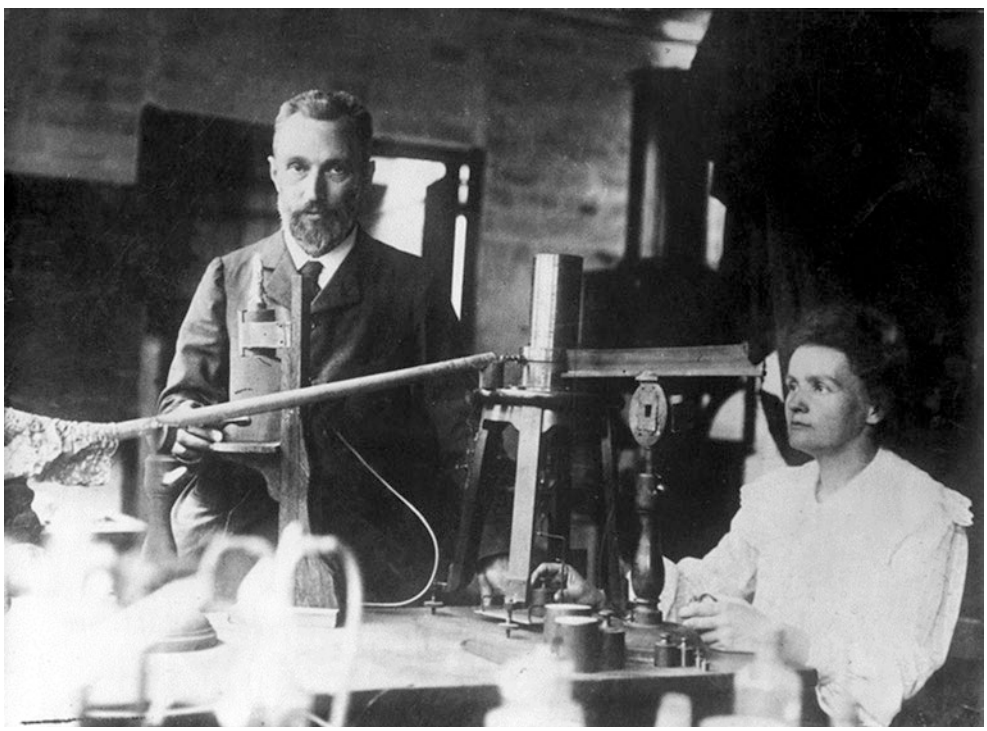

Fig. 3 Pierre and Marie Curie at work in their laboratory at the Sorbonne (Wikimedia: The copyright of this image has expired because it was published more than 70 years ago without a public claim of authorship (anonymous or pseudonymous), and no subsequent claim of authorship was made in the 70 years following its first publication. https://commons.wikimedia.org/wiki/File:Pierre_and_Marie_Curie.jpg)

proton—was central to understanding atomic structure and to the advancement of the field of radionuclide production. Indeed, neutrons are produced by nuclear fission (discovered by Otto Hahn, Fritz Strassmann, and Lise Meitner in 1938) and can be incorporated into the nuclei of elements to produce new, typically beta-emitting radionuclides.

The Discovery of Artificial Radioactivity and the Tracer Principle

In 1934, following in the footsteps of Pierre and Marie Curie, Irène and Frédéric Joliot-Curie created radioactive elements by irradiating stable nuclides with alpha particles. More specifically the Joliot-Curies bombarded a series of elements with alpha particles, including H, He, Li, B, Be, C, N, O, F, Na, Al, Ca, Mg, Ni, and Ag. Of these, only three produced artificial radioactivity. The bombardment of aluminum ($Z = 13$) by alpha particles produced from polonium decay produced radioactive phosphorus ($Z = 15$) plus a neutron.

$$^{27}_{13}Al + {}^{4}_{2}He \rightarrow {}^{30}_{15}P + {}^{1}_{0}n$$

They then observed that this phosphorus decayed to silicon, releasing a positron.

$${}^{30}_{15}P \rightarrow {}^{30}_{14}Si + {}^{0}_{1}p$$

Following a similar reaction with boron, they were able to condense the positron-emitting radionuclide nitrogen-13—which gave off radiation with a ~10-min half-life—into a separate vessel to confirm that they had in fact created a different element artificially (Fig. 4).

Due to some earlier misinterpretations of their experiments—which led to others discovering both the neutron and the positron—there was initially some doubt surrounding the Joliot-Curies' observations. Soon, however, they were able to reproduce and confirm their discovery of the production of artificial radioactivity [3]. As a result, Irène and Frédéric Joliot-Curie won the Nobel Prize in Chemistry in 1935 "in recognition of their synthesis of new radioactive elements" [4], work that laid the foundation for modern day nuclear medicine and radiopharmaceutical chemistry.

At about the same time, Ernest O. Lawrence developed the first cyclotron at the University of California at Berkeley. Interestingly, Lawrence was also producing artificial radioactivity with the cyclotron, but he failed to notice these residual emissions because the same switch that operated the cyclotron also operated the Geiger counter in the lab. This work of Lawrence's team—along with the work of the Joliot-Curies in the early 1930s—led to the discovery of iodine-131 (Glenn Seaborg and John Livingood) and technetium-99m (Emilio Segre and Glenn Seaborg) in 1938 at Berkeley and set the stage for the use of cyclotrons for the production of radionuclides for positron emission tomography (PET) and single-photon emission computed tomography (SPECT). In recognition of his work, Ernest Lawrence received the Nobel Prize in Physics in 1939 "for the invention and development of the cyclotron and for results obtained with it, especially with regard to artificial radioactive elements" [5].

George de Hevesy (Fig. 5)—who has been called the "father of nuclear medicine"—first described the radiotracer principle that underpins the use of radionuclides to investigate the behavior of stable atoms and molecules [6]. Simply

Fig. 4 Irène and Frédéric Joliot-Curie in their laboratory in 1935 (Agence de presse Meurisse. Bibliotheque national de France. Wikimedia: This work is in the public domain in its country of origin and other countries and areas where the copyright term is the author's life plus 70 years or less. https://commons.wikimedia.org/wiki/File:Ir%C3%A8ne_et_Fr%C3%A9d%C3%A9ric_Joliot-Curie_1935.jpg)

put, the tracer principle states that radiopharmaceuticals can participate in biological processes but do not alter or perturb them. In this way, radiopharmaceuticals facilitate the imaging of normal and disease processes without interfering with them. This phenomenon, of course, is predicated on the fact that minute molar amounts of radiopharmaceuticals can be detected with relative ease. The first radiotracer experiment in animals used bismuth-210 to follow the circulation of Bi-containing antisyphilitic drugs in rabbits. De Hevesy received the 1943 Nobel Prize for this discovery [7]. De Hevesy's other seminal contributions to radiochemistry include his study of reactions with neutrons. More specifically, he exposed dysprosium to a neutron stream, upon which the element became exceedingly active; this was the first demonstration of neutron activation analysis. Based on these initial experiments, he determined the relative neutron flux of various irradiation positions and activated other samples, including rhodium foils and europium samples. Neutron activation analysis is the most powerful nondestructive analytic technique for elemental analysis of solid samples.

Fig. 5 George de Hevesy received the Nobel Prize (Chemistry) for elucidating the tracer principle. (Wikimedia: This image is in the public domain because its copyright has expired and its author is anonymous. This applies those countries with a copyright term of 70 years after the work was made available to the public and the author never disclosed their identity. https://commons.wikimedia.org/wiki/File:George_de_Hevesy.jpg)

The Discovery and Use of the Radionuclides of Iodine

Iodine was discovered in seaweed in 1811 and first used to treat goiter in 1819 [8]. The Massachusetts General Hospital (MGH) Thyroid Clinic—established by Dr. James H. Means in 1920—began using stable iodine to treat hyperthyroid patients. In 1936, MGH's Dr. Saul Hertz (Director, 1931–1943) solely conceived of the medical uses of radioiodine (RAI) and asked MIT President Karl Compton, "Could iodine be made radioactive artificially?" [9]. Saul Hertz's pivotal question lead to a collaboration between MGH's Saul Hertz and MIT physicist, Arthur Roberts. Roberts produced I-128 ($t_{1/2}$ = 25 min) using a neutron source to study the effect of I-128 on the altered thyroid gland of rabbits. The Hertz/Roberts animal study demonstrated the tracer quality of RAI to investigate thyroid physiology [10]. Berkeley's Joe Hamilton and Mayo Soley confirmed the tracer quality of RAI. In 1936, using the Berkeley cyclotron, Glenn Seaborg and John Livingood bombarded tellurium-128 and created iodine-130 ($t_{1/2}$ = 12 h) and iodine-131 ($t_{1/2}$ = 8 days) [11] (Fig. 6).

Hertz and Roberts were the first to develop the experimental data and apply it in the clinical setting. Iodine-131 allowed the in vivo tracking of the radionuclide over long time periods [12]. The first therapeutic use of MIT cyclotron-produced RAI was administered by Saul Hertz in early 1941.

Dr. Hertz conceived of using RAI to treat thyroid carcinoma at the time of the rabbit studies in 1937, and he administered and reported clinical trials of RAI to treat thyroid carcinoma in 1942. In 1943, Dr. Hertz advised Montefiore Hospital's Dr. Samuel Seidlin, who treated a patient with metastasized thyroid cancer. Dr. Seidlin et.al. confirmed that ablation of the normal thyroid—which eliminated the thyroid's competition for the uptake of iodine—was necessary for the treatment of metastases [13, 14]. Thyroid cancer changed from an almost certain death sentence to a disease with an overall survival rate of about 85% [15].

Early Studies with Radionuclides of Carbon

In the late 1930s, Ernest Lawrence's laboratory at Berkeley was producing carbon-11 (C-11; $t_{1/2}$ = 20 min) on a more or less routine basis by bombarding boron oxide with deuterons. Martin Kamen, Sam Ruben, and I.L. Chaikoff used carbon-11 to study the metabolism of carbohydrates. In these studies, ^{11}C-labeled glucose was prepared by feeding [^{11}C]CO_2 to plants, which produce radioactive glucose via photosynthesis that then could be used for the investigation of metabolism in lab rats. The photosynthesis-based method of producing ^{11}C-labeled glucose was later applied in the 1970s by both the Welch lab [16] and Raichle and colleagues [17].