**William C. Eckelman:**

**An Anchor of Stability with a Quiet Voice that Nurtured a New Field**

John A. Katzenellenbogen,1 Michael R. Kilbourn,2 Heinz H. Coenen,3 and Wynn Volkert4

1Department of Chemistry, University of Illinois at Urbana-Champaign, Urbana, IL 61801 USA

2Department of Radiology, University of Michigan School of Medicine, Ann Arbor, MI 48109 USA

3Institute of Neuroscience and Medicine, INM-5: Nuclear Chemistry, Forschungszentrum Juelich, 52425 Juelich, Germany

4Department of Radiology, University of Missouri, Columbia, MO 65211 USA

*Abbreviated Title* (32/45 characters and spaces): A Tribute to William C. Eckelman

*Corresponding Author*:

Michael R. Kilbourn

Department of Radiology

Michigan School of Medicine

Ann Arbor, MI 48109, USA

[mkilbour@med.umich.edu](mailto:mkilbour@med.umich.edu)

phone: 734-763-9246

*Abstract* (80 to 300 words with subdivisions of Introduction, Methods, Results, and Conclusions, Advances in Knowledge and Implications for patient) **Editor: WE ASSUME THIS IS NOT NEEDED FOR AN INTRODUCTION**

We are delighted, in this Introduction and through the many contributions comprising this special issue of *Nuclear Medicine and Biology*, to pay tribute to William Charles (Bill) Eckelman. We hope to highlight here the many different ways Bill molded the field of radiopharmaceutical chemistry with a remarkable combination of intellect, enthusiasm and persistence. With deep insight and a quiet hand, he made major contributions that guided radiopharmaceutical sciences through its adolescence, spawning a vibrant new field. His broad areas of interest and research can perhaps be aptly summarized by the keywords: radiopharmaceutical chemistry, receptor-targeted radiotracers, translationally relevant in vivo imaging, monitoring disease and therapy response, PET imaging, and precision medicine. As colleague and friend, Bill meant much to each of the four of us, often in many different ways.

**Scientist, Educator and Leader**

Bill Eckelman’s work in radiopharmaceutical chemistry and nuclear medicine started early in his career. After he did graduate studies with Peter Gaspar at Washington University on the chemistry of recoiling silicon atoms [1] (the field of hot-atom chemistry was pursued by many of his well-known colleagues, who are recognized today the ‘founding fathers’ of radiopharmaceutical chemistry), Bill did research as a postdoc at Brookhaven National Laboratories on the fundamentals of technetium-99m chemistry and generator systems. That introduction to radiopharmaceutical chemistry laid the foundation for some of his important contributions to the field of nuclear medicine, including the development of “instant kits” for 99mTc-radiopharmaceuticals [2], and later activities while serving as the Vice President of Diagnostics R&D at the Squibb Institute for Medical Research, leading the group that developed the Sr-82/Rb- 82 generator, [99mTc]teboroxime (CardioTec®) and gadoteridol (Prohance®).

After pushing forward the field of radiometal and radioiodine labeling for diagnostic imaging, Bill recognized early on the potential of PET and SPECT radiotracers to target receptors, thereby providing images that might reveal important information about disease severity and predict favorable options for therapy. Bill provided leadership early in this new area of research by convening a workshop in Washington DC in May of 1980 on “Receptor-Targeted Radiotracers” that led to the publication of a definitive two-volume series of the same name and laid a firm groundwork for how the development of such tracers might best be approached and in what ways they might prove useful [3]. The essence thereof and the state of the art is comprehensively highlighted in a very instructive article in this special issue [4].

In his research laboratories at George Washington University and the National Institutes of Health, Bill pioneered the development, evaluation and validation of new radiotracers for estrogen, opioid, dopamine, muscarinic and serotonin receptors. Together with Richard Reba and colleagues, he used SPECT and radioiodinated 3-quiniclidinyl-4-iodobenzilate, a high-affinity ligand for the M1/M2 muscarinic receptor, to achieve the first *in vivo* human imaging of a brain receptor in 1983 [5]. The many research advances he made throughout his career in this and several related areas of radioisotope production, radiolabeling technology, and targeted receptor imaging, are well documented in the published literature. Notable beyond these primary accounts of his work are many contributions over several decades in the form of book chapters, editorials and essays by Bill and his colleagues that are found in many different international journals on radiopharmaceutical chemistry and nuclear medicine. These contributions served as guidelines for the emerging field of radiopharmaceutical sciences and pointed out the increasing opportunity for clinical impact from translational studies [6-20].

But Bill’s influence extended far beyond simply publishing his work and his thoughts about science. As the field of radiopharmaceutical chemistry began to grow rapidly, Bill was always at the forefront, and with deep insights couched in calm leadership, he nudged the field in the appropriate direction at critical points in its evolution. He played a huge supporting role by undertaking the development of the bylaws for the professional group that is now the Society of Radiopharmaceutical Sciences (SRS), thus helping with its birth. He also provided strong support to at least the first six presidents of SRS, also serving the society through his own presidency. In 1985 he took over the editorship of *Nuclear Medicine and Biology*, where he had been on the editorial board for several years already, sensibly changing its prior historic but archaic name, *International Journal of Radiation Applications and Instrumentation. Part B. Nuclear Medicine and Biology*. As Editor-in-Chief for 33 years, Bill guided NMB progressively upward as this journal celebrated the marriage of chemistry and biology in the emerging field of radiopharmaceutical sciences, and in 2002 he made it the official flagship journal of the Society for Radiopharmaceutical Sciences (SRS).

With his guiding presence at national and international meetings, Bill continued to counsel leaders as well as the rank and file, including radiochemists, nuclear pharmacists, biologists, and nuclear medicine practitioners. Important examples to mention here are his services in the Society of Nuclear Medicine through participation in leadership committees and annual meetings, as well as his support of the International Symposia on Technetium and other Radiometals in Chemistry and Medicine at Bressanone, Italy, as described by C. Giron and U. Mazzi in this issue [21].

Most impressive of Bill’s many contributions was his thoughtful and frequent documentation of the evolution and progressive refinement of models for receptor-targeted imaging. His approach combined static parameters from *in* *vitro* binding assays with kinetic parameters that influenced *in vivo* distribution and metabolism, and to improve the success of obtaining a medically meaningful image. He was an early proponent of the use of transgenic animals as an adjunct to the classical target-blocking control to validate tracer engagement with specific receptors. Bill supported and encouraged a generation of radiochemists all over the world to think broadly, helping them to go beyond the essentials of chemistry to understand and embrace the full complement of issues involved in imaging with radiotracers. He accomplished this through his articulation of several key considerations, including general receptor binding theory, *in vitro* characterization, tritium-labeled receptor tracers, short-lived isotope preparation, the wide range of receptor targets for imaging, modeling principles for receptor targets, pharmacokinetics by imaging, distribution by flow vs. target binding, 2D vs. 3D imaging, impact of genomic variations in disease on the utility of imaging, clinical relevance of receptors and changes in their concentration in disease, and finally the integration of imaging into delivering on the promise of precision medicine [6-20].

To achieve this, Bill always seemed to be thinking down the road. As the SRS meetings grew larger and larger, Bill chose to democratize them at the 8th meeting he hosted at Princeton in 1990. By downplaying the major lectures in favor of expanded poster presentations and short talks, he provided greater exposure to a multitude of young investigators, which stimulated and energized them in their developing careers while also providing new feedstock to support an expanding field. Versions of this symposium model have proved to be a persistent change. To further encourage the next generations of students, Bill was an unflagging proponent of education and travel bursaries to SRS and other important meetings, successfully facilitating the engagement of many students from around the world.

As the field of radiopharmaceutical chemistry matured, much of it due to his efforts, Bill urged researchers and practitioners in the field to go beyond technical advances and to take to heart the importance of delivering on the promise of *in vivo* imaging for improving health care outcomes in a biomedical world that increasingly emphasized and valued clinical translation [11, 15, 18]. He worked both in the public and private sectors to both guide the development and facilitate the approval of new agents for clinical use, and he encouraged funding agencies to support cross disciplinary training programs to create a workforce with the knowledge base required to accomplish this.

Through his unflagging devotion to science (basic medical research in particular) and education, Bill has influenced generations of young people who now make up the vibrant field of radiopharmaceutical chemistry. While his more than 50 years of research work may be represented by > 400 publications, his impact on the field extends far beyond that. All his many achievements and service have received broad recognition and cumulated in numerous awards from scientific societies. To name just the most prestigious ones: Herman L. Blumgart Pioneer Lecture Award: 1985; The Paul C. Aebersold Award for Outstanding Achievements in Basic Science Applied to Nuclear Medicine: 1988 (J Nucl Med 29:586-7); 1995 Corporate Committee Achievement Award of the American College of Nuclear Physicians: 1995; The Swedish Society of Medicine Medal in Recognition of the “Bertil Noslin Lecture”, presented December 1995; The Georg deHevesy Nuclear Pioneer Award, Society of Nuclear Medicine, 1997 (J Nucl Med 38, 23N, 1997); Institute for Clinical PET Distinguished Scientist Award, 2000; Great Golden Seal of Padua University in Recognition of Contributions to Radiopharmaceuticals Development, 2002.

**Colleague, Mentor and Friend**

Probably all who have met Bill, recognize him as a polite and friendly colleague, always interested, with an open ear and ready to help or advise. He is famous for his almost instant responses (although sometimes short and cryptic) to whatever mailings, reflecting his respectful manners and well-organized, effective workstyle. Although completely focused on the advancement of science, he is always open for a good joke and a laugh, and showing-off is alien for him, never wasting time on sensitivities. “The field is too small to have enemies!” is his typical response to any gratuitous attempt at provocation. We have tried to exemplify certain of his personality characteristics in the following individual reflections by some of the authors of this Introduction.

*Quiet demeanor in a sea of high energy activists – how to have impact without making a fuss* — In the preceding section, we have noted the many roles that Bill has played on the emerging and now vibrant field of radiopharmaceuticals for *in vivo* imaging during its early years. Beyond his contributions, however, it is worth reflecting on how he managed to do this. From John Katzenellenbogen’s perspective, given a long-lasting and fruitful relationship and collaboration with Bill (see [22] and refs. therein), this is his principal recollection: In the early 1970’s, I was quickly swept into this newly-born field of radiopharmaceutical imaging agent development, and I soon experienced how it was driven by a highly committed cadre of strong-willed, vociferous, and penetrant personalities, Alfred Wolf, Gerhard Stöcklin, Henry Wagner, Mike Welch, Mike Phelps, among others. Great intellectual energy and political debates characterized the almost tempestuous meetings of this growing group at its early gatherings. Just beyond this “Type-A personality” group, however, I began to recognize the presence of a quiet figure, who seemed to know all of the principals, and I also made note that whenever he was present, at conference session debates, lectures, cocktail receptions and dinners, he seemed to contribute in a thoughtful, honest and minimalist manner that had a remarkable calming effect on those around him, easing them towards making sensible decisions: This was Bill Eckelman! When I related this observation to my former student, Marty Pomper at Johns Hopkins, he replied, “Well, Eckelman is well-known as the “Yoda of Radiopharmaceutical Sciences”! An apt descriptor indeed.

*Trust in young people – development through challenges* — One of us remembers when he was a post-doc with Bill at the George Washington University (D.C.): Bill was initially reluctant to let me attend his teaching lectures (instead of staying at the bench!). When he agreed that I could attend, however, he demanded that I had to pass the mid-term test before Christmas like all of the regular students. When I returned after the New Year, he “condemned” me on a one-day’s notice to be the lecturer for the rest of the winter term! At first I choked (mainly about being unprepared to teach in English!), but then soon recognized that this was an unusual opportunity for me to gain teaching experience. Wisely, Bill managed to save his more precious time to think and create, than my time spent tinkering around at the bench. This is only one example of Bill’s trust in young scientists and his interest in advancing their careers. Besides many post-docs from around the world in his group, we all know that Bill encouraged and motivated many young scientists over the years. As an example he appointed youthful greenhorns like Mike Kilbourn and Heinz Coenen as members of the editorial board of *Nuclear Medicine and Biology* right from the start, at their rather unripe ages of about 30 years.

*A quiet influence* —Mike Kilbourn reports: Throughout the years, I was fortunate to have many remarkable mentors and supporters – foremost among these John Katzenellenbogen, Alfred Wolf, Michael Welch, and David Kuhl, each of whom had a unique personality that left long-lasting impressions. But on reflection, there was another individual who quietly shaped my more broad-view thinking about radiopharmaceutical science: Bill Eckelman. Through collaborations on editorials, vigorous discussions over reviewing manuscripts for NMB, quiet moments together at scientific meetings or during grant reviews, or by just observing Bill’s steady but purposeful demeanor, I gained a much deeper perspective on both the science and the people behind our mutual love of radiopharmaceutical chemistry. Undoubtedly, I was not the only young person who benefitted from the wisdom and guidance of Bill Eckelman through the formative years of their career.

*Sports – interest, love, and carefully hidden talent, among others* —Heinz Coenen recalls: With a European family background (half Italian, half German), Bill has always been an enthusiastic fan of soccer, having played the sport in younger years and even managing youth teams. He always closely followed TV accounts of European soccer as well of the other US sports leagues, but in particular at those critical moments when games pitted the national team of Italy versus Germany or England. The latter caused regular, heated debates with his late best friend Mike Welch. Even less well known is that Bill’s bi-national heritage also revealed in his strong preference for German cheese cake and his ability to prepare lasagna of an excellent quality rarely found even in good Italian restaurants.

John Katzenellenbogen reflects: I cannot remember at which meeting this took place, but on an evening some years ago when Bill and I had a few hours to spare, we learned that there were squash courts nearby. Realizing that we both enjoyed this fast-paced, quasi-geometric game, we decided to play together. I harbored considerable hidden bravado from having learned squash in college and having played quite a bit there and later as a young faculty member, honing my stills and stamina by playing with even younger, athletically proud faculty colleagues. So, I figured it would be an easy win for me. Not to be so! Again, Bill took his characteristic quiet and unassuming approach, masterfully controlling the center of the court, and without any boast, he managed to beat me quite handedly! It was a good workout for both of us, and after the game, to cheer his crestfallen rival, Bill remarked that it would be wise for both us to be careful in undertaking such rash attempts at high athleticism, “Because working ourselves this vigorously—at our middle age—could lead to arthritis in our older years”. Now, with one hip replaced and a knee that may need future work, I can better appreciate the prescience of this sage advice from the match victor to the vanquished.

With this last anecdote it is fitting to mention that we all are hoping that Bill is faring well in this and all other domains of health and life, and we would like to express our gratitude for his contributions as a scientist and for his cheery personality and friendliness during all encounters. We are thus delighted to offer him this tribute in this celebratory volume of *Nuclear Medicine and Biology*, which has been prepared in his honor as thanks for his many contributions in support of the journal and the field in so many ways. Certainly, all of the authors who have contributed to the realization of this special issue in honor of Bill Eckelman, will join in these sentiments and best wishes. This is clearly confirmed by their spontaneous, positive agreement to prepare their articles. Their dedication in preparing their reviews or original articles is very thankfully acknowledged, as they constitute the fundamental material needed to consummate this special issue.

**References**

1. Gaspar PP, Bock SA, Eckelman WC, Reactions of recoiling silicon atoms with phosphine, silane and ethylene. J Am Chem Soc 1968;90:6914-6922.

2. a) Eckelman WC, Richards P, Instant 99m-Tc-DTPA. J NuclMed. 1970:11;761. b) Eckelman WC, Richards P, Instant 99m-Tc compounds. Nuclearmedizin 1971;10:245.

3. Eckelman WC. Receptor Binding Radiotracers (2 vols.): CRC Press, Boca Raton, FL,1982.

4. Krohn KA, Vera DR. Concepts for design and analysis of receptor radiopharmaceuticals: The Receptor-Binding Radiotracers series of meetings provided the foundation. Nucl Med Biol 2021 (this volume).

5. Eckelman WC, Reba RC, Rzeszotarski WJ, Gibson RE, Hill T, Holman BL, et al., External imaging of muscarinic acetylcholinergic receptors. Science 1984;223:291-3.

6. Eckelman W. The use of in vitro models to predict the distribution of receptor binding radiotracers in vivo*.* Nucl Med Biol 1989;16:233-45.

7. Eckelman WC. The application of receptor theory to receptor-binding and enzyme-binding oncologic radiopharmaceuticals*.* Nucl Med Biol 1994;21:759-69.

8. Eckelman WC. Sensitivity of new radiopharmaceuticals*.* Nucl Med Biol 1998;25:169-73.

9. Eckelman WC, Frank JA, and Brechbiel M. Theory and practice of imaging saturable binding sites*.* Investigative radiology 2002;37:101-6.

10. Eckelman WC and Vera DR. From bench to bedside*.* Nucl Med Biol 2003;30:793–794.

11. Kelloff GJ, Krohn KA, Larson SM, Weissleder R, Mankoff DA, Hoffman JM, et al. The progress and promise of molecular imaging probes in oncologic drug development*.* Clinical Cancer Research 2005;11:7967-85.

12. Eckelman WC, Kilbourn MR, and Mathis CA. Radiopharmaceutical space. Nucl Med Biol 2006;33:829.

13. Eckelman WC and Mathis CA. Targeting proteins in vivo: in vitro guidelines*.* Nucl Med Biol 2006;33:161-4.

14. Eckelman WC and Mathis CA. Molecular targets. Nucl Med Biol 2006;33:1.

15. Eckelman WC, Reba RC, and Kelloff GJ. Targeted imaging: an important biomarker for understanding disease progression in the era of personalized medicine*.* Drug discovery today 2008;13:748-59.

16. Eckelman WC, Kilbourn MR, and Mathis CA. Specific to nonspecific binding in radiopharmaceutical studies: it's not so simple as it seems!. Nucl Med Biol 2009;36:235–237.

17. Cannon DM, Klaver JK, Gandhi SK, Solorio G, Peck SA, Erickson K, et al. Genetic variation in cholinergic muscarinic-2 receptor gene modulates M2 receptor binding in vivo and accounts for reduced binding in bipolar disorder*.* Molecular psychiatry 2011;16:407-18.

18. Eckelman WC, Lau C-Y, and Neumann RD. Perspective, the one most responsive to change*.* Nucl Med Biol 2014;41:297-8.

19. Eckelman W. Choosing a target for targeted radionuclide therapy using biomarkers to personalize treatment*.* J Diagn Imaging Ther 2014;1:103-9.

20. Eckelman W, Windhorst A, and O'Hara C. The past, present, and the promise of the future of nuclear medicine and biology*.* Nucl Med Biol 2017;55:47-8.

21. Giron C, Mazzi U. Molecular imaging of microbiota-gut-brain axis: Searchning for the right targeted probe for the right target and disease. Nucl Med Biol 2021 (this volume).

22. The quest for improving the Management of breast cancer by functional imaging: The Discovery and development of 16α-[18F]fluoroestradiol (FES), a PET radiotracer for the estrogen receptor, an historic review. Nucl Med Biol (this volume).

 **Figure 1**. William C. Eckelman at the International Symposium on Radiopharmaceutical Sciences in Aachen, 2007. (Photo: courtesy by J.A. Katzenellenbogen)