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iSTORY

HISTORICAL PERSPECTIVE

Development of *m*IBG as a Cardiac Innervation Imaging Agent

David M. Raffel, PHD, Donald M. Wieland, PHD

Ann Arbor, Michigan

The development of radioiodinated *meta*-iodobenzylguanidine (*m*IBG) as a cardiac sympathetic innervation imaging agent is probably best thought of as a serendipitous outcome of another successfully realized scientific goal: the invention of a clinically useful marker of the adrenal medulla and related adrenergic tumors. It is impossible to fully appreciate the development of *m*IBG as a cardiac radiotracer without discussing events that led to its conception as a noninvasive imaging tool for clinical endocrinology (1).

Without question, the driving force behind the development of novel radiopharmaceuticals for imaging adrenal tissue at the University of Michigan was William H. Beierwaltes, MD, Chief of the Division of Nuclear Medicine, Department of Internal Medicine, from 1959 to 1986. Bill Beierwaltes was a strong and charismatic leader whose infectious enthusiasm and keen ability to establish productive collaborations were key factors in the foundation supporting the invention of *m*IBG at the University of Michigan.

In 1963, Dr. Beierwaltes' aspiration to develop scintigraphic imaging methods for adrenal diseases led him to recruit the medicinal chemist Raymond E. Counsell, PhD (currently Professor Emeritus of Pharmacology and Medicinal Chemistry). Their collaborative work on radiotracers for adrenal cortical diseases produced [^{131}I]iodo-19-cholesterol (2) and its ultimate successor, 6-beta-[^{131}I]iodomethyl-19-norcholesterol (NP-59) (3). These agents represented a significant advance in noninvasive assessments of adrenal cortical diseases; NP-59 still finds clinical use today. However, although these compounds provided scintigraphic assessments of the adrenal cortex, an important need remained for agents capable of imaging the adrenal medulla and the associated and elusive neoplasms such as pheochromocytoma and neuroblastoma.

Beierwaltes and Counsell's early efforts in this direction, reported in 1967, focused on biodistribution studies of ^{14}C-labeled epinephrine and its precursors phenylanaline, tyrosine, DOPA, dopamine, and norepinephrine (4). Among the compounds studied, ^{14}C-dopamine was found to have the highest adrenal medulla-to-blood ratios (740-to-1 at 6 h and 1,055-to-1 at 24 h). These important pilot studies demonstrated the feasibility of using radiolabeled catecholamine analogs as a means of concentrating an imaging agent in the storage vesicles of adrenergic tissues, a key conceptual step that set the stage for *m*IBG's later development.

Ray Counsell later collaborated with cardiovascular pharmacologist Benedict Lucchesi, MD, PhD, on structure-activity studies of several antiarrhythmic drugs, among them the adrenergic blocking agent bretylium. This work fostered a clinical collaboration with Edward (Ted) Carr, Jr., MD, who was interested in scintigraphic imaging of myocardial infarcts. At that time, few radiopharmaceuticals were known to concentrate in the heart, but ^{201}Tl was introduced for perfusion imaging in 1975 (5). Because bretylium was known to concentrate at high levels in cardiac tissue, Counsell and Carr tested a few radioiodinated analogs of

From the University of Michigan, Ann Arbor, Michigan. Dr. Wieland is retired.

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bretylium as potential "myocardial scanning agents" (6). Their initial imaging studies in dogs demonstrated significant cardiac uptake of an *ortho*-iodo-bretylium analog called RIBA, for "radioiodinated bretylium analog" (7). However, in later searches for adrenal imaging agents, they concluded that the corresponding *para*-iodo-bretylium analog, p-RIBA, was better suited than RIBA for portrayal of the adrenal medulla (8).

Over the next few years, Ray Counsell's career at Michigan continued to thrive and evolve, and in 1972, he became a professor in the Department of Pharmacology, with a joint appointment in the School of Pharmacy. His departure from nuclear medicine prompted Dr. Beierwaltes to seek a radiochemist who would work full time on developing imaging agents targeting the adrenal medulla. In late 1972, Beierwaltes contacted Richard G. Lawton, PhD, a professor in Michigan's chemistry department, to ask whether he knew talented chemists who would be good candidates for an open synthetic chemist position. Dr. Lawton suggested Donald M. Wieland, PhD, a young organic chemist who had recently been hired as a lecturer in the chemistry department.

A native of Titusville, Pennsylvania, Don Wieland began his college education with the goal of becoming a high school chemistry teacher. However, after completing his education degree at Edinboro State College in 1965, Don pursued a doctoral degree in organic chemistry at West Virginia University, which he received in 1970. He moved to Detroit, Michigan, for a postdoctoral fellowship in organic chemistry at Wayne State University. It was here Don met his future wife Kathleen Taffe; Don and Kathy were married on October 23, 1970. Shortly after this, motivated by his lifelong interest in birds, Don began work on a second doctoral degree in zoology at the University of Michigan. To support his studies in Ann Arbor, Don became a lecturer in organic chemistry at Michigan.

When Don heard about the synthetic chemist position in nuclear medicine from Rich Lawton, he was intrigued, seeing it as an opportunity to merge his interests in chemistry and biology. Although Don had no formal training in radiochemistry, he was impressed by Dr. Beierwaltes' description of the project and the bright future of nuclear medicine. He quickly accepted the proffered position, joining the Division of Nuclear Medicine in December 1972.

The initial projects Don worked on were efforts to extend the promising pilot studies obtained earlier with ^{14}C-dopamine to develop a radiopharmaceutical that would concentrate in adrenal medullary tissues. This included work on ^{35}S-labeled dopamine analogs (9) and ^{125}I-labeled adrenocortical enzyme inhibitors (10,11). Both of these met with limited success, and it was evident that additional approaches were required.

Looking for a new direction for adrenal imaging agents, Don reviewed Ray Counsell's published iodo-bretylium work. Don was surprised that the data from Counsell's group showed that their *para*-iodo-bretylium analog was more adrenospecific than the corresponding *ortho*-iodo analog, as *ortho*-substituted bretylium compounds were known to be more potent neuron blocking agents than corresponding *para* or *meta* series (12). Don felt that if the adrenal medulla could be considered a specialized sympathetic nerve ending, then the *ortho*-bretylium analogs should show higher localization in the adrenal medulla than the *para*-substitituted analogs. Don decided that a reinvestigation was warranted, so he set out to repeat Counsell's previous work and extend it to include a number of new tracers.

In early 1978, Don synthesized 5 ^{125}I-labeled bretylium analogs: Counsell's *para*- and *ortho*-iodo bretylium analogs (RIBA and p-RIBA), plus 3 new analogs that were arguably closer in structure to bretylium itself. Biodistribution studies clearly demonstrated that the *ortho*-iodo bretylium analogs had higher uptake levels in adrenal medullas than the corresponding *para*-iodo compounds. Furthermore, 2 of the 3 new radioiodinated bretylium analogs were superior to the RIBA compounds for imaging the adrenal medulla. The precise reasons for the discrepancies between these results and the previous studies of the RIBA compounds are unknown, but one explanation may be that the compounds in the Wieland study were prepared at more than 15-fold higher specific activity. A manuscript describing these findings was submitted in June 1978 (13), including the first scintigraphs of dog adrenal glands based on selective localization of a radiotracer in the adrenal medulla.

The demonstration that relative pharmacologic neuron blocking potency could be used to predict the degree of localization in the adrenal medulla was, in Don's estimation, an important point to establish, as it signified a rational approach to designing optimal radiotracers. Armed with the knowledge that the neuron blocking potency of compounds could be used