A Mighty Oak Forest from a Single, Well-Planted Acorn

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As medical researchers, we hope that our scholarship will have lasting and positive effects on patient care. Perhaps in the night we dream of dramatic impacts that could result from our work. It is hard to imagine, however, that Don Wieland and colleagues could have foreseen the enduring benefits and legacy of their work on a myriad of patients with various benign and malignant conditions (*1*). Indeed, in the four decades since their seminal publication, there have been over 4,500 articles on metaiodobenzylguanidine (MIBG), the drug first described in *JNM* in 1980. Furthermore, since its discovery there have been more papers on MIBG in every decade than in the one before it. This is a discovery that continues to grow and foment investigation. Of course, Don was passionate about forests and loved planting trees whenever he could, so it is quite possible he anticipated what the future could hold when the starting product is so carefully nurtured. We are gratified at the opportunity to comment on this paper, given the huge impact MIBG has had on our careers, as well as the honor and privilege it was to have worked with some of the coauthors at various points in our careers.

We have all been taught the scientific method, and this article is a beautiful tutorial. The authors observed a problem: the adrenal medulla is functionally distinct from the cortex and requires a dedicated imaging agent. Interestingly, they mention the already available adrenal cortical imaging agents that have been consigned to history whereas their discovery remains ever more relevant today. They stated their goal and a hypothesis and then tested it with careful objectivity. The method worked, and the end result was both robust and rigorous.

In addition to the scientific method in general, the authors also had a keen understanding of their specific field. Radiopharmaceutical development poses considerable challenges, and the successful radiochemist must also be an anatomist, physiologist, and physicist. Here, they have developed a drug with an uptake ratio of nearly 1,000:1 in the adrenal medulla compared with the liver, but because of the tiny size of the adrenal gland, adjacent to the much

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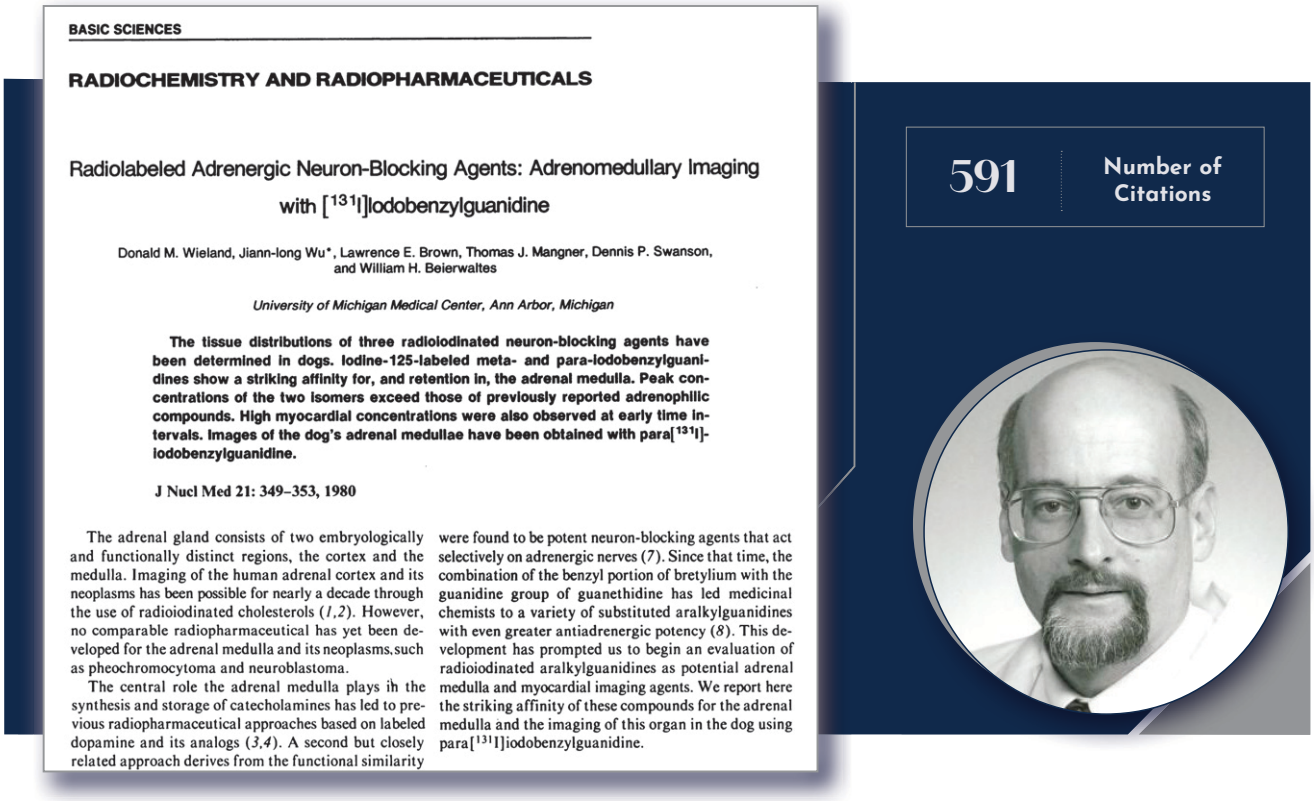

BASIC SCIENCES

RADIOCHEMISTRY AND RADIOPHARMACEUTICALS

Radiolabeled Adrenergic Neuron-Blocking Agents: Adrenomedullary Imaging with [^{131}I]Iodobenzylguanidine

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The tissue distributions of three radioiodinated neuron-blocking agents have been determined in dogs. Iodine-125-labeled meta- and para-iodobenzylguanidines show a striking affinity for, and retention in, the adrenal medulla. Peak concentrations of the two isomers exceed those of previously reported adrenophilic compounds. High myocardial concentrations were also observed at early time intervals. Images of the dog's adrenal medullae have been obtained with para[^{131}I]-iodobenzylguanidine.

J Nucl Med 21: 349–353, 1980

The adrenal gland consists of two embryologically and functionally distinct regions, the cortex and the medulla. Imaging of the human adrenal cortex and its neoplasms has been possible for nearly a decade through the use of radioiodinated cholesterols (*1,2*). However, no comparable radiopharmaceutical has yet been developed for the adrenal medulla and its neoplasms,such as pheochromocytoma and neuroblastoma.

The central role the adrenal medulla plays ih the synthesis and storage of catecholamines has led to previous radiopharmaceutical approaches based on labeled dopamine and its analogs (*3,4*). A second but closely related approach derives from the functional similarity were found to be potent neuron-blocking agents that act selectively on adrenergic nerves (*7*). Since that time, the combination of the benzyl portion of bretylium with the guanidine group of guanethidine has led medicinal chemists to a variety of substituted aralkylguanidines with even greater antiadrenergic potency (*8*). This development has prompted us to begin an evaluation of radioiodinated aralkylguanidines as potential adrenal medulla and myocardial imaging agents. We report here the striking affinity of these compounds for the adrenal medulla and the imaging of this organ in the dog using para[^{131}I]iodobenzylguanidine.

591 Number of Citations

larger liver, it remained difficult to detect any adrenal uptake above background liver level. However, their chemistry was good and their reasoning sound. The relatively crude "unclear medicine" images available in 1980 would be supplanted by the exquisitely sensitive devices we have today, resulting in ever greater utility for their discovery. Indeed, 40 years after their discovery, MIBG imaging plays a central role in response assessment in neuroblastoma (*2*).

Careful attention to detail for various applications is also of critical importance. Although iodobenzylguanidine labeled in either the *para* or the *meta* position has excellent affinity, MIBG has the superior stability in vivo, showing the importance of the structure–function relationship—an important focus of the lab's. Although potentially less important for diagnostic uses, this relationship is of critical importance for radiotherapeutic uses, for which a prolonged retention time at sites of disease is critical for a beneficial therapeutic ratio. Thus, MIBG is a successful therapeutic that plays a critical role in children with relapsed or refractory neuroblastoma, and it recently became the first treatment ever approved by the Food and Drug Administration for advanced pheochromocytoma and paraganglioma (*3,4*).

Interestingly, the authors envisioned the use of their agent for cardiac imaging, given the rich adrenergic innervation of the myocardium. They were seemingly discouraged by a low uptake ratio in the heart compared with that in the lungs and liver. However, their initial characterization was correct: MIBG in the myocardium is a measure of adrenergic innervation. It would be some time, however, before the observation was made that MIBG can be used to detect the relative lack of myocardial uptake. Specifically, a low heart-to-mediastinum ratio predicts a higher event rate in patients with heart failure (*5*). And so it is that the authors' discovery has impacted the lives of thousands of patients with congestive heart failure because the science was sound and robust even if the specific use had not yet been discovered.

Shortly after the discovery of MIBG, efforts were started to improve on it both diagnostically and therapeutically. For example, PET agents, both analogs and other substrates for the norepinephrine transporter, have been developed (*6*). Indeed, even today, fluorinated analogs for PET imaging are in clinical trials, and astatinated analogs are nearing clinical trials for α-particle therapy. In the coming years, these may finally supplant MIBG for diagnostic and therapeutic uses. However, for the time being, MIBG—exactly as described in 1980—remains the gold standard. Every day, patients around the world and across the age spectrum benefit from this wonderful drug so concisely and elegantly reported in *JNM* 40 years ago.

DISCLOSURE

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

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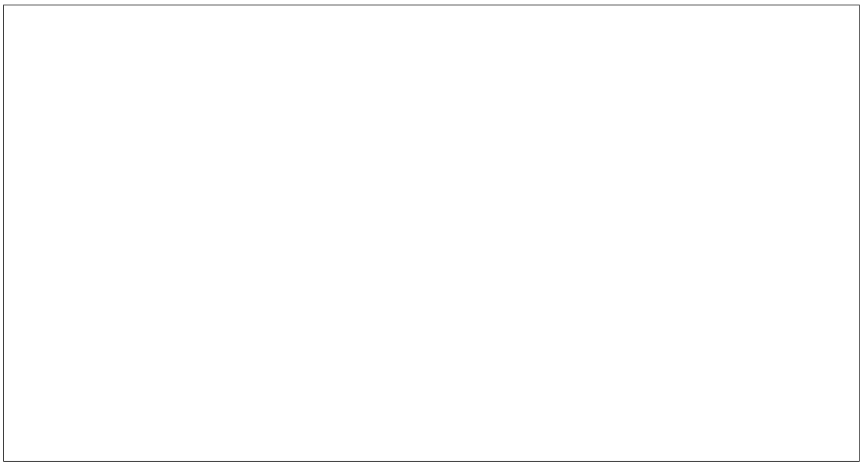

FIGURE 1. Computer displays of the same male dog (30.0 kg) at 3 days (left) and 5 days (right) after injection of Compound 1 labeled with I-131, showing posterior images of the dog s adrenal medullae.

As in the bretylium series, the pharmacological potency (neuron-blocking activity) of the isomeric iodo benzylguanidines parallels their respective affinities for the adrenal medulla, but in contrast to the bretylium series, it is the para- isomer and not the ortho- isomer that shows the greater potency and higher adrenomedullary uptake (6,8).

With Compound 1, nearly all of the radioactivity in the thyroid is due to sequestration of free radioiodide, as evidenced by the low thyroid activity in two dogs maintained on an oral potassium iodide supplement. The thyroid concentrations of all three isomers indicate that the meta-isomer is the most resistant to in vivo deiodi nation.

From the standpoint of possible myocardial imaging, the heart concentration of 1 was equivalent to that of thallium-201, and the heart-to-blood concentration ratio was favorable (; 25 at 30 min). However the heart-to-liver and heart-to-lung ratios were near unity.

Although the iodobenzylguanidines, like norepinephrine, are most likely taken up into adrenergic nerves by a saturable, carrier-mediated process, we have observed no increase in uptake in either the heart or adrenal medulla with carrier-free I-125-1. Details of this experiment will be included in the final full paper.

The remarkably long retention of 1 and 3 in the adrenal medulla may derive from their sequestration within the chromaffin storage granules. In adrenergic nerves, guanidines such as guanethidine and phen ethylguanidine are thought to share the same transport pathway as norepinephrine and to accumulate in and displace norepinephrine from intraneuronal storage granules (7,14). If 1 and 3 are mimicking norepinephrine in both transport and storage, their lengthy medullary retention is reasonable in view of the physiological role the adrenal medulla plays in the long-term storage of catecholamines. The study of subcellular elements in the adrenal medulla should help to clarify the mode of retention of these compounds.

Although adrenomedullary images in this report were obtained with the I-131-labeled compound, efforts are currently used to shorten the radiosynthesis time so that I-123-1 or I-123-3 can be utilized. This is important because the avidity of these radiochemicals for the adrenal medulla results in a high radiation dose to that organ. The combined use of I-123-1 or I-123-3 with a tomographic imaging technique, such as the coded aperture (15), may provide images of the human adrenal medullae in less than 1 day.

FOOTNOTES

Analtech Silica GF,
Bio Rad,
Pfaltz and Bauer, Inc., Stamford, CT.
§ Varian EM360A Spectrometer,
¶ Beckman Acculab 8,
** Waters Model ALC/GPC 204 Chromatograph with a Bondapak C18 column (3.9 mm • 30.9 cm) from Waters Associates, Milford, MA.
Kodak

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