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OBITUARY

In memoriam: a celebration of the autonomic contributions of David Robertson (1947–2024)

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We mourn the passing of David H. Robertson, a caring physician, visionary scientist, outstanding mentor and dear friend. David died on January 12, 2024, surrounded by the family he so much loved. We write this commentary to pay tribute to the many and important contributions David made to the autonomic field, which in addition to advancing science, improved patient care. David was Professor of Medicine, Pharmacology and Neurology, and Elton Yates Professor of Autonomic Disorders at Vanderbilt University Medical Center. He was both the founder of the Autonomic Dysfunction Center at Vanderbilt University Medical Center, and a founding member of the American Autonomic Society. The authors are members of the American Autonomic Society and his former trainees.

We will focus on his scientific contributions but, first and foremost, David was a remarkable human being and an extremely caring and approachable physician. He trained numerous individuals from all over the world with patience and kindness that inspired us to excel. He was universally loved, and his vision led to the creation of the American Autonomic Society, which has flourished and will hold its 35th Annual International Symposium later this year.

David had a keen talent for learning from patients. Their complaining about worsening of symptoms after meals led him to characterize postprandial hypotension [29], its treatment with caffeine [21], and more recently

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with acarbose [32]. A casual mention from a patient that he felt better after drinking water, which was dismissed by others, led David to discover the water pressor effect [12], and define it as a "novel" autonomic reflex [9] that had not previously been recognized by physiologists or autonomic neuroscientists. He then demonstrated its usefulness in the treatment of orthostatic hypotension, which has the advantage of its potent effect and quick onset [30], and its ability to potentiate other pressor agents [11]. David translated these clinical observations to basic science using very elegant mice models to identify that this pressor effect is triggered by hypo-osmolality in the portal circulation and involvied Trpv4 receptors [16].

David discovered novel congenital autonomic diseases before full genome sequencing was available. He did this based on the clinical presentations and detailed physiological, biochemical, and pharmacological investigations uncovering the patients' autonomic pathophysiology. He evaluated patients presenting with severe isolated sympathetic failure but with intact parasympathetic and sympathetic cholinergic (sweating) functions, and deduced that they suffered from dopamine-beta-hydroxylase deficiency [27]. He used direct sympathetic recordings to confirm that sympathetic nerves and autonomic reflexes were intact [26], but dopamine, instead of norepinephrine, acted as the neurotransmitter from sympathetic fibers. Furthermore, he showed that the excess dopamine, not only norepinephrine deficiency, contributed to orthostatic hypotension [4]. He also showed that droxidopa (then known as D,L-DOPS) could bypass the enzymatic defect and restore endogenous levels of norepinephrine [5]. This was arguably the first cure for an autonomic disorder leading to complete resolution of the disease [6]. It took 16 years for science to confirm the genetic defect [14, 15], but the knowledge derived from the discovery of this rare congenital disease has had a much wider impact. The pioneering work of David and other members of the American Autonomic Society eventually paved the way for droxidopa to be only the second drug approved for the treatment of orthostatic hypotension [2, 3, 13].

David was the first to systematically study patients with (afferent) baroreflex failure. He described the clinical phenotype of the condition, which is characterized by volatile arterial hypertension with the highest blood pressure readings encountered in the clinic [28]. Using elegant biochemical and pharmacological tests, he proved that these hypertensive surges were mediated by excess sympathetic activation unrestrained by the baroreflex. However, he also noted that these patients could suffer from hypotensive episodes and bradycardia, particularly a subgroup of these with selective baroreflex failure and intact vagal efferents to the heart [10]. Finally, based on the underlying pathophysiology, David developed and implemented treatments for patients with baroreflex failure that ameliorated the extreme blood pressure swings.

In evaluating a patient with Postural Tachycardia Syndrome (POTS) who mentioned she had a twin sister with similar problems, he noticed that her plasma catecholamine pattern was characterized by excess plasma norepinephrine but reduced levels of its intraneuronal metabolite dihydroxyphenylglycine (DHPG). David deduced that these patients had impaired norepinephrine reuptake, which was confirmed by selective sequencing of the candidate gene [7, 31]. Knowledge of the importance of the norepinephrine transporter led to the discovery of norepinephrine reuptake blockers for the treatment of orthostatic hypotension [19, 20, 25, 33].

David also defined neuropathic POTS based on the selective decrease of norepinephrine spillover in lower limbs [8], and made significant contributions to our understanding of the pathophysiology and therapy of this syndrome [1, 17, 18, 22–24].

This is only a snapshot of his many contributions to science, but these discoveries were not made in a vacuum. We would like to think that he did benefit from his interactions with us (at least a little bit). The same is true with his many and close interactions with other members of the American Autonomic Society. We feel fortunate to have trained under his mentorship. David left a legacy that we treasure and an example that we can only hope to follow. David is survived by his wife Rose-Marie, his daughter Rosie, and the numerous trainees and collaborators that he invited into his extended family.

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