Thirty years of questions and beyond

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When, 30 years ago, I entered into subspecialty practice in autonomic neurology, a senior colleague took me aside and advised me to choose a different career path because autonomic disorders, he thought, are far too rare to supply a medical practice. And yet, I was seeing autonomic syndromes that other physicians had been unable to explain or had overlooked. Some were quite fascinating. Many were disrupting patients' quality of life. Perhaps, I thought, we are underestimating their prevalence and their clinical importance because we are just not asking the right questions.

One question in my mind was whether an autonomic condition analogous to myasthenia gravis might exist, in which autoantibodies directed against acetylcholine receptors disrupted, not the neuromuscular junction, but autonomic ganglia. Eventually, I encountered a case and, ten years later, reported it as part of a series with two colleagues who had been asking the same question [1]. Autoimmune autonomic ganglionopathy is now a well-established clinical entity. The next question was whether botulinum toxin might block the sudomotor effector junction. After putting that question to the test, we saw that it did [2].

By asking the right questions, underdiagnosed conditions have increasingly been brought to light and identified as autonomic disorders that can be recognized, explained, and, in many cases, treated. Some questions are new; others are not asked often enough. Has the clinician obtained a thorough history informed by knowledge of autonomic neuroanatomy and physiology [3]? Has the heat-intolerant patient lost the ability to sweat? What are the implications for morbidity and mortality of an autonomic neuropathy in a patient with diabetes mellitus? What early autonomic symptoms precede the onset of motor deficits in neurodegenerative disorders and may facilitate early diagnostic discrimination [4]? Has dream-enactment behavior occurred?

A frequently omitted yet vital question still is, what is the patient's blood pressure when standing [5]?

Other questions are sometimes asked indiscriminately or without confirming subjective answers with objective findings, leading to overdiagnosis. For example, some well-intentioned websites list a plethora of symptoms that can signify autonomic dysfunction, so many that any healthy reader might claim at least one or two. However, not every occasional symptom mediated by the autonomic nervous system indicates a malfunction of the autonomic nervous system.

Asking the right questions also helps to prevent under- and overtreatment. Not recognizing postural tachycardia syndrome sometimes leads to the recommendation to avoid symptomatic physical activity or to follow the general recommendation to limit dietary salt, either of which amounts to undertreatment that can delay recovery. On the other hand, overtreatment of orthostatic intolerance without assessing objective results of interventions can lead to cardiovascular risk [6]. Undertreatment of orthostatic hypotension may contribute to fall risk. Overtreatment of neurogenic orthostatic hypotension can worsen supine hypertension with potential end-organ vascular consequences [7].

Autonomic consultations now fill my clinical calendar, as clinical autonomic research fills the pages of this journal. Some conditions are rare, but many others are quite common [8]. The field has benefited greatly from multidisciplinary collaboration, standardization of terminology, universal diagnostic criteria, and the development of validated, non-invasive testing methodologies [9].

Looking forward, answers to the questions of the past three decades have led to new questions and exciting new possibilities for the twenty-first century. I here suggest 10 questions among the many that may guide the ongoing development of autonomic medicine in the next thirty years:

1. Is the category "abnormal" too narrow and rigid when describing functional disorders of the autonomic nervous system? Perhaps we need a new paradigm of nomenclature that recognizes physiologic diversity and

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explains autonomic conditions, validating symptoms, and facilitating their management without stigmatizing patients with a disease label.

2. What are the potential long-term health consequences of interventions such as salt and α -adrenergic agonists that are effective in the short term for chronic orthostatic intolerance, and what is the best way to balance their benefits and risks [10]?
3. What causes α -synuclein to misfold and accumulate in patients with Parkinson disease, multiple system atrophy, dementia with Lewy bodies and pure autonomic failure; and how can that be detected in its earliest stages, prevented, and reversed?
4. In what ways does the immune system relate to the autonomic nervous system? When autoantibodies are detected, how can we disambiguate causation from association? Instead of steroids or intravenous immunoglobulin, which have broad-ranging effects, what targeted immunomodulatory approaches would be safe and effective for treating autoimmune autonomic disorders?
5. How will increasing knowledge about the human genome and epigenetic factors lead to increasing personalization of diagnosis and individualization of the treatment of autonomic disorders? Might a personalized profile of norepinephrine transporter function, for example, become a standard metric to guide therapy in patients with symptoms of hyperadrenergic activation?
6. Where are the opportunities for artificial intelligence to analyze large data sets and expand the horizon of knowledge in autonomic medicine?
7. How should health data from personal nonmedical devices be harnessed to monitor autonomic conditions and evaluate their treatment and progress over time? Could a smartwatch predict syncope? Could a wearable monitor signal a significant reduction in blood pressure to the patient with orthostatic hypotension who is unaware of symptoms? Could a miniature electronic device warn the wearer of a change in core temperature to prevent heat stroke or hypothermia?
8. What are the best ways to empower patients to be active participants and decision-makers in managing their health without burdening them with so much data as to arouse excessive worry, anxiety, or hypochondriasis, and without dangerously elevating their perception of self-expertise?
9. What are the best clinical practice models for diagnosing and treating patients with autonomic disorders in ways that are productive and satisfying to patients? Best practices should be not only effective in achieving optimal outcomes but also efficient and cost-effective in a healthcare environment where time and expertise may be scarce.

10. What more can be done to inspire young people to consider a career in autonomic medicine?

The first-century Greek astronomer Ptolemy counted 1022 stars in the night sky. Using telescopes on Earth thirty years ago, astronomers estimated that our galaxy contains 200 billion stars. Following the launch of the Hubble Telescope in 1990, which has given us breathtaking images of the deepest reaches of space, according to current estimates, there are no less than 70 billion trillion stars in the observable universe. Likewise, the universe of autonomic medicine is not empty. It sparkles with the possibility of endless discoveries.

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Compliance with ethical standards

Conflict of interest The author declares that he has no competing interests.

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