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EDITORIAL

Reflections on the past three decades of autonomic neurology

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I enthusiastically congratulate *Clinical Autonomic Research* for its growth and recognition on the thirtieth anniversary of its founding. In such a relatively small field, the journal now enjoys a readership, influence and impact factor that is achieved by few subspecialty journals. This growth and development in no small part reflects the dynamic and visionary leadership that has steered this important journal. I take this opportunity to make some observations on the growth of autonomic neurology and autonomic medicine from a "Cinderella" of medicine to a respected and established subspecialty. What are the major motive forces that have led us from what we had thirty years ago to what we are today? These observations are of course, my personal opinion.

Neurologists and clinicians have long recognized that the autonomic nervous system is relevant, since some important diseases are characterized by autonomic failure or dysfunction. Autonomic failure can be dramatic, leading to fainting or loss of bowel or bladder control or heat intolerance. To the clinician, the presence of autonomic failure often aids recognition of common or rare disorders. While manifestations such as neurogenic bladder or orthostatic hypotension are easy to recognize, lesser degrees of the entities were poorly recognized. For a long time, clinicians approached autonomic disorders with trepidation since tools to diagnose and measure autonomic function, such as a blood test or laboratory test, were not clinically available. Autonomic physiology has been studied in research laboratories but poorly applicable to practice since techniques to study autonomic function were often considered too invasive (such as intra-arterial cannulation), or risky (such as infusion of vasoactive agents). In addition, normative dataset by age and gender were generally not available.

The first major driver to growth of the field was the development of clinical autonomic testing and the clinical autonomic laboratory. To illustrate this contribution, let us consider the Mayo Clinic Autonomic Laboratory, the first of its kind, founded in 1983. Its goal was to quantitate the severity and distribution of autonomic failure. In turn, its founding depended on the availability of new approaches to autonomic quantitation. The first discovery was the development of the Finapres® device (Finapres Medical System, Enschede, Netherlands), which enabled the usually accurate reproduction of arterial waveform beat to beat. The device is a finger cuff, which employs a servo-null approach to generate a counterforce dynamically that exactly nulls the deforming force (the arterial wave form). The device obviated the need for intra-arterial cannulation, which was too invasive an approach for everyday testing. The second development was the discovery of the quantitative sudomotor axon reflex test (QSART) which tests the integrity of the postganglionic sudomotor axon [5]. The test is usually done at four different sites, to provide information on both volume and distribution of postganglionic sudomotor impairment. These devices were incorporated into a number of reflex tests that together evaluated the severity and distribution of sudomotor, cardiovagal, and adrenergic failure, the autonomic reflex screen. These tests are non-invasive and can be completed in about 1 h. Improvements in the thermoregulatory sweat test (TST) with identifying a powder that did not usually sensitize the skin and identifying proper endpoints, catapulted TST into a clinical test [2]. A large normative dataset for all these tests became available. The success of the Autonomic Laboratory is reflected in the large number of laboratories that now exist. For instance, there have been 325 Q-Sweat® units (WR Medical Electronics, MN) sold, suggesting a large number of clinical autonomic laboratories. The number of such tests is growing in number. In the Mayo

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Clinic Rochester Autonomic Laboratory alone, more than 4500 autonomic screens and more than 2000 thermoregulatory sweat tests were performed, only in 2019. Part of the reason for such high demand relates to the medical referral base. They come from all areas of medicine, especially neurology, cardiology, gastroenterology, family practice, and general internal medicine. Patients are referred for multiple indications. The major five indications are: (i) suspicion of an autonomic neuropathy; (ii) orthostatic intolerance; (iii) peripheral neuropathy; (iv) rule out an autonomic disorder; and (v) neurodegenerative disorders, especially the synucleinopathies. The non-invasive testing approach results in a low threshold for referral. Many patients have non-specific, but possibly autonomic symptoms and the referring physician will often try to reassure the patient that they do not have significant autonomic failure. In these cases, autonomic testing can provide that reassurance.

A second motive force is the growth of the subspecialty of autonomic medicine itself. In the early days, Roy Freeman, Horacio Kaufmann, and myself were very active within the *American Academy of Neurology* (AAN) in advancing the development of autonomic testing and autonomic neurology. Judiciously, David Robertson pointed out that ours was too narrow an approach, that we should broaden the field to autonomic medicine. He emphasized that we would be shortchanging ourselves by not drawing on the expertise of non-neurologist clinicians, pharmacologists, researchers, and geneticists. He, together with Dorothy Trainor-Kingsbury (founder of the Shy-Drager support group), was the driving force to form the *American Autonomic Society* (AAS) to offer a broader umbrella than the one offered under the AAN. The AAS was formed in 1990 with *Clinical Autonomic Research* as its official journal. The society welcomed clinicians and scientists sharing an interest in basic and clinical autonomic medicine and research. Success in this field is manifested by a number of parameters. Today, there are a number of neurology programs that offer clinical fellowships in autonomic disorders, with at least 1 year of training. The importance of this field is such that the *United Council of Neurologic Subspecialties* (UCNS) offers board certification to candidates who successfully complete their fellowship and pass the board examination. Growth of the autonomic medicine field is also manifest by the discovery of new disorders such as acquired afferent baroreflex failure [9], dopamine β-hydroxylase deficiency [1], and the description of the postural tachycardia syndrome [10]. Development in the field extends to therapeutics resulting in randomized controlled clinical trials with midodrine [6] and droxidopa [3]. There is an evolving interest in linking randomized clinical trials using disease-modifying therapeutics to target basic pathogenetic mechanism. An example is the recent discovery of α-synuclein oligomers that are specific to multiple system atrophy [11], and the development of approaches to block its generation using antibodies or genetic therapies. The autonomic medicine subspecialty is closely linked to the autonomic laboratory, movement disorders (because of shared interest in the synucleinopathies), gastroenterology, urology, and autoimmune neurology.

A third driver for growth of the autonomic medicine field is the success of neuroimmunology laboratory testing and the novel field of autoimmune neurology [4]. The neuroimmunology laboratory has identified a very large number of autoantibodies that cause autoimmune disorders, with dramatic growth in the identification of pathogenic antigenic sites and antibody tests since 1960. There are numerous antibodies that target nuclear or cytoplasmic protein as well as membrane proteins. This specialty has evolved from neuroimmunology into a specific subspecialty that intersects multiple disciplines including neuroimmunology, gastroenterology, epilepsy, oncology, psychiatry, and autonomic neurology. Apart from classical autoimmune disorders such as multiple sclerosis and neuromyelitis optica, diagnostic tests are available for disorders with autonomic impairment like Lambert-Eaton myasthenic syndrome. Some autoimmune antibody-mediated disorders are specific autonomic syndromes, such as nicotinic ganglionic antibodies causing autoimmune autonomic ganglionopathy [12] and the recent identification of muscarinic antibodies causing postganglionic cholinergic dysautonomia [8]. There has been identified a large number of antibodies related to malignancies (paraneoplastic syndromes), some of which are associated with autonomic failure. Linkage between autoantibodies and autonomic dysfunction is such that finding autoantibodies is a frequent reason for referral for autonomic testing. Related to the neuroimmunology laboratory is the subsequent development of the subspecialty of autoimmune neurology. This subspecialty, with its training program, had significantly enhanced recognition of autoimmune and some autonomic disorders. This field and these tests together result in a large number of referrals for autonomic testing. Growth of this field together with improved treatment options have resulted in an explosive growth in new entities, multiple publications, and treatment trials.

Autonomic medicine is a burgeoning subspecialty and there are multiple reasons for high expectations [7]. First, the base is very broad geographically, in that autonomic medicine through its organization extends globally, with strong linkages with Europe and Asia in particular. Second, the field is truly multidisciplinary and has effective working relationships with other societies, such as the *International Parkinson and Movement Disorders Society* (MDS). Third, linkage with autonomic neuroscience provides improving understanding of disease pathogenesis, with the hope of improved understanding of cause and treatment. To illustrate, MSA involves misfolding of α-synuclein and generation of toxic oligomers. This hypothesis that the oligomer

might be responsible for pathogenesis, leads naturally to blocking the oligomer in treatment trials using antibodies or genetic approaches. The past 30 years have been very successful. The next 30 years should be even more successful.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interests.

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