The autonomic nervous system from a morphofunctional perspective : historical overview and current concepts over the last two centuries highlighting contributions from Eastern Europe

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Special issue intro/commentary

The autonomic nervous system from a morphofunctional perspective: historical overview and current concepts over the last two centuries highlighting contributions from Eastern Europe.

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From its earliest days, the Anatomical Record (AR) has paid ample attention to the autonomic nervous system by publishing multiple seminal papers on this particular field of research. Definitely worth mentioning in this respect are Martin R. Chase's pioneering article on sensory ganglia (1909) and the works of Albert Kuntz (Kuntz, 1909; Kuntz et al. 1956, Hoffman and Kuntz, 1957) on the histogenesis of the ortho- and parasympathetic nervous system as well as the latter author's article in collaboration with John W. Hamilton on the afferent innervation of the skin (Kuntz and Hamilton, 1938). In 1958, the journal dedicated an entire volume comprising no less than 4 issues (Volume 130, January 1958) in honor of Albert Kuntz' widely acclaimed work. In the 30s, the AR published further seminal articles on the autonomic nervous system, for example by Stephen W. Ranson and Peter Mihalik, who provided a detailed description on the structure of the vagal nerve (Ranson and Mihalik, 1932) and by David Bodian, who introduced the famous 'Bodian staining' to stain nerve fibers and nerve endings in mounted paraffin section (Bodian, 1936). This trend continued during and shortly after WWII, with highly relevant papers, for instance, on the anatomy of the lumbosacral and posterior sacral nerve plexus (Horwitz, 1939), the origin and structure of the sympathetic and parasympathetic ganglia in chicken (Smith Jones 1941, 1942). Noteworthy, the journal also published reviews on 'approved films in anatomy and biology', including a 3-hour movie dedicated to the studies of Ivan Pavlov, produced by Techfilm Studio and recorded in the Physiological Laboratory of the Institute of Pediatrics in Saint-Petersburg (Leningrad) (Addison, 1941). In the post WWII period, numerous important AR contributions by Russell T. Woodburne (on the sacral parasympathetic innervation of the colon, 1956), John S. Dixon (on the fine structure of parasympathetic cells in the otic ganglia, 1966), Alan M Laties and David Jacobowitz (on the autonomic innervation of the eye, 1966), Keith C. Richardson (on the ultrastructure of autonomic nerve fibers, 1966, 1969), and Per Freitag and Milton B. Engel (on the autonomic innervation of salivary glands, 1970), further attest to the importance and justified recognition attributed by the journal to this field of research. Somewhat surprisingly, the autonomic innervation of the urogenital system remained largely underexposed in the journal's earlier history. A first extensive report on this topic that I managed to trace back in the historical AR collection, is a paper by DJ Gray of Stanford University (not to be confused with Henry Gray of the Gray's Anatomy textbook) dealing with the intrinsic nerves of the testis (Gray, 1947). Later on, Roberts and Taylor (1970) reported in the AR on the relation of the autonomic nerve supply to the visceral pelvic fascia, in particular the parasympathetic supply to the bladder musculature and the importance to make a clear distinction between the presacral fascia and the fascial sheath of the rectum proper during pelvic surgery in order to avoid functional damage. Using for that time modern neurohistochemical techniques such as acetylcholinesterase staining, Klück (1980) provided an extensive description of the autonomic innervation of the human urinary bladder and urethra. A seminal AR paper on the hepatic innervation by Robert McCuskey and his lab was published in 1978 (Reilly et al. 1978). More recently, the AR devoted several special issues to subjects dealing with the autonomic nervous system, i.e. "The enteric nervous system and its targets" (Volume 262(1), 2001), "Morphology, cell biology, physiology and pathology of airway receptors" (Volume 270A, 2002), and the "Hepatic nervous system" (Volume 280A, 2004) (fig 1).

Strikingly, the vast majority of the reviews covering historical and conceptual views on the autonomic nervous system, including those published in the Anatomical Record, are very much marked by biased referencing to pioneering studies in this scientific domain. With very few exceptions (e.g. Carlson BM, 1968), references to studies from colleagues in Eastern Europe in the 19th and 20th centuries are not included, which is largely due to both language barriers and lack of access to scientific sources, but definitely also to a number of geopolitical events such as both world wars and the associated postwar period. Therefore, I am grateful to our guest editor, Prof. Dr. Petr Masliukov from the Yaroslavl State University, who despite the very difficult current geopolitical situation, succeeded in engaging a substantial number of colleagues from Eastern Europe in providing a detailed view of the past and current research achievements in the field of the autonomic nervous system. I am also greatly indebted to all contributors to this special issue for their willingness to participate and in this way let science prevail over today's geopolitical issues and blocs.

The groundwork for earlier and, by extension, many of the current concepts on anatomical organization and function of the autonomic nervous system (ANS) was laid by a number of pioneering morphological, pharmacological and physiological papers by well-known researchers, such as Gaskell (1886), Dogiel (1895, 1896, 1899) Bayliss and Starling (1899), Pavlov (1902) Elliot (1905), Langley and Orbeli (1910), Langley (1921), Loewi (1921), Von Euler and Gaddum (1931), Orbeli (1932), Lawrentjew (1934) and Dale (1935). For a more comprehensive overview of all peripheral and central components of the autonomic nervous system I highly recommend reading all the volumes of the Autonomic Nervous System Book Series, edited by the late Geoffrey Burnstock and published at Harwood Academic Publishers.

The first contribution to this special issue by Prof. Alexandr Nozdrachev of the State University of Saint Petersburg (Nozdrachev, 2023) provides a comprehensive review on the pioneering achievements of researchers from Eastern Europe in the field of the autonomic nervous system since the 19th century and also includes an overview of the recent advances in this domain by researchers from this geographical region. Particularly the earlier works were published in either Russian or German and therefore remained somewhat unacknowledged or unknown until translated editions became available.

In contrast to what is still stated in many modern textbooks, the autonomic nervous system extends beyond the classic division between the ortho- and parasympathetic system and should in fact be subdivided into three anatomically distinct parts, i.e. the orthosympathetic system (OS), the parasympathetic system (PS) and the enteric nervous system (ENS). Indeed, already 100 years ago, Langley (1921) – and later on many other authors - provided arguments that the ENS cannot just be considered as a postganglionic component of the PS. All three components in the peripheral nervous system communicate and interact with the central nervous system and comprise both motoric and sensory pathways. In recent decades, growing evidence has accumulated that there is also an intense bidirectional interaction with the endocrine and immune systems. The first anatomical descriptions of the enteric nerve plexuses by the German anatomist and physiologist George Meissner (1857), the German physician and biologist Leopold Auerbach (1862) and the Russian anatomist Arnold Schabadach (1930), and the subsequent morphological typing of the enteric neurons based on silver impregnation by the Russian histologist and neuroscientist Alexander Stanislavovich Dogiel (1899) and further refined by the East German anatomist Werner Stach (1980, 1981, 1982a, 1982b, 1985, 1989) (fig 2), were later on complemented by studies that exploited then novel techniques, such as intracellular electrophysiological recordings, immunocytochemical stainings and neuronal tracings, allowing scientists to link morphological features to electrophysiological subtyping (S-neurons and AH-neurons) (Nishi and North 1973; Hirst at al. 1974, for a comprehensive review see Wood, 1987) and to a detailed neurochemical coding of these morphologically classified enteric neurons in several mammalian species including human (see for instance Furness and Costa 1987; Bornstein and Furness, 1988; Furness et al 1988; Timmermans et al 1997, 2001; Brehmer et al 1999; Hens et al. 2000; Nurgali et al 2004; Furness 2006; Brehmer 2006, 2021; Lindig et al. 2009). Even today, these early studies continue to serve as a solid base for a plethora of exciting new studies applying fascinating novel techniques that involve optical recording and optogenetic activation (Spencer et al 2020) or the simultaneous application of live cell calcium imaging and whole cell patch clamp even at different topographical levels (Li et al 2022), in attempts to further unravel the complex enteric neurocircuits. Similarly, and in much more detail, single-cell sequencing opens up new perspectives in further exploring the molecular taxonomy of enteric neuronal classes as elegantly shown recently by the Marklund lab (Morarach et al 2021). The guest editor of this special issue, Prof. Dr. Petr Masliukov from Yaroslavl State Medical University, in collaboration with several national and international colleagues, studied for more than 20 years the sympathetic innervation of the gastrointestinal tract at the developmental, neonatal, adult and aged stages of life. His main findings, including neuroplasticity of the sympathetic gastrointestinal innervation, are nicely summarized in a review in this issue (Masliukov et al 2023, this issue), while the original contribution of Proseva and Preobrazhensky (2023, this issue) and those of Budnik and Masliukov (2023, this issue) and Kirov and Lazarov (2023), this issue) focus on the neurochemical profiles of sympathetic preganglionic neurons and myenteric neurons, respectively.

Sympathetic and parasympathetic nerves are the main modulators of the cardiovascular system, regulating heart rate, blood vessel caliber and the contractile behavior of atrial and ventricular myocardiocytes. Chemoreceptors sensitive to a decrease in arterial PO_2, a rise in PCO_2, or a drop in pH as well as baroreceptors measuring blood pressure are located in the carotid and aortic bodies. A first detailed historic overview of the innervation of the carotid body in this journal was provided by Gerard and Billingsley (1923). In the November issue of 1929 and the June issue of 1930 Ralph F Shaner reviewed the then current knowledge of the development of the conduction system in the heart and the development of the innervation of the mammalian heart. In the special AR issue dedicated to Albert Kuntz, AM Rappaport and WD Wilson (1958) published their observations on the ultrastructure of the carotid body. In the late sixties and early seventies, McKibben and Getty (1969), RB Smith (1971) and Walter C. Randall and colleagues (1971) reported in the AR their first observations on the distribution and functional morphology of the intrinsic cardiac innervation of the human neonate,

primates and domestic cattle, respectively. In this special issue, Dainius Pauza and colleagues from the Lithuanian University of Health Sciences in Kaunas (Lithuania) share their long-standing expertise and further elaborate on the comparative anatomy of the cardiac and epicardiac innervation as well on the cardiac conducting system validating several models for cardiac research and cardiac pathology (Saburkina et al, 2023; Pauziene et al, 2023; Inokaitis et al 2023). This part on the autonomic innervation of the heart is further complemented by a review article from Filipovic and collaborators from the University of Split (Croatia) on our current knowledge of the pathophysiological mechanisms and diagnostic approaches related to cardiac autonomic neuropathy (Filipovic et al, 2023), by a joint study from the Bulgarian Academy of Sciences, the Trakia University in Stara Zagora and the Medical University of Sofia demonstrating the neuronal plasticity displayed by the carotid body in hypertension (Atanasova et al, 2023) and by a contribution of Vakhrushev et al (2023) dealing with the significant contribution of ANS dysfunction to the development of cardiovascular diseases such as arterial hypertension, coronary artery disease and chronic heart failure. In most cases the observed symptoms are due to an increase in sympathetic activity and a decrease in parasympathetic activation. Standard treatment consists of catheter-based renal artery denervation by means of radiofrequency ablation. Considering the large variability in outcome of this technique, these authors from the Almazov National Medical Research Center in Saint-Petersburg propose transcatheter laser renal denervation as a valid alternative approach and demonstrate that this technique is as effective as radiofrequency ablation while causing much less damage to the intimal layer.
The last two contributions to this special issue deal with neurochemical features of specific areas in the brain (Romanova et al, 2023) and the spinal cord (Veshchitskii et al, 2023), known to be part of the central nervous system control of the autonomic outflow.

While I do recognize that this special issue has inevitably been subject to some degree of selectivity and hence does cover only some aspects of the autonomic nervous system, I am convinced that the contributions in this special issue provide a good picture of how the achievements of researchers in Eastern Europe and ~~the former USSR~~ have contributed to our current insights into the morphofunctional organization of the autonomic nervous system. and would hence like to offer my heartfelt thanks to our Guest Editor Prof. Dr. Petr Masliukov for his time and efforts in making this exciting special issue possible and to all contributing authors from distinct countries in Eastern Europa illustrating that science and unity between scientists from Russia and colleagues from independent democratic countries can still surmounts threathening geopolitical situations.

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Figure Legends:

Fig 1: Covers of AR special issues dealing with different aspects of the autonomic nervous system.

Fig 2: (a, c) Images taken from the historical collection of a silver-impregnated intestinal whole-mounts of Prof. Em. Werner Stach (Rostock). (a) Myenteric ganglion of the porcine small intestine showing Dogiel type I, II and III neurons. Inset: picture of Werner Stach taken this year at the age of 87 (left) and Alexandr Dogiel (right). (b) Outer submucous ganglion immunostained with an antibody raised against neurofilaments showing the typical type II morphology seen with silver-impregnation. (c) Detail of a myenteric Dogiel type I neuron after silverimpregnation. (d) confocal 3D reconstruction of a similar myenteric Dogiel type I neuron after immunostaining for the tachykinin receptor, neurokinin 1. (e) Additional morphological classification of enteric neurons according to Stach (*modified from Timmermans et al, 1997*).

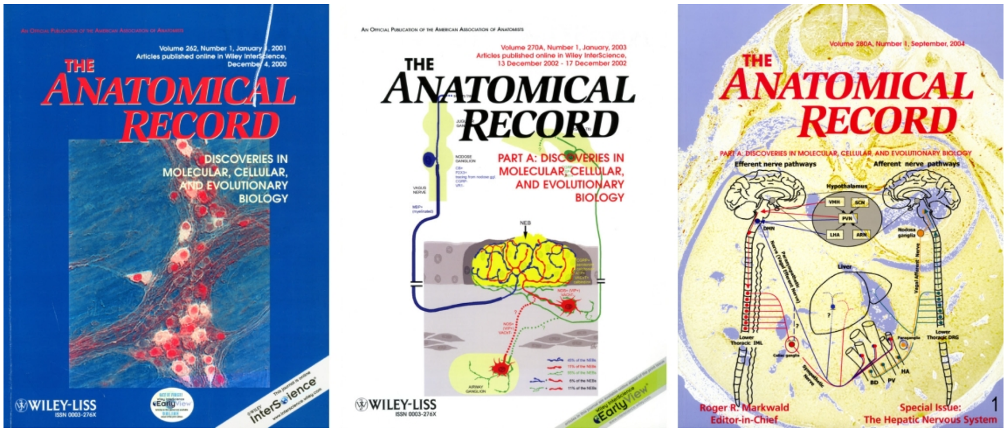

Figure 1.

171x72mm (300 x 300 DPI)

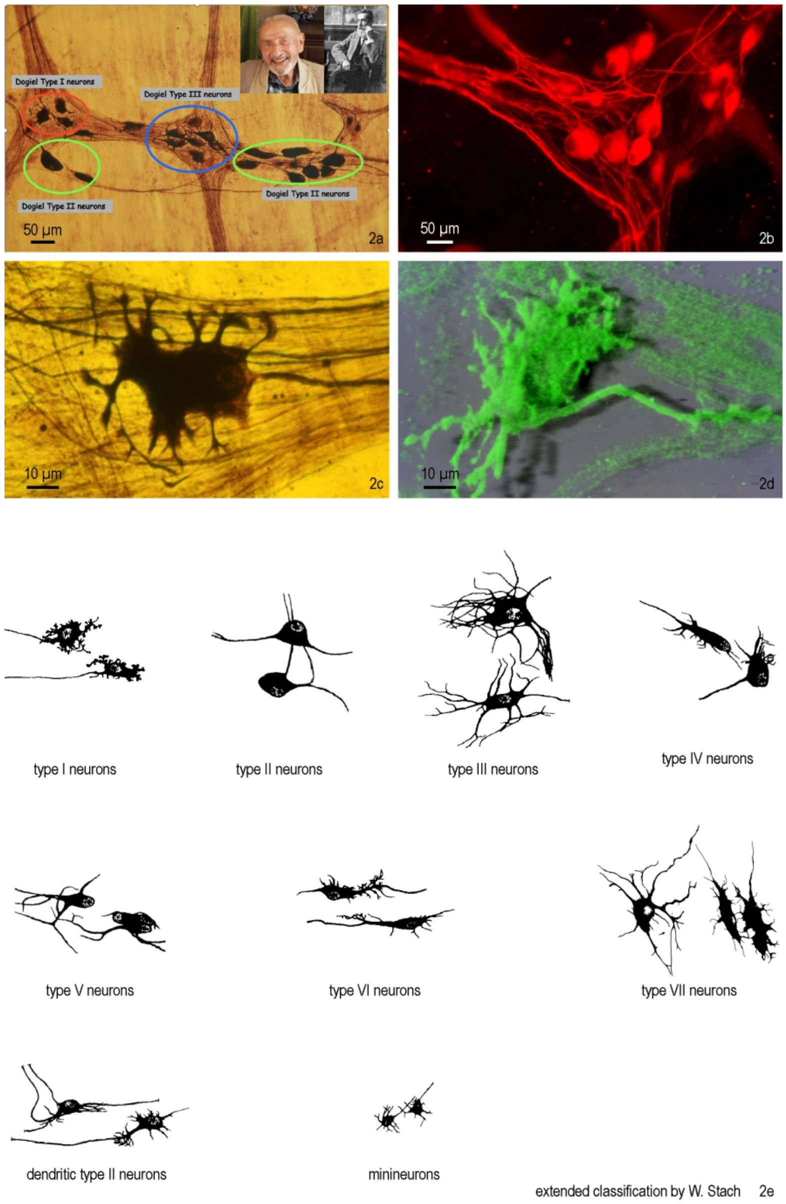

Figure 2.

171x265mm (300 x 300 DPI)