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In memory of Professor Jan Herget: A Legacy of Passion and Dedication in Pulmonary Circulation Research

This special issue was prepared in commemoration of the five-year death anniversary of a remarkable personality in pulmonary circulation research, and an outstanding physiology teacher and mentor, Professor Jan Herget, M.D. (March 16, 1945 Prague - March 14, 2019 Prague).

Jan Herget entered the international scientific scene with his methodological paper on how to catheterize the pulmonary artery in the intact rat [1]. This method is still the gold standard for assessing pulmonary circulation in this animal model. It heralded his lifelong interest, essentially a hobby, of "playing" in the lab with

how things could be done. Until his last days, he spent at least as much time in the lab as he did in his office.

He then contributed significantly to the discovery of various factors influencing the development of pulmonary hypertension, e.g. the effect of perinatal insults [2-6]. A number of his papers contributed to elucidating the role of oxygen radicals [7-13], mast cells [14-17], macrophages [18] and changes in the connective tissue of the pulmonary vascular wall [7,16,19-21], as well as the interaction of these factors, in the development of pulmonary hypertension. He also collaborated on the practical application of pulmonary circulation knowledge for the purposes of lung transplantation [22,23].

In 1984-1999, together with Prof. Jiří Widimský Sr. (1925-2020), Jan Herget was the main organizer of four international conferences "Pulmonary Circulation" in Prague. Especially those that took place during the communist regime in Czechoslovakia (1984 and 1988) were extremely difficult to organize, but they were also invaluable for the isolated Czechoslovak scientific community.

His lifelong scientific contributions to the field of pulmonary circulation were recognized in 2011 by the American Thoracic Society with the Robert F. Grover Award (Figure 1).

Jan Herget was a passionate teacher of both undergraduate medical students and PhD students (on average, he “produced” one PhD graduate every year). He cared a lot about his beloved Alma Mater, the 2nd Medical Faculty of Charles University in Prague. For 13 years, he served as its vice dean for research and international cooperation. He also participated in the establishment of the Grant Agency of the Czech Republic and thus the whole system of grant funding in the Czech Republic after the end of the communist regime in 1989. He was active on the Board of the European Society of Respiratory Physiology and Pathology in the first half of the 1990s (before its merger into the emerging European Respiratory Society). For decades, he was an active member of the editorial board of this journal.

But the most important thing that Prof. Herget had been always appreciated for by his subordinates, colleagues and students was his honest, unpretentious and humble commitment to science without any concern for his own promotion. His greatest concern was that his students would eventually outgrow him. He devoted a great deal to this priority, but he has set the bar high for his followers. He died full of ideas shortly after his beloved wife Hana.

The issue is composed of the works of scientists closely associated with Jan - his students, friends, and collaborators, both those at his home Department of Physiology at the 2nd Faculty of Medicine of Charles University in Prague - Motol, as well as the international ones.

In addition to the authors, other friends and colleagues of Jan Herget have generously contributed to this volume by helping with the review process. Of those, I would like, with their permission, to thank Andrea Olschewski, Kurt Stenmark, Ivan McMurtry, Ken Weir, Stephen Archer, and Hikmet Al-Hiti. Still other experts willingly participated in the review process even without their previous close personal experience with Jan Herget (e.g., Drs. Aaronson, Dřevínek, Melenovský, Kittnar, Wearing, Sedmera, Svatoň, Merkus).

After a personal remembrance of Jan's former PhD student Ivana Kawiková, the issue opens with a review article by Drs. Thenappan and Weir on the role of the gut microbiome in the mechanism of pulmonary hypertension [24], and a primary publication by Lorna Moore and colleagues on the effect of hypoxia on the fetus [25]. The choice of these seemingly disparate topics came about because Ken Weir and Lorna Moore were Herget's colleagues during his one-year fellowship funded by the B. Francis Parker Foundation at the *Cardiovascular and Pulmonary Research Laboratory* at the University of Colorado in 1984. This pair of papers is complemented by a review by Stephen Archer *et al.* [26] on the mechanisms of hypoxic pulmonary vasoconstriction (also co-authored by Ken Weir, once Stephen Archer’s mentor).

Next is a review by Ošťádal and colleagues on sex differences in cardiac tolerance to oxygen deprivation [27]. Prof. Ošťádal had been Jan Herget's friend and collaborator since their beginnings together in Prof. Otakar Poupa's laboratory in the 1960s. Although their professional paths soon diverged (Herget focused on pulmonary circulation and Ošťádal on myocardium), the collaboration continued (e.g. in the Center for Experimental Research of Cardiac and Vascular Diseases, jointly established by them in 1998) and showed that the mechanisms of ischemic cardioprotection (Ošťádal) and hypoxic pulmonary hypertension (Herget) have surprisingly much in common. Another strong research group at the Centre was led by Prof. Luděk Červenka, whose team is featured in this issue with a short communication on sex-linked differences in cardiac atrophy after heart transplantation [28]. These two articles illustrate that the Center explicitly focused on sex

differences long before they became mainstream in biomedical research. Prof. Herget contributed significantly to this trend [4,13].

Towards the end of the 1980s, Prof. Herget's group turned their attention to the lifelong consequences of perinatal insults on the pulmonary circulation [2-6]. They showed that, consistent with the then new Barker hypothesis [29], hypoxia acting at the time of birth, but not later in life, has a lifelong, irreversible effect on pulmonary vasoconstrictor reactivity, which likely contributes to the development of pulmonary hypertension in adulthood. This idea was taken up especially by the group of Prof. Jean-François Tolsa in Lausanne, focusing on the possible mechanisms of this effect [30-33]. This group's contribution in this issue [34] further develops this topic and also marks the 25th birthday of the Neonatal Research Laboratory at the University of Lausanne (October 1st, 1999).

Examples of the close interdisciplinary collaboration necessary for today's science are represented in this issue by the contributions of histologists Kamila Procházková & Jiří Uhlík [35] and biophysicist and cell biologist Lucie Bačáková (and her team) [36]. Herget's collaboration with both of these teams, including the prematurely deceased colleagues Jana Novotná (1954-2016), Václav Pelouch (1941-2010) and Luděk Vajner (1954-2018), was key to Herget's series of publications on the role of changes of extracellular matrix, particularly collagens, in the development of pulmonary hypertension [7,19-21]. These are summarized in a review by Bačáková *et al.* in this issue.

Herget's students are represented in this issue by the works of Drs Koubský [37] and Kawiková *et al.* [38]. Both articles well illustrate that guiding and mentoring PhD students in physiology and pathophysiology of pulmonary circulation can ultimately be a good preparation for successful work even in fields not necessarily directly related to the pulmonary vascular bed (pediatric cardiology for K. Koubský and even psychiatry in the case of I. Kawiková).

We have prepared this issue in the belief that individual personalities matter in science. May this commemoration of the legacy of the outstanding personality of Jan Herget contribute to a better understanding of the pathophysiology of his favorite pulmonary circulation and, in general, to the further advancement of his beloved science.

Václav Hampl
Department of Physiology
Second Faculty of Medicine
Charles University in Prague

Fig. 1. Jan Herget (right) and Robert F. "Bob" Grover during the American Thoracic Society Robert F. Grover Award ceremony in Denver, CO, on May 17, 2011.

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