

Jan Herget's impact on the field of pulmonary hypertension and beyond

In this Special issue of Physiological Research, we celebrate the life and work of Professor Jan Herget (1945-2019). He was a pathophysiologist focused on the responses of pulmonary circulation to hypoxia, which is highly relevant to common conditions, such as left heart failure or lung diseases. Jan, alias "Honza", pioneered experimental testing of the concept that events at early life may shape the course of a disease in adulthood. The topic has become intensively studied many years later, particularly concerning such complex organs as the brain or microbiota. In addition to being recognized as a significant player in his field, Honza was a genuinely enthusiastic teacher and supportive mentor. He also served for over two decades as the Head of the Department of Physiology at the 2nd Medical School of Karlova University in Prague and also as the Vice-Dean for Research and International Relations.

In 1968, after graduating from the Pediatric Medical School (today 2nd Medical School), Honza joined the laboratory of Professor Otakar Poupa to pursue

his Ph.D. training at the Department of Pathological Physiology. However, as Allen Saunders said and John Lennon sang, "Life Is What Happens When You're Busy Making Other Plans", on August 21st, 1968, Czechoslovakia was occupied by the Soviet Union and its allies, and Jan's mentor left the country promptly, as did many others, and could not return until after 1989 when the communist regime collapsed. Another outstanding physiologist became the head of the Department, Prof. Jiří Křeček, but he was removed after a short time for political reasons. These blows must have been challenging for a young trainee, but Jan continued pursuing science and searching for his research identity.

At the end of 1970s, Honza spent almost a year in the laboratory of Professor Gwenda R. Barer at Sheffield University in the U.K. where he studied the role of hypoxia on pulmonary circulation. That hypoxemia causes vasoconstriction in lungs, in contrast to vasodilation in systemic circulation, was discovered in 1940's [1].



Jan Herget (right) with his colleague Ken Weir from the University of Minnesota (left) and their trainee, Vaclav Hampl (middle) at the Pulmonary Circulation Conference in Warsaw, Poland in June 2006.

Professor Barer contributed tremendously to understanding how hypoxia affects pulmonary arteries in acute and chronic settings [2]. Honza's stay in her lab was very productive and they became life-long friends. Professor Barer visited Prague on several occasions. She was like Agatha Christie's Miss Marple: mind sharp as a laser, kind and compassionate, and unassuming.

In 1982, Honza received the Parker B. Francis Fellowship that enabled him to spend one year in the National Jewish Center For Immunology and Respiratory Medicine in Denver, Colorado (today called National Jewish Health) with Robert Grover and John T. Reeves, two reknown high altitude physiologists and physicians. Whenever he spoke about Denver, his face lit up.

Shortly after returning to Prague, Honza became an Associate Professor and set up his independent lab focused on mechanisms of pulmonary hypertension. The assigned space was within a shabby underground of the old orphanage building at Ke Karlovu in Prague. A thin door separated the lab from the loud voices of construction workers and heaps of tools scattered on the corridor. Behind the doors, the world was neatly organized. The labyrinth of four interconnected rooms housed a large hypoxic chamber designed by Honza, a perfusion pump for studies on isolated lungs, a new marble stand for a beautiful, ancient mechanical balance, and some old wooden desks for two trainees (Vaclav Hampl and Ivana Kawikova) and a technician (Ruzena Ticha). The unforgettable aroma encompassed the old wall's sweat, odor from lab rat cages, coffee made in a beaker sitting above a Bunsen burner, and Honza's tobacco pipe. Behind the cellar windows was the world of communistic regime slowly crumbling away, while inside were done thought-provoking experiments on a remarkably skinny budget [3-8].

As a graduate and a faculty member of the Pediatric Medical School, Honza emphasized the need to view human health or diseases in the context of events during critical developmental stages. He followed steps of Professors Babak, Krecek, and others who founded the Pediatric Medical School in Prague with the notion that children are not small adults. The clinical observations were there, but there was no experimental evidence. Honza designed a landmark experiment where pregnant rats were placed into hypoxic chambers and were kept there until their offspring were ten days old. After placing the animals into the normoxic air, the animals recovered from hypoxia and had comparable pressure in pulmonary circulation as control mice unexposed to perinatal hypoxia. However, when these animals were re-exposed

to acute hypoxia in adulthood, their responses were more severe than in animals born in normal air. The mechanism of this intriguing effect of early childhood events on the adaptation process in adulthood is not yet fully understood. Honza published 126 papers and his work helped clarify how chronic hypoxia influences pulmonary vascular remodeling and the role of various cellular and molecular factors in this process.

Honza's laboratory, or rather a den, was separated from the rest of the nearby Department of Pathophysiology and offered a refuge of openness, trust, and enthusiasm for research and teaching. Honza, his friend and colleague Martin Vizek, and several scientists from the Czechoslovak Academy of Sciences (such as Bohuslav Ostadal, known as "Boja," who served for five years as a Director of Institute of Physiology, Academy of Sciences of the Czech Republic) continued nourishing the legacy of systematic work, open-mind and tolerance fostered by Otakar Poupa (1916-1999), a Chair of the Department in 1961-1968. Professor Poupa was a physician-scientist, artist, philosopher, and a founding member of the interdisciplinary community of cardiology-oriented scientists, the so-called "Prague School [9]. His charismatic and insightful leadership influenced them, even though it was only early in his research career. In 1968, Professor Poupa contributed to formulating the manifesto "2000 Words," which expressed widespread frustration with the Communist regime and became a symbol of the reform movement Prague Spring 1968. The manifesto provoked a strong reaction from the establishment, and after the Warsaw Pact Army invaded Czechoslovakia, Professor Poupa and several other influential scientists emigrated in order to avoid grave consequences (e.g., Karel Rakusan, an internationally respected physician-scientist who left Prague for Ottawa, Canada). It was brave to leave everything behind and reinvent himself abroad in the sixth decade of his life, but Professor Poupa used to say that those who stayed behind and continued doing something meaningful were at least as courageous, if not more. Professor Poupa continued to follow events in the Czechoslovak research community from his new home in Goteborg, Sweden, but news about him was very sporadic and filtered by the Iron Curtain. He stood once on the border of Czechoslovakia, wanting to enter his homeland where his mother was passing away, but the entry was denied. We can only imagine how far Honza would fly under the mentorship of the man who established the field of comparative cardiology.

Then came 1989, and with it, the regime was changed. It was finally possible to freely cross the border,

to say what was on the mind, the military service was not obligatory anymore. The latest became critical for the Department of Pathophysiology because the army vacated barracks where the university's male students received military training. These buildings were near the main hospital campus of the Pediatric Medical School in Prague-Motol. Honza was critical in claiming these buildings for the medical school and creating an adjacent campus for pre-clinical fields. Who cared that the walls were as thin as paper? It was a significant step forward.

How did Honza affect other research areas? About a decade after the study on the effects of perinatal hypoxia [3-8], Paul Paterson published a paper demonstrating that exposure of dams to an infectious stimulus affects the behavior of their offspring in adulthood [10], which models phenotype of autism [11] and schizophrenia [12]. Altogether, these papers opened a new avenue to studies on neurodevelopmental disorders and may bring biological foundations to the socio-economic findings of the British birth cohort studies, which revealed the long-lasting impact of early childhood socio-economic conditions [13].

Honza's legacy continues also through his trainees. His mentoring was well-thought-through. He had well-defined goals and visualized a path towards reaching them. His expectations were realistic, and he provided as much support for his trainees as possible. There was always an air of informality, friendship, and generous space for self-realization. Honza was multifaceted, and when something was needed but was missing, he went on the limb and got it done. His trainees were around him and learned by osmosis. To name at least the trainees from the cellar on the street Ke Karlovu, Vaclav Hampl became an outstanding researcher in pulmonary circulation, and that per se was not a tiny deed at times when so many left science. He also became the youngest rector of Karlova Universita in its almost seven hundred-year history, served in this function for eight years, then went on to become Senator for another five years while never leaving the lab bench and medical students. He shaped graduate education at the University and supported research by facilitating multiple, long-lasting infrastructure projects funded by the European Union, e.g., BIOCEV. Meanwhile, Ivana Kawikova tackled some other unknowns related to metabolism in the immune system or the role of the immune system in neuropsychiatric diseases. Honza

equipped her with interdisciplinary thinking [3,4], encouraged her to develop solid foundations in pathophysiology through teaching and instructed her on communicating complex problems to various audiences. This preparation became a real asset while building bridges between distant disciplines such as immunology and psychiatry. With Martin Vizek they also opened the path to Sweden for her and encouraged her to reach out to Otakar Poupá, who then quickly adopted her as his informal advisee and friend.

The careers of several other Honza's PhD students continued towards successful clinical work (Bíbová, Mizera, Ošťádal, Šnorek, Lachmanová, Šedivý,...), clinical-academic combination (Vytásek, Chovanec, Al-Hiti, Koubský,...) [14,15], or health care management (Hodyc, Šnorek).

If there is something like the river Styx, we can imagine elegant Professor Poupá and always energetic Honza gazing curiously into our world and cheering any success of anyone from their teams. They must have danced happily when they saw the recent opening of a modern Theoretical Institute building on the campus of 2nd Medical School of Charles University in Prague. All scientists are finally at the same place! Collaborating and teaching together! And somewhere, there is likely also Jan Evangelista Purkinje, a man who founded the first two independent institutes of physiology in the world—the first one in Wrocław, Poland, and the other one in Prague. One hundred and seventy years later, Charles University has five medical faculties (each with a department of physiology and pathophysiology) and a Faculty of Science (also with a department of physiology), and the Czech Academy of Sciences has the Institute of Physiology. Honza was a remarkably functional part of this web, and it is an honor to raise a glass, blow a kiss in his direction and whisper: "Thank you!".

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