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Editorial

Prof. László Hársing's prescient contribution to the discovery of tubuloglomerular feedback mechanism by studying renal glucose transport inhibitors

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Diabetes mellitus (DM) (Types 1 and 2) affects millions of people worldwide and exerts a tremendous healthcare burden on societies throughout the world (9, 25, 35). DM is a major risk factor for chronic kidney disease in the United States and is responsible for the majority of end-stage renal failure patients on dialysis (1). It is estimated that 30% of patients diagnosed with DM will develop diabetic nephropathy, which is characterized by mesangial expansion, thickening of the glomerular basement membrane, glomerular sclerosis, and microalbuminuria (8, 22, 30). This progresses into greater microalbuminuria and kidney failure (8, 19). Although extensive studies have attempted to delineate the mechanisms responsible for the development of end-stage renal disease, the hyperglycemia that is a hallmark of both Type 1 (T1) and Type 2 (T2) DM is clearly associated with the development of progressive renal disease. Thus, numerous therapeutic strategies have been developed through the years to control blood glucose levels and maintain them close to the normal levels. Among the more classical treatments, one more recent approach to reduce the plasma glucose levels has been to block the renal tubular glucose transport mechanisms thus causing more glucose to be excreted in the urine. Glucose reabsorption in the proximal tubule is mediated by sodium glucose transporter 2 (SGLT2) and 1 (SGLT1) (21). In particular, blockers of the luminal SGLT2 have proven to be the most promising agents (2, 3, 38, 39). SGLT2 inhibitors are derivatives of the compound phlorizin, a naturally occurring compound found in certain species of apple trees (7). Phlorizin is a glucoside, which binds to SGLT2 and SGLT1, and prevents glucose entry by acting as a competitive inhibitor (39). Phlorizin has been used in research to study the mechanisms of renal transport by blocking the proximal reabsorption of glucose, sodium, and water (5, 14). Because it promotes glycosuria, phlorizin was investigated for its potential as a treatment for diabetes. However, because it also blocks SGLT1, it interferes with intestinal glucose reabsorption, causing gastrointestinal side effects (2).

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The major drawback to phlorizin as a therapeutic agent stems from the fact that its binding affinity for SGLT2 is only approximately sixfold higher than that for SGLT1, meaning, it has relatively low selectivity for SGLT2 (39). Accordingly, synthetic derivatives of phlorizin were developed to increase the selectivity for SGLT2. Modern SGLT2 inhibitors have a 300- to 1,200-fold higher selectivity for SGLT2 compared with SGLT1 (18, 38). This reduces the side effects associated with phlorizin, making the drugs more valuable as therapeutic agents. Thus, the development of SGLT2 inhibitors has led to marked improvement in regulation of plasma glucose levels, as well as body weight and blood pressure, especially in T2DM (4, 20, 37). Moreover, SGLT2 inhibition ameliorates glomerular hyperfiltration in DM (3, 36).

In view of these recent developments and utilization of the SGLT2 inhibitors for the treatment of DM, it is appropriate to recognize the prescient contributions to our understanding of the actions of glucose transport inhibitors on kidney function by Professor László Hársing, a giant in the world of Hungarian renal physiology. Sixty years ago in 1957, Hársing published a paper on "Effect of Phlorizin and of Mercurial Diuretics on Renal Hemodynamics" in the journal of *Acta Physiologica Academiae Scientiarum Hungaricae* (14). In that study, he used phlorizin to inhibit glucose reabsorption in the proximal tubule and thus cause an overload of volume and solute delivery to the macula densa plaque located at the end of the ascending loop of Henle. This increased solute load to the macula densa causing reductions in renal plasma flow and glomerular filtration rate (GFR). Hársing explained the results by invoking the ability of the macula densa to sense an increase in the filling pressure or solute load and, in turn, send impulses from the macula densa to the afferent arterioles thus regulating renal blood flow (RBF) and GRF through a "tubuloglomerular equilibrium." While such a feedback mechanism from the macula densa to the glomerular vasculature had been postulated on the basis of morphological observations (6), this study provided the first functional data to support the existence of such a feedback mechanism. In addition to the study using phlorizin, Hársing simultaneously published two additional papers using other approaches to evaluate the properties of tubuloglomerular equilibrium (13, 15). Accordingly in 2017, we are commemorating his prescient studies from 1957, 60 years since the publication of his papers (13–15).

Dr. László Hársing, a gold-graduate doctor and doctor of medicine, started his career as a university lecturer at the Institute of Physiology of the University of Medicine in Budapest, and progressed over 16 years to become Professor and Director of the Pathophysiology Institute until his retirement. During his retirement, he continued working as a Scientific Advisor for the Oral Biology Department until April 8, 1995, when he passed away at the age of 75.

In 1944, Hársing earned a doctor of medicine degree from the Medical School of Péter Pázmány Catholic University in Budapest, a preeminent medical school in Central Europe, currently known as Semmelweis University. He began his professional activities and research work under professors István Rusznyák, Pál Gömöri, and Péter Bálint of the Department of Internal Medicine, and studied the pathomechanism of tubular azotemia. In 1950, he joined the Institute of Physiology, where his scientific work on the tubuloglomerular feedback mechanism, in which he first described the renal functional specificity of this basic feedback-regulating system, gained greater recognition both nationally and internationally. His observations came to the forefront of nephrology research only 10–15 years later and many publications have dealt with this very phenomenon ever since. Like so many other Hungarian scholars working at that time behind the "Iron Curtain" of Central

and Eastern Europe, Hársing was not assisted by good luck regarding his discoveries. His publications in the early 1950s featured in the International English-language ACTA Conference provided only relatively low-key publicity and were left without appropriate recognition from abroad.

It was a belated satisfaction that in the 70s, many comprehensive summaries of this topic in publications and in congressional state-of-the-art lectures brought this story back to light and correctly recognized the pioneering work of Hársing and thus contributed greatly to his reputation acquired in the field of nephrology. In 1957 using animal studies, Hársing demonstrated that Goormaghtigh's (6) assumption was right in that the juxtaglomerular apparatus is involved in the regulation of GFR. In his studies, Hársing examined the effects of diuretics and hypertonic solutions on dogs, which increased urine flow, distal tubular fluid osmotic load, and solute concentration that led to the resulting changes in renal plasma flow and GFR (13–15). He dubbed the phenomenon "tubuloglomerular equilibrium," which is known today as the "tubuloglomerular feedback mechanism" a modified term suggested by Thurau (33, 34).

According to his observations, when the macula densa senses an increased osmotic/sodium load or pressure in the tubular fluid passing in front of it, the sensory organ will start a complicated feedback process, which causes the afferent arterioles to contract, thus increasing the vascular resistance and reducing the renal plasma flow and GFR, leading to a restoration of the distal tubular osmotic/sodium concentration or pressure. Specifically, he postulated that:

> "*It is possible that in osmotic diuresis associated with an increase in filling of the distal tubule impulses coming from the macula densa play a role in the regulation of RBF and GFR.*" (14)

In essence, the system is a classic negative feedback controller (24). This study gained greater recognition when the Tubuloglomerular Feedback Mechanism Symposium in Washington, DC was introduced by recognizing Hársing's seminal discoveries. Historically, it is of interest that a breakthrough came when about 30 years later Rosivall László sent a copy of Hársing's article to about 50 laboratories in the world dealing with this very topic. The following year, Navar opened the Tubuloglomerular Feedback Mechanism Symposium in Washington as follows: "As Hársing et al., 1957, experimentally proved for the first time the existence of tubuloglomerular feedback mechanism in Budapest..."

In subsequent years, Hársing studied the functional and morphological organization and the regulation of renal microcirculation with emphasis on methodological approaches and the autoregulation of both the cortex and medulla (17, 26, 28, 29, 31, 32). He developed a new method for measuring the distribution of blood flow in the kidney, which led to a number of fundamental observations made regarding the renal medullary circulation and the ability to concentrate urine (10, 16, 27).

In 1955, Professor Hársing defended his PhD thesis. In 1969, he earned the degree of DSc from the Hungarian Academy of Sciences, the highest academic recognition in the Hungarian system and was appointed professor at the Institute of Physiology. Between 1974 and 1990, he was director of the Institute of Pathophysiology. In his new position, he formed the Kidney and Circulatory Research Group with his closest colleagues and students, following in his footsteps until this day by continuing the research projects initiated by him. After 1978, his interest turned toward the exploration of the mechanisms of

compensatory renal hypertrophy. He continued his scientific activities even in his retirement serving in the Department of Oral Biology as a scientific consultant.

Throughout his career, Hársing published about 150 scientific papers, two thirds of which were in English. In the last three decades of his life, he visited all major European and overseas nephrology centers on demand and participated regularly in international physiology, pathophysiology, and nephrology world congresses as an invited speaker, president, and symposium organizer.

Professor Hársing dedicated himself to teaching at his university for 50 years and he played a crucial and leading role in the development of modernized curriculums in physiology and pathophysiology. He authored and edited seven undergraduate textbooks. Generations of medical doctors and pharmacists have been studying from both his physiological and pathophysiological textbooks along with a number of notes and textbook chapters that he wrote. Hungarian medical students were introduced to the concept of tubuloglomerular feedback decades ahead of their peers around the world. His logically structured and exquisitely delivered lectures live vividly in the memory of his students and disciples. Each and every sentence of his lectures, carefully worded and well placed, is rhetorically exemplary. His elaborate choice of words came as an especially gracious gift of destiny, which he elevated to new heights in his constant search and never ending respect for quality.

Professor Hársing was a member of several national and international scientific societies; he played a leading role in the International Union of Physiological Sciences (IUPS). He was also a founding member of the International Society for Pathophysiology, a member of the Hungarian National Committee of the IUPS and of the International Council of Scientific Unions (ICSU). As president of the Hungarian Society of Laboratory Medicine and board member of the Hungarian Society of Nephrology, he invested heavily in developing these disciplines. However, his service, worthy of an entire lifetime, associates him primarily with the Hungarian Physiological Society of which he became a member in 1948 and Secretary General between 1966 and 1982, then president from 1982 to 1990. During this period, Hungarian physiological scientists of that era visited physiological world

Fig. 1. Prof. Dr. Hársing László with colleagues, faculty, and students during the 1980s. He is in the middle of the first row, on his left side Prof. Dr. Szollár Lajos, and on his right side Prof. Dr. Rosivall László (Picture from 80s)

congresses in unprecedented high numbers thanks to his great efforts. Professor Hársing also contributed to the World Federation of Physiological Society, which finally responded to an invitation by the Hungarian Physiological Society dating back to the 1930s (subscribed by Verzár, Beznák, Mansfeld, Szentgyörgyi, and others) by organizing the XXVIII Physiological World Congress in 1980 that had over 6,000 foreign participants in Budapest and was overseen and co-organized by Hársing. This Congress became a great international success, and opened a vast series of major international events that has since become the norm, thus increasing not only the popularity of the subject discipline itself but also giving a boost to Hungary's international reputation in the biomedical sciences. At that meeting, several lectures and symposia were focused on the role of the macula densa in the regulation of renal hemodynamics (11, 12, 23, 33).

In honoring Professor Hársing, we honor a great and outstanding representative of the famous and well-established Hungarian nephrology elite. He gained profound international recognition for organizing scientific studies and meetings. His contributions as lecturer and educator to generations of medical doctors laid down the foundations of higher medical education in theoretical subjects. He spent his entire life in the service of his beloved university and was immensely respected by his family, colleagues, students, and friends as well as by his national and international scientific colleagues. Figure 1 shows him with his colleagues and students.

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