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Gunnar Flemström's legacy in intestinal bicarbonate secretion - *A Homage to Gunnar Flemström and his work in intestinal bicarbonate secretion*

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10 years ago, in 2009, the year of his presidency of the SPS meeting in Uppsala, also the year of his retirement from the chair of Physiology of Uppsala University, Gunnar Flemström organized an international Acta Physiologica Symposium "acid-base transporters and epithelial electrolyte transport", bringing together a group of internationally acclaimed scientists and a lot of young ones to focus in particular on gastrointestinal bicarbonate transport, from the molecular mechanisms to neurohumoral regulation and its implications for human disease (1). It was the last symposium of several ones that he had organized on this topic in which the focus was on acid/base and in particular bicarbonate transport in the gastrointestinal tract. The 10 year anniversary of that meeting is a time to remember.

With Gunnar Flemström´s death in 2016 we lost one of the great gastrointestinal physiologists, a superb thinker, a generous mentor and promoter of the Scandinavian Physiological Society. He was also the first who observed the phenomenon of active alkalinization of the luminal fluid by gastrointestinal epithelia, and he pioneered the field of gastrointestinal acid/base transport and bicarbonate secretion throughout his scientific career. Born and raised in Uppsala he obtained his doctorate on ion transport mechanisms in the stomach under the guidance of Karl-Johan Öbrink. He worked on the permeability of the gastric mucosa to weak acids, their effect on mucosal permeability, morphological alterations and gastric acid secretion. It was therefore logical to spend a postdoctoral period in the laboratory of George Sachs in the department of Basil Hirschowitz in Birmingham, Alabama. During this period, he studied the ion transport characteristics of the isolated bullfrog antrum in Ussing-chambers, and found HCO_3^- transport pathways in the apical and basolateral membranes of the antral epithelium, as well as an apparent secretion of alkaline moieties into the luminal fluid (2). Having returned to Uppsala, he also discovered this phenomenon in the amphibian, and shortly afterwards in the mammalian gastric and duodenal mucosa. Highly productive collaborations with AstraZeneca and clinicians at Karolinska hospital enabled the team of researchers to quickly establish various *in vitro* and *in vivo* models for the study of gastroduodenal bicarbonate secretion in various species including man. They reported such milestone findings as the stimulation of duodenal bicarbonate secretion by exogenous and endogenous prostaglandins and by luminal acid (3). Together with the Finnish surgeon Eero Kivilaakso, who had spend several years with the study of the gastric barrier components and the pathophysiology of gastric ulceration in the laboratory of Willian Silen in Boston, he demonstrated the existence of a pH-gradient and its regulation by the alkaline secretory rate and its stimulation by luminal acid (4). Through ingenious experiments, the team realized that the contact of the mucosa with acid causes the release of substances into the lamina propria that are able to stimulate HCO_3^- secretion in another duodenal mucosa that shared only the serosal medium with the acid-stimulated one (5). Gunnar´s group continued to study the mecha-

nisms of paracrine, hormonal and neural stimulation of duodenal bicarbonate secretion for several decades. They demonstrated the important role of the central nervous system in the stimulation of duodenal bicarbonate secretion, including the complex interaction between stimulating vagal as well as dopaminergic, and inhibitory sympathetic influences, and the role of a variety of neurotransmittors, either released in the periphery or in the central nervous system (6,7). He and his team intensely studied the effects of melatonin in the duodenum. Melatonin is released under central nervous system control predominantly in the periphery into the lumen of the gut and exerts a protective action in the gut, via the stimulation of bicarbonate secretion, but also via other effects on the mucosal barrier (8).

For these experiments, he developed ingenious ways to apply the peptides close to the epithelium by selectively infusing them into the gastroduodenal artery. Contributing to the uniqueness of his scientific work were the enormous skills and experience to perform demanding in vivo experiments and thus drive integrative physiology of the gut mucosa forward. In collaboration with his colleague Karl E. Akerman he also investigated the molecular mechanisms behind the stimulatory effect of peptides by fluorometric experiments studying cellular signaling in isolated duodenal crypts. They made the discovery that the receptor levels for some stimulatory hormones on the duodenocyte were differently expressed between the fasted and fed state (8). So far, most in vivo studies of gastrointestinal ion transport processes had been performed in the fasted state and by his initiative the influence of other gut peptides on bicarbonate secretion related to the feeding status were investigated.

He generously shared his technical knowledge and his deep insight into GI physiology with other scientist to help their respective progress. Senior scientists like Jon Isenberg, Catherine Chew and many others, some of whom still focus on gastrointestinal bicarbonate transport and thus carry on his legacy, spend sabbaticals in Uppsala or were visited by members of Gunnar´s group to make progress in their research on the molecular transport and signaling mechanisms of the duodenocyte.
Likewise, he was an admirable reviewer. He was always fair, always positive, and he was able to see what was interesting and novel, and stimulated improvement for manuscripts that needed to be optimized.
Gunnar became a scientific role model to many of us and served in the board and as meeting president of the Scandinavian Physiological Society and in the Editorial Board of Acta Physiologica. His deep and unrelenting interest in his research area, his modesty and absolute fairness, the mentorship qualities that allowed his young team members to quickly establish their own area of interest and get scientific recognition for it, and his foresight and shrewdness which allowed him to focus on

highly interesting aspects and make discoveries that were relevant for a much broader spectrum of gastrointestinal physiology and pathophysiology than the area of duodenal bicarbonate secretion, was fascinating and inspiring.

Conflict of Interest

There is no conflict of interest to declare.

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Figure 1: Gunnar Flemstrom Skandinavian Physiological Society meeting in Bergen, Norway 2011