EDITORIAL
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EDITORIAL

The unique contribution of Professor Lars E Gustafsson to the field of breath research

Marieann Högman1 and Terence Risby2

1 Department of Medical Sciences, Respiratory, Allergy and Sleep Research, Uppsala University, Uppsala, Sweden
2 Department of Environmental Health Sciences, Bloomberg School of Public Health, The Johns Hopkins University, Baltimore, Maryland, United States of America

E-mail: marieann.hogman@medsci.uu.se and trisby1@jhu.edu

This special issue of the Journal of Breath Research is dedicated to Professor Lars E Gustafsson of the Karolinska Institute. Lars Gustafsson holds a special place in the history of breath research because of his 1991 studies that identified nitric oxide in breath. These novel findings, coupled with nitric oxide being named ‘Molecule of the Year’ in 1992 by the journal Science [1] and the award of the 1998 Nobel Prize in Physiology and Medicine to Furchgott, Ignarro and Murad ‘for the discoveries concerning nitric oxide as a signaling molecule in the cardiovascular system’, drew the attention of clinicians to the potential use of breath analysis in diagnostic medicine. Before this time, breath analysis was viewed as an academic research area. A demonstration of the clinical interest for breath research was the organization of the first international conference on Disease Markers in Exhaled Breath: Basic Mechanisms and Clinical Applications by a group of clinicians (Marczin, Yacoub and Barnes) in 2001. The proceedings of this conference were subsequently published in 2002, as a book consisting of 61 chapters based upon oral presentations [2]. The popularity of the measurement of breath NO can be demonstrated by the increase of publications in this area. A search in PubMed with the MeSH terms breath test and nitric oxide identified in the period of 1991 to 1995 only 22 papers; over five year intervals, including 2015, publications increased rapidly from 250 to 410, 582 and 673 papers respectively.

The International Society for Breath Research (IABR) awarded Lars Gustafsson the Anton Amann Medal for outstanding achievements obtained in the field of theoretical and practical science of breath gas in 2016.

Lars Gustafsson is a prototypical researcher who is driven by curiosity of human physiology. His research spans from bench-top to multicenter clinical trials. When there are no methods available, he modifies existing methods or develops novel methods to reach his goals. His motto has been ‘Don’t find the problem—identify the problem and find the solution!’ His interest in oxygenation and hypoxic vasoconstriction was initiated while working as a medical student in an intensive care unit. The difficulties associated with satisfying oxygen saturation in these critically ill patients inspired him to conduct research in tissue oxygenation. Most of his research has been on the lung and its smooth muscle regulation in both health and disease. More recently, he has expanded his research interests to include other organs, e.g. the smooth muscle of the urinary bladder [3].

Lars Gustafsson is a Senior Professor at the Department of Physiology and Pharmacology at the Karolinska Institute, Stockholm, Sweden. He was born in Lund in 1950, obtained his M.D. and PhD degrees in 1974 and 1980, respectively, at the Karolinska Institutet. There he was also appointed as Professor of Physiology in 1999. Over the course of his career, many scientists have met him at conferences all over the world and enjoyed his lectures, presented with humor and knowledge.

We were both trained as physiologists at Karolinska Institute—Lars in...
autonomic transmission and myself in environmental physiology. He was and still is a shining star in his field and showed an open mind to new ideas and collaborations. Based on his discovery of NO in exhaled air, he developed not only a strong research group but also created a tool for improved monitoring of airway inflammation in patients. These concepts had applications also in my research field, and we developed together methods to monitor possible airway inflammation in astronauts and now we study the effects of weightlessness and reduced gas density on pulmonary NO turnover. With his sharp mind, encyclopedic knowledge and friendly attitude, he is the ideal partner in this work.

Dag Linnarsson, Senior Professor at the Karolinska Institute

When, in 1991, he published, together with his research team, the discovery of the presence of NO in exhaled gas [3] it was a breakthrough for exhaled biomarkers. NO had been known as a molecule with important effects on the cardiovascular and nervous system. The finding of a short-lived molecule such as NO in exhaled breath paved the way for extensive preclinical and clinical research. He postulated in this first publication on exhaled NO that NO may play roles in both vascular regulatory and host defense in pulmonary physiology and pathophysiology. A year later he proposed that exhaled NO could become important for both diagnosis and treatment of lung diseases, especially when hypoxia is present. Together with one of his many PhD students, Magnus Persson, he studied changes in exhaled NO during exercise. They discovered that NO peaked when the CO2 signal plateaued, that it increased with breath holding and that the peak declined after exercise [5]. They also performed some interesting studies that could implicate the anti-inflammatory role of NO. Both animals and humans were given ethanol, and a dose-dependent decrease in NO levels was found [6]. Lars Gustafsson has not limited his research to small animals and humans, but has also been involved in veterinary research where they found considerable species differences in nasal NO excretion, with pronounced amounts only in primates and elephants [7]. This was at the same time as the flow dependency of exhaled NO was discovered in his laboratory [8]. His research has further not been limited to the Earth, and he has participated in studies on the International Space Station where basic factors that affect exhaled nitric oxide such as gravity and ambient pressure have been studied [9]. Today, when we have had more than 25 years of NO research and a Nobel Prize 1998 for the regulatory role of NO in the vasculature, Lars Gustafsson’s early thoughts in 1991 about NO were certainly correct.

I first met Lars when I was a young PhD student. At this time he was already famous for just having discovered the presence of NO in exhaled breath. We were working in the same area, the competition was fierce, and Lars and our group hardly spoke to each other. In fact, we were outright antagonists and as a young student I was immensely afraid of him. Later we lay down all arms and instead started working together. It was then I discovered what an exceptionally friendly and loyal person Lars is. He is extremely knowledgeable and a fabulous scientist with an eye for those strange small details that are so easy to miss out on but that make all the difference.

Jon Lundberg, Professor at the Karolinska Institute

Lars Gustafsson has been deeply involved in the technical development of NO analysis. In the early days of NO research, the only analysers available had a very long response time and these monitors were designed for environmental research based in airplanes or on the ground aviation. His first instrument for the analysis of nitric oxide, based upon chemiluminescence, was a gift from Salvador Moncada, research director at the Wellcome Laboratories in London. It had to be redesigned and equipped with pressure transducers for exhaled flow measurement. This led him and other researcher at the Karolinska Institute to start a company that manufactured NO analysers. These early productions of clinical analysers, along with subsequent handheld devices, have helped the acceptance of NO measurement in clinical practice around the world.

The profound contributions of Lars Gustafsson to the field of exhaled biomarkers and NO can serve as a good example from discovery to clinical practice. The first recommendations on how to measure exhaled NO were presented at a European task force the year after its flow dependence was discovered [10]. That was followed by an American recommendation and then a joint document by two task forces in 2005 [11]. There are now reference values for breath NO [12, 13]. These publications have been followed by one practical guideline [14]. Thanks to the discovery of the flow dependence, we are now able to study the NO dynamics of the lung, and this year we have guidelines for this NO modelling [15]. In this issue we present reference
values for this NO modelling to be used as a guide in clinical work with patients (Högman et al [16]). A comparison of different mathematical methods to calculate NO parameters is also presented (Karvonen et al [17]). The widespread knowledge of the use of exhaled NO is found in an article from Nepal (Shrestha et al [18]) and in a perspective of exhaled nitric oxide (Ricciardolo &Silkoff [19]).

Lars Gustafsson’s contributions have had a marked and lasting impact on the field of exhaled breath analysis, particularly NO. His foresight is prophetic since NO was one of the first gases on Earth and later on developed a pathway of NO formation to serve useful biological functions [20]. Visitors to Lars Gustafsson will find him now, as ever, in his research laboratory where he loves to work, most likely discovering yet another new function of NO. We are grateful for the inspired leadership of Professor Lars Gustafsson in the field of exhaled breath molecular discovery and research.


During the publishing process for this special issue we were notified that Professor Lars Gustafsson had passed away suddenly. Since this issue is a tribute to his outstanding scientific achievements in the field of breath research we elected not to change its focus. The editors of this special issue, the Journal of Breath Research, and the International Association of Breath Research wish to express our sincere condolences to the family of Lars Gustafsson. We will miss him and his thoughtful and insightful comments.

References