

Legends of allergy/immunology: John Bienenstock and mucosal immunity

John Bienenstock is a multifaceted gentleman (Figure 1). When I first met him, he was internationally recognized for his contributions to the emerging field of mast cell and nerve association at mucosal sites with implications for mast cell biology, mediation of pain, and —of particular importance for asthma and allergy—regulation of mucosal inflammation. Alongside Dean Befus, he found that mucosal mast cells have a unique phenotype and are functionally different from those in connective tissue.¹ Together with Ron Stead, he showed first in rats, then humans, the importance of nerve-mast cell association for mucosal homeostasis and mucosal barrier damage.² This research was the basis for new directions in science that developed subsequently such as impairment of nerve-mast cell association in diseases like asthma resulting in bronchial obstructions or irritable bowel syndrome associated with pain. His pioneer findings were highlighted at that time in demonstration that Pavlovian conditioning could cause degranulation of mucosal mast cells.³

This is now almost 30 years ago. At that time, Dr John Bienenstock was at the beginning of his 50s and held the title of Distinguished University Professor at McMaster University. Later on, he was nominated as Fellow of the Royal Society of Canada and a Member of the Order of Canada. He has published more than 500 peer-reviewed

articles and other publications and has an h-index of 94. He has supervised some 60 postdoctoral fellows and 10 doctoral students.

In 1990, when I first met him, he served (together with Dr Holgate) as the organizer of the symposium of the distinguished Collegium Internationale Allergologicum. This society was founded in 1954 by respected scientists in medicine and allerge-immunology like RRA Coombs, Carl Prausnitz, Karl Hansen, Paul and Liselotte Kallós, W. Kaufman, W. Löffler, and J. Waldenstroem. Later on, this exclusive society limited to 200 living members was shaped by scientists like Alain de Weck and Erich Fuchs, Johannes Ring and Larry Lichtenstein, Steven Holgate and John Bienenstock, just to name a few. As a young scientist from the de Weck lab, it was quite impressive to see these high-profile researchers networking in a relaxed scientific meeting. All participants agreed to present especially unpublished data, and the conference allowed not only exchange of scientific results but also personal interactions often resulting in friendship and fruitful scientific discussions. John Bienenstock contributed greatly to this unique spirit of the “CIA” which was the funny acronym given to the Collegium (Figure 2). John Bienenstock served as the President of the Collegium Internationale Allergologicum (1999–2003).

John Bienenstock is not only a scientist, but also a teacher and a very successful book author and editor. He has authored, edited and co-edited 10 books on mucosal immunology and allergy. Among



FIGURE 1 Dr John Bienenstock in 2016



FIGURE 2 Marriage of John Bienenstock and his wife Dody in 1960

these, the "Handbook of Mucosal Immunology" deserves particular mentioning, because it was probably the first comprehensive textbook released in 1994 in the emerging field of mucosal immunology. A second extended edition was published only 5 years later under the shortened title "Mucosal Immunology" and a third edition in 2005. These books have influenced several generations of young scientist who made the field of innate immunity and mucosal immunology most prominent in current science.

His highest-ranked citation is his relatively recent entry into the gut-brain axis story of bugs and the brain. Bienenstock's group joined with John Cryan's to show for the first time that an oral treatment with bacteria (*Lactobacillus rhamnosus*) induces alterations in GABA mRNA in specific brain regions and reduced stress-induced corticosterone and anxiety- and depression-related behavior. Section of the vagus nerve prevented these effects, identifying the vagus as a major modulatory constitutive communication pathway between the gut bacteria and the brain.⁴ This work extended his earlier milestone work on *Lactobacillus reuteri* that inhibits the allergic airway response in mice by inducing regulatory T cells in the spleen.⁵

Dr Bienenstock contributed over 50 years to the research of allergy and immunology. An early highly cited paper was a review written together with his mentor Tom Tomasi on secretory immunoglobulins published in *Advances in Immunology* (1968). This paper helped to kick off the whole mucosal immunology field and led to his discovery of bronchus-associated lymphoid tissue which in turn led to the delineation of the common mucosal immune system. His memorable research in the field of allergy and immunology began with his work with Jerry Dolovich in his definition of the late cutaneous allergic response, followed by his identification of the unique functional characteristics of mucosal mast cells. It is likely that that the microbiota-gut-brain axis which he now studies intensively will come full circle to again include the regulation of the mast cell-allergy cycle.

A multifaceted gentleman is not only a scientist but also a lecturer. Dr Bienenstock is also a physician and a university administrator. Looking at his biography, one expects a rich life that started in October 6, 1936, in Budapest, Hungary. He left his country with his Jewish family and moved to London to escape the impending scorch of World War II. He became a British subject and finally a Canadian citizen. He obtained his clinical training at King's College in London in the 1960s. In 1964, he received the Membership of the Royal Colleges of Physicians (MRCP), the postgraduate medical diploma in internal medicine in the UK and moved to Boston to become a research fellow with Kurt Bloch at the Massachusetts General Hospital. In 1968, he was appointed assistant professor at McMaster University in Hamilton/Ontario and 2 years later associate professor of Medicine and Pathology. In 1974, he received full professorship and was chairman of the Department of Pathology from 1978 to 89. He served as Vice-President (1989-97) and Dean (1991-97) of the Faculty of Health Sciences, and from 2001 on as Director of the Brain-Body-Institute of his University.

During his time in London, he married his lovely wife Dody (Figure 2) with whom he has three children. We know him as a man who has a great sense of humor, who is very outgoing and a tremendous mentor, always supportive especially to the young scientists.

He is a chef de cuisine, a painter, and a member of the Dundas Valley School of Art and the Art Gallery of Hamilton. He is one of the persons you always like to see again. He always provided constructive criticism to the work and will always remain a reliable friend.

In 2011, John Bienenstock was honored as a Canadian Medical Hall of Fame Laureate for his landmark research on mucosal immunology and allergy. In 2019, we thank him for all his contributions in the field of Allergy and Immunology.

CONFLICTS OF INTEREST

None declared.

MAJOR CONTRIBUTIONS

- 1972 First description of the 'late phase responses' in IgE-dependent reactions
- 1973 Discovery of bronchus-associated lymphoid tissue (BALT)
- 1979 Delineation of the common mucosal immune system (CMIS)
- 1987 Mast cell-nerve cell interactions at mucosal sites
- 2007 Inhibition of allergic airway responses by oral bacteriotherapy
- 2011 Gut-brain axis story of bacteria in the intestine regulating brain functions

Stephan C. Bischoff 

Institute of Nutritional Medicine, University of Hohenheim, Stuttgart, Germany

Correspondence

Stephan C. Bischoff, Institute of Nutritional Medicine, University of Hohenheim, Stuttgart, Germany.

Email: bischoff.stephan@uni-hohenheim.de

ORCID

Stephan C. Bischoff  <https://orcid.org/0000-0003-2614-5948>

REFERENCES

1. Befus AD, Pearce FL, Gaudie J, Horsewood P, Bienenstock J. Mucosal mast cells. I. Isolation and functional characteristics of rat intestinal mast cells. *J Immunol.* 1982;128:2475-2480.
2. Stead RH, Dixon MF, Bramwell NH, Riddell RH, Bienenstock J. Mast cells are closely apposed to nerves in the human gastrointestinal mucosa. *Gastroenterology.* 1989;97:575-585.
3. MacQueen G, Marshall J, Perdue M, Siegel S, Bienenstock J. Pavlovian conditioning of rat mucosal mast cells to secrete rat mast cell protease II. *Science.* 1989;24:83-85.
4. Bravo JA, Forsythe P, Chew MV, et al. Ingestion of *Lactobacillus* strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. *Proc Natl Acad Sci USA.* 2011;108:16050-16055.
5. Forsythe P, Inman MD, Bienenstock J. Oral treatment with live *Lactobacillus reuteri* inhibits the allergic airway response in mice. *Am J Respir Crit Care Med.* 2007;175:561-569.