

## Lelio Orci 1937–2019

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Lelio Orci, May 2016. Photo taken by his wife, Catherine

On 22 October 2019, the international community of cell biologists lost one of its most eminent members, an exceptional scientist who made a monumental contribution to our understanding of the microanatomy and function of the endocrine pancreas, as well as the molecular mechanisms of cell secretion.

Born in San Giovanni Incarico (Frosinone, Italy) on 22 March 1937, Lelio Orci obtained his MD at the Faculty of Medicine of Rome University in 1964. After moving to the Medical School of the University of Geneva (Switzerland) in 1966, he was named Assistant Professor at the Institute of Histology and Embryology in 1967. An impressive scientific productivity driven by an outstanding talent earned him a full

professorship a few years later, then the chairmanship of the Department of Morphology (now Department of Cell Physiology and Metabolism) of the University of Geneva, until his retirement in early 2000 with the title of Professor Emeritus.

The best way of honouring a truly unique scientist is to provide a brief summary of his most influential scientific achievements. The leading motif of Lelio's career was a constant drive to understand, in minute detail, the relationship between cell structure and function, using light and electron microscopy and a variety of cell biological techniques that were complemented later, in the course of collaborative works, by biochemistry and genetics.

The first period of Lelio's activity unravelled, with exquisitely refined immunocytochemical techniques, the complex organisation of the pancreatic islets of Langerhans, with its four distinctive endocrine cell types present in different relative proportions depending on the dual embryonic origin of the islets [1]. This epoch was also characterised by the identification of a whole panel of endocrine cells in the gastrointestinal tract, which, since then, is considered a fully equipped endocrine organ [2].

In collaboration with Jürgen Roth and Moïse Bendayan, Lelio Orci developed the immunogold technique for the ultrastructural localisation of intracellular proteins, particularly hormones. By combining this methodological approach with radioactive labelling of newly synthesised proteins in pulse-chase experiments, he was able to follow, through time and space, the travel of insulin from its site of synthesis (as proinsulin) to its site of release into the extracellular space. During this journey, proinsulin migrated, enclosed in transport vesicles, from the endoplasmic reticulum to the Golgi apparatus, then to secretory granules, where it underwent enzymatic conversion to mature insulin. The entire process of insulin manufacturing was at last understood [3].

In another series of innovative experiments, Lelio Orci pioneered the use of the freeze-fracture technique to study the internal organisation of cell membranes [4]. Through this

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novel approach, he identified the occurrence of gap junctions (clusters of closely-packed intercellular channels) between adjacent islet cells and demonstrated their crucial role in the regulation of insulin secretion [5]. At that time, Lelio Orci had already raised himself to the status of a most gifted morphologist and electron microscopist, a status with still no match at the present time.

Rich with innumerable skills and insights, Lelio then embarked in transatlantic collaborative work with two renowned American scientists, James (Jim) Rothman, a biochemist, and Randy Schekman, a geneticist. Armed with powerful and complementary tools, they succeeded in discovering and elucidating the mode of formation of two types of intracellular vesicles implicated in the transport of proteins within the cell. Specifically, coat protein complex (COP)I vesicles, discovered by Jim and Lelio, mediate retrograde transport from the Golgi cisternae to the endoplasmic reticulum [6], while the COPII-coated vesicles discovered by Randy and Lelio are responsible for anterograde transport from the endoplasmic reticulum to the Golgi cisternae [7]. Their collective endeavour also unveiled the unique role of individual coat proteins and cytosolic components in the budding and subsequent fusion of the transport vesicles with the respective target compartment to deliver their cargo. This finely orchestrated convergence of morphological, biochemical and genetic techniques was essential in deciphering the molecular machinery underlying orderly intracellular protein transport [6, 7].

Lelio Orci's exceptional talents for detecting fine, but highly relevant details of cell structure that would have been overlooked by most of his peers, were instrumental in the discoveries summarised above.

Many prestigious distinctions honoured Lelio Orci's outstanding achievements in research, such as the Banting Medal of the American Association for the Study of Diabetes, the King Faisal Award for Medicine, the Otto Naegeli Prize, a foreign membership of the National Academy of Sciences of the USA, and honorary degrees in Medicine from the Universities of Geneva, Leuven (Belgium), McGill and Guelph (Canada) and Padua (Italy). Importantly, Lelio Orci received the Minkowski Prize in 1973 (Brussels) and was made an Honorary Member of the EASD in 2007.

One cannot conclude without a few words about Lelio's personality: he was a very strong and warm person to whom

nobody could remain indifferent (he would not permit indifference) and was endowed with an insatiable curiosity, not only for science but for all aspects of life. Outside the lab, Lelio was a passionate and talented amateur painter. Lelio was most sensitive to the beauty of cell organisation, which he celebrated with micrographs of legendary aesthetic quality. His 'uncompressible enthusiasm' (as he used to call it) seeped through the entire academic department he chaired. Lelio set very high standards for research, perseverance and quest for excellence for all the department's members. His teaching to medical students was guided by the same fervent passion and the superbly illustrated lectures he delivered were often rewarded with a vigorous applause.

What legacy is left to us, former pupils, doctorate students, collaborators or colleagues? The values Lelio Orci stood for: experimental rigour, quest of the highest possible technical quality, unflinching self-criticism and pursuit of excellence.

We think affectionately of his surviving wife, Catherine, and his three adult children, Lelia, Gregory and Lorenzo.

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