



Elio Raviola, obituary

Citation: Cinti, S., Mazzarello, P., & Ribatti, D. (2024). Elio Raviola, obituary. *Italian Journal of Anatomy and Embryology* 128(1): 3-8. doi: 10.36253/ijae-15323

Copyright: © 2024 Cinti, S., Mazzarello, P., & Ribatti, D. This is an open access, peer-reviewed article published by Firenze University Press (<https://www.fupress.com/ijae>) and distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Competing Interests: The Author(s) declare(s) no conflict of interest.

SAVERIO CINTI^{1,*}, PAOLO MAZZARELLO², DOMENICO RIBATTI³

¹ *Scientific Director Centre of Obesity, Marche Polytechnic University, Ancona, Italy*

² *Department of Brain and Behavioral Sciences and University Museum System, University of Pavia, Pavia, Italy*

³ *Department of Translational Biomedicine and Neuroscience, University of Bari Medical School, Bari, Italy*

*Corresponding author. Email: saverio.cinti@icloud.com, s.cinti@staff.univpm.it



Elio Raviola, a scientist and professor emeritus in the Department of Neurobiology at Harvard Medical School passed away on December 23, 2023, at the age of 91. Elio was born on June 15, 1932, in Asti, Italy, son of Giuseppe and Luigina (Carbone) Raviola. While at Ghislieri College in Pavia in 1953, as a third-year medical student, Raviola met Giuseppina d'Elia (1935-1986), a first-year student at Collegio Castiglioni-Brugnatelli, just across the street from Ghislieri. Both worked on similar research topics, and Giuseppina became a member of the same Institute of Anatomy at the University. Elio and Giuseppina were married in Pavia in 1960. With his medical degree Raviola spent several years engaged in training as a specialist in neurology and psychiatry, managing a unit at the local mental hospital. Elio obtained his Ph.D. in 1963 at the age of 31 and was an Assistant Professor in the Institute of Human Anatomy from 1958 to 1971.

PAVIA TO BOSTON, 1965-70

In 1960, Elio found himself frustrated by the pace of his academic progress and felt that he needed mentorship. He took a train to meet with Professor Rodolfo Amprino (1912-2007) at the University of Bari. Amprino was a student of the famous Italian anatomist Giuseppe Levi (1872-1965). The schools of Golgi and Levi had been intellectually in disagreement with one another at the time, as Levi was an acolyte of the Spanish neuroscientist Santiago Ramón y Cajal (1852-1934). So, when Elio asked Amprino if he would take him in his department, Amprino suggested that such a change would destroy Raviola's career in Italy. Amprino suggested that Elio go to the U.S. for several years for a new experience, and then later transfer to his lab in Bari. In 1963 Amprino provided Elio with the address and the name of an Italian scientist working in the US, Rita-Levi Montalcini (1909-2012). From Levi-Montalcini he received advice for a possible research activity in the United States. Then Elio hoped to spend time in the labs of Don Fawcett at Harvard University. Fawcett invited both Elio and his wife Giuseppina to work for a year as Research and Teaching Fellow, respectively, in Anatomy at Harvard Medical School, from 1965-66. On arrival to Boston, Elio and Giuseppina, were given an empty lab space by Fawcett, who told them to make a list of reagents and other equipment they needed to demonstrate their scientific aptitude in short order. The trial period went well. However, while he was offered a position by Fawcett, Elio and Giuseppina returned to Italy due to her developing an illness, requiring treatment. She recovered in Italy, and they were pursued by Fawcett to return to Boston. In 1970 Raviola accepted Fawcett's invitation as Associate Professor of Anatomy.

Elio remembered the day, October 23, 1970, arriving at Logan Airport and being greeted by various professors in the department, including Susumu Ito (1919-2015), Jean-Paul Revel (1932-2021), Betty Hay (1927-2007) and others. The couple led the introductory medical school courses in Anatomy at Harvard and Boston University, respectively, while also developing successful, separate, research careers focused on the retina.

Over many years he developed a very close friendship in the department, with Torsten Weisel. It was a very collaborative scientific environment, in which everyone was proud of the success of mentors and colleagues like Weisel, Fawcett, Stephen Kuffler (1913-1980), Ito, David Hubel (1926-2013), Baruj Benacerraf (1920-2011), and others from the very beginning. Elio would say, "Don was an extraordinary man. Torsten is an extraordinary man. Sus was an incredible scientist".

SCIENTIST AT HARVARD MEDICAL SCHOOL, 1970-2023

Elio became Associate Professor of Anatomy in 1970, Professor of Anatomy in 1974, Bullard Professor of Neuroanatomy and Professor of Ophthalmology in 1989, Bullard Professor of Neurobiology in 1993, and Professor Emeritus in 2013. He dedicated himself to research on the nervous system for sixty-six years. He led a laboratory in the Departments of Anatomy and Neurobiology at Harvard Medical School for fifty-three years, from 1970 to 2023. Elio received numerous offers for leadership roles in other departments early in his Harvard career. These included offers for chairs at Cal Tech, the position of Dean at Washington University in Saint Louis and the University of Pennsylvania, and an invitation from Johns Hopkins as well. He stayed at Harvard because, simply, he didn't want to be a Chair, and was happy in the department at Harvard.

Elio evolved to become an expert of cell biological, electrophysiological, and molecular techniques, solving problems of structure, connectivity and physiology of the retina, the part of the eye that received and processes signals from light. He was interested in how the retina can encode information from the visual scene, and then send the encoded information to the brain. Over six decades he contributed to evolving, foundational knowledge in the field of neurobiology, while continuously learning new methods to effectively respond to new scientific questions.

With Wiesel, 1981 Nobel laureate in physiology or medicine, he developed not only a wonderful friendship, but also an experimental model of myopia (near-sightedness). They studied how alterations of the visual experience during the postnatal growth of the eye leads to myopia. They discovered that the eye elongation that leads to myopia is mediated by the nervous system, specifically by growth regulating chemicals produced in the retina itself. Also, with Ramon Dacheux II (Ray) in the 1980's he conducted novel studies of the way in which the photoreceptors, the cells that receive and process light, interact with secondary neurons in the initial processing of visual information.

After Raviola obtained an NIH grant entitled "Cell Communication in the Retina", Ray built a setup for visual stimulation and intracellular recordings from the rabbit eyecup and thus began a fruitful collaboration that lasted 14 years.

Throughout the years of their collaboration, twice a week Ray and Raviola were recording from rabbit retinal cells and injecting them afterwards with horseradish peroxidase (HRP). The experiments lasted from ear-

ly in the morning through most of the following night and Ray would then sleep at Raviola's house. They spent more time together than both did with their families and became intimate friends. Ray was a virtuoso of the job well done and was endowed with unusual manual skills: his were the hands of an artist. Very few things in life are as rewarding as sharing the joys and frustrations of scientific discovery with a trusted colleague of great intellectual integrity and the same aspiration for excellence. Ray and Raviola devoted their investigations to the neural network encoding the signals of rod photoreceptors in the rabbit retina: they analyzed the structure of rods isolated from the adult retina and correlated the response properties of horizontal cells with their morphology and synaptic connections with the photoreceptors (1982, 1990). They obtained the first electrophysiological recordings from H1 horizontal cells in the rhesus macaque and showed that these cells were homologous to the axon-bearing horizontal cells of other mammalian retinas (1990). At the time, there were uncertainties on the response properties of rod bipolars, until Dacheux and Raviola showed that they responded to light with a transient-sustained depolarization dominated by rods and had a center-surround organization of their receptive field. Therefore, the dyad synapse established by rod bipolars with the two depolarizing amacrine cells postsynaptic to them (A2 and A17 or S1/S2) was excitatory and sign-conserving (1986, 1987, and 1989).

This work was followed by a series of papers with Enrica Strettoi (now a senior investigator in the Institute of Neurophysiology of the National Research Council in Pisa, Italy), in which the synaptic connections of the neurons that carry rod signals to ganglion cells, rod bipolars, A2 amacrine and cone bipolars, were reconstructed from continuous series of thin sections analyzed with the electron microscope. These papers established unequivocally that 'the rod pathway in the rabbit piggybacks the cone pathway and thus gains access to a single set of ganglion cells that are driven by both rods and cones (1990, 1992, 1994).' (Visual Neuroscience, 2007;24:445-447). Elio had several other collaborations within the department and with experts at other institutions. Most often these collaborations were grounded both in professional respect, and in loving friendship forged over both warm exchanges of scientific ideas, as well as time spent together outside of the laboratory. This included Tom Reese, Steve Sugrue, and others. Through the 1990's Elio was able to transition from an anatomist to cell biologist, to a molecular biologist. He had most recently directed his efforts to characterizing the role of each neuron cell type, focusing on the ways in which amacrine cells in the retina uniquely release

the neurotransmitters dopamine and GABA, as well as seeking to understand the specific function of this mechanism in human adaptation to light. Using a multidisciplinary approach with colleagues he identified all the transcripts present in dopamine amacrine cells, discovered the presence of the common clock-related proteins in those cells (with Stefano Gustinich et al.), showed that some amacrine cells spontaneously release dopamine and GABA through different mechanisms (with Michelino Puopolo et al., and Hajime Hirasawa et al.), and he described a unique set of synaptic contacts made by dopamine amacrine cells at nodal points of the retinal network needed to optimally shape retinal light adaptation (with Massimo Contini et al., Richard Masland et al.). He described much of this work as follows: "Our understanding of the computations carried out by neural networks in the central nervous system is limited by our incomplete knowledge of the diversity of cell types and the multiplicity of their functions. In the retina, over fifty cell types encode the spatial, temporal, and chromatic parameters of the incoming light stimuli to generate the messages of action potentials that travel to the brain along the fibers of the optic nerve. We have combined molecular techniques with microscopy and electrophysiology to study a rare cell type in the retina, the dopaminergic amacrine (interplexiform cells)." (Raviola E. A molecular approach to retinal neural networks. Functional neurology. 17(3). 2002.). Constance L. Cepko, Bullard Professor of Genetics and Neuroscience at Harvard Medical School remembers when Elio approached her at the turn of the 1990's about her supporting his learning newer methods in her laboratory. While he was a visiting professor in her lab, he behaved as a visiting post-doctoral student: "He came to my lab to learn molecular biology. He kept the most beautiful, neat, and complete lab notebook that I had ever seen. I used it as an example to my students and he was so courageous, at his august stage in life (in his 60's), to become a novice in a new field. He was able to learn enough to return to his lab and use the new methods to make a transgenic mouse that labelled the dopaminergic neurons that he wanted to understand. It led to a beautiful study of the synapses of that cell type, made possible by his mastery of anatomy and physiology, combined with molecular biology." Moving into the new millennium and beyond, Elio continued to be deeply engaged in the intellectual life of the Department of Neurobiology at HMS and found the department to be "extraordinary." Of the strengths of the department, he recently wrote: "A varied approach to neuroscience, total freedom to express oneself, a friendly atmosphere of openness, mutual respect and generosity that leads to rapid circula-

tion of ideas and collaborations, and a Chair concerned about the welfare of the faculty.” He saw the mission of the department to be one of “advancing knowledge of the brain by combining rigorous molecular, cellular and behavioural techniques.” He greatly appreciated both formally and informally convening with his departmental colleagues in an environment that encouraged the sharing of ideas on a wide range of topics related to science, culture and the personal. During COVID-19, he continued going into the department five days per week for most of the pandemic, when physical return to the medical school was permitted. He continued to have close rapport with several close friends and colleagues in the department. He felt at home in the Department as well as an incredible feeling of gratitude for the community of scientists and friends he had there.

Raviola did not only deal with the retina and the nervous system. It is important to mention that the clearest morphological evidence concerning the existence of the blood–thymus barrier may be attributed to the collaborative work published in 1972 by Morris Karnovsky and Elio Raviola. Raviola and Karnovsky, using HRP as a permeability tracer, demonstrated that the venules at the corticomedullary junction are the site of leakage for blood antigens, while the capillaries draining the cortex are largely impermeable. Other permeability studies have confirmed the existence of a blood–thymus barrier, which allow the access to low molecular weight tracers, while most exclude high molecular weight particles.

TEACHING OF ANATOMY, 1970-2002

He was responsible for the Introduction to Anatomy course for entering, first-year Harvard medical students. He directed the course for thirty years, from 1972 through 2002, also lecturing extensively in Histology and Neurobiology to both medical and graduate students. His excellence as a teacher was recognized instantly by students and faculty alike. In 1972 Raviola received the Boylston Society Award for excellence in teaching at Harvard Medical School, as well as multiple subsequent pre-clinical teaching awards. He was called by some students “The Italian Master” In the dissection room he not only taught the students methods of dissection and anatomical detail, but also reviewed the history of anatomical discovery over the past several thousands of years.

With a remarkable memory, he could quote Cicero, Julius Caesar and Dante verbatim from his high school lessons.

Elio was known for his remarkable lectures, which were a dramatic and artistic performance, cherished by

students for decades. He would come to the lecture hall early in the morning and draw detailed, beautiful pictures in colour on the black board, using French art chalks.

Between 1986 and 2002 Elio co-led the human anatomy course at Harvard Medical School with Daniel Goodenough. His excellence as a teacher was documented in the television documentary series *Chronicle and Nova*. Trudy Van Houten, former Director of the Clinical Anatomy Course and Co-director of the Human Body Course at Harvard Medical School, notes that “His lectures were legendary: beautifully organized, original and ingenuous, wonderfully humorous, and full of surprises. They were carefully crafted lessons that included exactly the information students needed, combined with the brilliance and charm necessary to keep students captivated from the first to the last sentence and in memory even decades later. They were, first and foremost, lessons directed at the students who listened to them. His lectures remain unforgettable...I also remember his incredible tact when I was a new anatomy instructor in his anatomy lab at HMS and how generously, and diplomatically, he shared both his knowledge of anatomy and his knowledge of effective anatomical teaching. I also recall, with admiration, how he managed the extraordinary feat of dividing his time, relatively evenly, among eight dissection tables all clamouring insistently for his attention.” “Elio was an amazing scientist and extraordinary person. His aesthetic sensibilities influenced his beautiful anatomical studies, as well as his students and admirers,” says Carla Shatz, Professor of Neurobiology at Stanford University and a pioneer in early brain development “Elio was a scholar and intellectual of the old school. He had a sense of his discipline’s history and tried to convey the same in his lectures, demonstration, and tutorials. His colleagues appreciated these attributes as well,” notes James Adelstein, Executive Dean for Academic Programs at Harvard Medical School from 1978-97.

MENTORSHIP OF YOUNG SCIENTISTS, AND SERVICE TO HARVARD AND SCIENCE IN ITALY

Elio was a dedicated mentor to many young scientists as well as a trusted advisor to leaders at Harvard Medical School.

Michelino Puopolo, Associate Professor at Stony Brook University notes that “when I first arrived in Boston in 1998, Elio was like a second father to me.”

Richard Born, Professor of Neurobiology and a former director of the HMS Ph.D. Program in Neuroscience recalls: “Elio was such a wonderful man, colleague and scientist”.

Matthew Lawrence at the St. Kitts Biomedical Research Foundation notes that “He was a source of wise and valued counsel at every important professional step from pursuing graduate training, then medical school and ophthalmology, and subsequent commitments to translational science and institution building”.

Elio was very active in efforts to strengthen Italian science, including the creation of the Italian Institute of Technology and the establishment of the Giovanni Armenise-Harvard Foundation. In advising the Armenise-Harvard Foundation, which supports basic scientific research at Harvard Medical School and in Italy, he worked in a focused way to help the careers of young, promising Italian scientists. He mentored Italian post-doctoral fellows in his laboratory, including Massimo Contini (University of Florence), Stefano Gustincich (Italian Institute of Technology Genova), Adalberto Merighi (University of Turin), Michelino Puopolo (Stony Brook University), and Enrica Strettoi (Institute of Neuroscience at the Italian National Research Council in Pisa). He cherished engaging with Italian collaborators with independent careers, including Giovanni Berlucchi (University of Verona), Emilio Bizzi (Massachusetts Institute of Technology), Saverio Cinti (University of Ancona), Cesare Montecucco (University of Padua), Enrico Mugnaini (Northwestern University), and Paolo Pinelli (University of Pavia, Catholic University in Rome, University of Milan).

Enrica Strettoi, Director of Research at the Institute of Neuroscience at the Italian National Research Council in Pisa notes that: “Elio was my undisputed scientific mentor, the one who believed in me when I was little more than a little girl, who convinced me that I could do it and win a place in the research academy. His enthusiasm, passion for microscopy, intuition of the importance of what you see but which not everyone is able to decipher, they infected me many years ago. I hope I have passed on a bit of all this also to my students, to whom I often turn using his own words...He was so generous, both in a human capacity and scientifically, and was for me my first home in professional terms, the place where I would mentally go when I feel in difficulty or had fear that I was not up to something scientifically that seemed too complex. I was incredibly fortunate to cross paths with him and equally lucky to maintain his respect and esteem. I went to him in very difficult moments as well as in those moments of great professional recognition: his consistency has always been admirable and striking, as he knew how to be himself on every occasion, with wit, clarity, and passion.”

He received honorary degrees from the University of Ancona in 1996 and the University of Turin in 2002.

In 2002 he was also awarded the Ottorino Rossi Award from the University of Pavia, presented to a scientist who has made an important contribution to research in the field of neurosciences.

Stefano Gustincich, Principal Investigator at the Italian Institute of Technology in Genoa, recalls 30 years of memories when “Elio was a father-like figure nurturing my growth as both a scientist and a human being.”

Massimo Contini, Professor at the Università Degli Studi di Firenze notes that “I loved him. It was certainly one of the fundamental meetings of my life. I can’t summarize the meaning of this friendship in a letter, we were lucky to have had him in our lives. The memory of his intelligence, his irony and his energy will remain forever.” Saverio Cinti, Professor at the University of Ancona, notes that “I always had the ambition to consider myself his student and his younger brother. I will always remember him with great affection, and I will greatly miss his passionate stories of the Pavia period. His words have always been an example and my entire academic life has been influenced by him, especially the great passion for scientific research so expertly pursued and appreciated about him throughout the world.” The period of his university education as a student at the Ghislieri College, in a University of Pavia that was still epically “Golgian”, because it was populated by professors who had known Camillo Golgi, has always remained alive in his mind. And throughout his life he always showed a great passion for the history of medicine. With one of us he wrote a historical-critical article on Golgi’s discoveries and theories of brain functioning (Raviola and Mazzarello, 2011).

Cesare Montecucco, Emeritus Professor at the University of Padua notes that “Elio put truly exceptional care and energy into advancing his students... He was a great man. We were different ages, but we came from the same world, and we immediately understood each other’s way of seeing life and science.”

Elio served the Departments of Anatomy and later Neurobiology at Harvard under the leadership of five Chairs: Don Fawcett, Betty Hay, Carla Shatz, Michael Greenberg, and David Ginty. He worked in the Departments of Anatomy and Neurobiology from October 1970 to April 2023. Raviola saw his mentorship of students (both medical and research) and colleagues in the department as central to his usefulness as he advanced in age. Into his 80s, he served on the HMS Subcommittee of Professors, the Prizes and Awards Subcommittee, the Honors Committee, the Armenise-Harvard Foundation Junior Faculty Grant Review Committee, the Armenise-Harvard Foundation Scientific Advisory Board, the Armenise-Harvard Foundation Italian Schol-

arship Advisory Committee on Career Development Awards, the Excellence in Mentoring Award Selection Committee, the Council of Mentors Subcommittee, and he chaired meetings of the Graduate Student Advisory Committees.

With a great pride in being a part of the American scientific experience, Raviola noted the difficulty of feeling neither Italian nor American, “a person without a country.” Fundamentally identifying himself as a scientist, Raviola had a clear vision for the evolution of science in the U.S. and globally; he connected the evolving scientific landscape to the political environment. He was concerned that “the best young scientists are no longer coming” to the U.S., a research environment which he felt had offered him the freedom and support to manifest his own creative capacities and gifts to the ultimate degree.

REFERENCE

Elio Secondo Raviola (June 15, 1932-December 23, 2023). Remembrances from his Family, Friends and Colleagues on the occasion of his Memorial Service April 21, 2024. The American Academy of Arts and Sciences Cambridge, Massachusetts, USA.