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IN MEMORIAM

In Memoriam: Marcello Costa (1940–2024) – a pioneer of the enteric nervous system

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It is with sadness that we announce that Marcello Costa, our dear friend and colleague, passed away peacefully at his home in Seacliff (Adelaide, South Australia) on Sunday 14 April 2024.

Professor Marcello Costa (AO, FAA) was a pioneer and leader in the field of autonomic neuroscience, specifically the intrinsic neural circuits of the enteric nervous system. From the mid-1970s to 2023 he led a series of studies characterising enteric neuronal pathways, particularly those related to gastrointestinal motility. His work traversed many disciplines including anatomy, histology, physiology and pharmacology through to electrophysiology. His papers often combined multiple approaches well before 'multi-disciplinary research' became fashionable. In later years he led the development of methods to objectively analyse gastrointestinal motility patterns, combining multi-dimensional maps of diameter, length and pressure with recordings of smooth muscle electrical activity. His quantitative accounts of complex motility patterns far surpassed the descriptive summaries that had previously characterised this field. His work was driven by a goal to demystify how cells of the gut work together to give rise to simple, adaptive behaviour patterns.

History

Marcello was born on 9 January 1940 in Turin, Italy. In his childhood, he spent a lot of time at the family's apartment in the High Susa Valley to the west of Turin. Here, he developed a life-long love of mountains. He and his family (mother: Verbena, stepfather: Augusto and older brother: Giorgio) moved to Buenos Aires, Argentina, in 1949. He attended the High School San Martin and the public Italian High School of Buenos Aires, finishing school in early 1960. Later that year, Marcello moved back to Turin to study medicine. However, between these moves he fitted in joining an expedition to explore the continental icepacks of Patagonia, venturing into barely mapped territory. A few months later, Marcello undertook another trip with his brother Giorgio, climbing mountains in Peru and descending the Ucayali and Amazon rivers.

His time at the Universita di Torino was intense. Not only did he become heavily involved in student politics (elected as Leader of the Student Centre Left Party) but he also trained in mountain climbing with the Gervasutti School of the Torino Alpine Club, played guitar in a jazz band and joined the student choir. He also undertook a research internship in the Departments of Anatomy and Histology under the supervision of Giorgio Gabella. Using a newly discovered technique (the 'Falckh–Hillarp method') to visualise monoamine transmitters (Falckh et al., 1962), Marcello undertook microscopy studies that led to 11 publications between 1965 and 1970 and award of his MD (Gabella & Costa, 1968).

After graduating in Medicine and Surgery in 1967, Marcello did compulsory military service, finishing in 1969. Shortly thereafter, at a scientific meeting in Venice, he got talking to Professor Geoff Burnstock. An offer soon arrived by mail, inviting Marcello for an 18 month post-doctoral fellowship in Geoff's lab at Melbourne University. Marcello married his girlfriend Daniela Tuffanelli in May 1970 and shortly after set out for Australia; Daniela followed a few months later.

On arriving at Melbourne University, Marcello met John Furness and they discovered many shared interests and ideas. Together, they extended studies on peripheral

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aminergic innervation. This was the start of a long and productive collaboration which continued until 1988. There was a brief interlude when Marcello's funding ran out and he had to return to Europe in 1973. Fortunately, he was soon invited back to Melbourne, within the year, but in 1974 Geoff Burnstock announced that he would be moving to University College, London. The group at Melbourne University dispersed; John Furness was offered a lectureship in Anatomy and Histology in the new Flinders University School of Medicine in Adelaide. In 1975 Marcello accepted a lectureship in Human Physiology also at Flinders University, where he remained for the next 47 years. He retired as Mathew Flinders Distinguished Professor in 2021, at the age of 81, retaining his links as Emeritus Professor.

Scientific achievements. At a young age, Marcello was given a small microscope; this opened up an intriguing new world of tiny objects. As a teenager he sold his beloved bicycle in order to buy a better microscope, capable of resolving bacteria. He spent many hours entranced by different types of protozoa moving in pond water.

This early love of microscopy may have prepared him for his research as an intern under the critical eye of Professor Giorgio Gabella. He carried out an extensive series of histochemical studies localising amine transmitters in the autonomic nervous system, working with Giorgio Gabella (Gabella & Costa, 1969), then John Furness (Costa & Furness, 1971) and, during a sabbatical at the University of Helsinki, with Olavi Erankö (Costa et al., 1974). These studies were notable for being more than simple descriptions – crushes and lesions were applied to identify the projections of aminergic nerves. For the first 10 years of his career, Marcello's publications were dominated by studies of aminergic pathways.

After his move to Flinders University, Marcello's head of department was Laurie Geffen. Robert Rush joined the department shortly after Marcello. Together with Bruce Livett at Monash, Geffen and Rush had published one of the first studies using antibodies to localise macromolecules in nerve cells (Livett et al., 1971). With Marcello's interest in localisation of neurotransmitters, the stage was set. In 1977 Marcello and colleagues obtained an antiserum that bound the neuropeptide somatostatin. They used it to reveal varicose axons and cell bodies immunoreactive for this neuropeptide in the gut wall (Costa et al., 1977). They concluded, with remarkable insight, that somatostatin may be expressed by a population of interneurons in the enteric nervous system – a proposal that was confirmed many years later.

Work on amines continued, but a new series of studies commenced, using immunohistochemical methods to reveal neuropeptides and other molecules including Substance P (Franco et al., 1979), VIP (vasoactive intestinal peptide) (Furness & Costa, 1979), tyrosine hydroxylase and dopamine beta hydroxylase (Furness et al., 1979), 5-hydroxytryptamine (Costa et al., 1982), enkephalin (Furness et al., 1983), GRP (gastrin-releasing peptide) (Costa et al., 1984), galanin (Furness et al., 1987) and calbindin (Furness et al., 1988). Costa, Furness and colleagues combined multi-labelling immunohistochemistry with methods to study projections of axons, including specialised operations. Enteric neural pathways were lesioned with a cut made around the circumference of the intestine ('myotomy') or by removal of a segment of myenteric plexus from the full circumference ('myectomy'). From the degeneration of axons and accumulation of axonal cytoplasm proximal to damage, the length and polarity of projections could be estimated. The publication of a method to optimise histochemical and immunohistochemical labelling in peeled whole-mount preparations further improved the analysis of projections and soma-dendritic morphology (Costa et al., 1980).

For many antigens, immunohistochemical localisation was supplemented by biochemical measurement of the antigens in tissue, adding a quantitative validation of methods. The discovery that many immunohistochemically detected molecules were expressed by subsets of enteric neurons led to the idea that they could be considered as 'markers'. Marcello and colleagues provided early reports showing that single neurons could express multiple neuropeptide transmitters (Costa et al., 1988). Their wide-ranging immunohistochemical analysis firmly established the reputation of Marcello and his colleagues as leaders in the field of enteric neurobiology. A review published in 1986 introduced the concept that combinations of markers could be used to distinguish different functional classes of autonomic neurons (Costa et al., 1986): 'the results point to the principle that the enteric neurons, and other autonomic neurons, are subdivided into groups with well-defined combinations of chemical messengers (chemical coding), well-defined projections (ie: origins, terminations and connections) and well-defined functions.' The influential concept of chemical coding of neurons was established.

A few years later, Joel Bornstein joined the laboratory, bringing expertise in electrophysiological recording which he combined with intracellular dye filling and immunohistochemical labelling to create a multi-faceted analysis of enteric neurobiology (Bornstein, Costa, et al., 1984). It quickly became apparent that not only were immunohistochemical markers selectively expressed, but so were electrophysiological features and soma-dendritic morphology. This methodology was then combined with selective lesions (Bornstein, North, et al., 1984) to investigate the pathways responsible for the mysterious slow excitatory post-synaptic potentials discovered by Jackie D. Wood in 1978 (Wood & Mayer, 1978).

A series of innovative studies followed, concentrating on the intrinsic and extrinsic innervation of the gut, mostly in guinea pigs. Findings included the identification of substance P and CGRP (calcitonin gene-related peptide) coexisting in a subset of spinal nociceptors (Gibbins et al., 1985). Sympathetic neurons projecting to the gut were shown to express different combinations of neuropeptides depending on their targets and function (Macrae et al., 1986). These approaches were expanded to human tissue obtained from elective surgery in the Flinders Medical Centre by David Wattchow and Janet Keast (Keast et al., 1984; Wattchow et al., 1988). Later, methods for maintaining the intestine for several days *ex vivo* in organ culture were developed by Marcello and his colleague Simon Brookes, allowing the application of retrograde tracing of neurons in both animal and human tissue (Brookes & Costa, 1990). This allowed more precise analysis of projections and pathways of enteric neurons in human and animal intestine in a series of papers.

These studies accumulated a huge amount of information about the enteric nervous system and its organisation, but the data were very fragmented. Marcello was determined to combine these data into a single, cohesive account by exhaustively studying many combinations of markers and quantifying their overlap. In a landmark paper in 1996, Marcello distinguished 14 classes of myenteric neurons, on the basis of co-localisation of nine different markers which could be combined with four classes of submucosal neurons identified previously. This made the enteric neurons of the guinea pig small intestine one of the most comprehensively characterised innervated preparations of any mammal and provided a foundation for interpretation of many later studies (Costa et al., 1996).

With this major goal achieved, Marcello used this account as a foundation to characterise the basis of motility patterns of the small intestine. With Marcello Tonini from the University of Pavia he measured smooth muscle activity in *ex vivo* preparations (Tonini & Costa, 1990) with novel watertight partitions so that drugs could be added selectively to specific parts of motility reflex pathways. This method has been widely used by a number of groups internationally.

In the late 1990s, Marcello led several studies of peristalsis in the guinea pig small intestine (Waterman et al., 1992; Waterman, Costa & Tonini, 1994; Waterman, Tonini & Costa, 1994). A PhD student, Grant Hennig, was charged with measuring diameter changes from video recordings. This was time-consuming and demanding, but Grant had programming skills and wrote a routine to count the total number of pixels across the gut wall using NIH Image software. This method created unmanageably large datasets of measurements. Grant tried converting the numbers to greyscale pixels, which elegantly visualised the data. When Marcello saw this image he instantly recognised its potential. The greyscale images showed pale, angled streaks of propagating contractions and darker areas where content was accumulating. A casual glance could distinguish peristalsis from other motor patterns. It was easy to quantify the wavelength, amplitude, rate of propagation and frequency of events. Marcello used these 'spatio-temporal maps' as a powerful new way to quantify motility patterns for quantitative study; this was a huge advance over previous descriptive analyses (Cannon, 1902). Interestingly similar maps were developed at nearly the same time in two other laboratories (Bercik et al., 2000; Bouchoucha et al., 1999).

In 2008, Nick Spencer joined Flinders University and soon after Marcello joined Nick's laboratory, for the next 13 years until his retirement in 2021. This was an incredibly productive and dynamic era – a time of great energy, vision and innovation. It was also Marcello's most productive publication period. It was a true honour having Marcello perform hands-on experiments in the laboratory of N.J.S., right up until he retired at 81 years of age. This period also involved extensive collaboration with Phil Dinning and Lukasz Wiklendt, where Marcello combined intraluminal pressure maps with spatio-temporal maps of wall movements and focal recordings of electrical activity (Fig. 1) (Costa et al., 2021; Dinning et al., 2011). During this time in Nick's laboratory, Marcello produced a series of at least 30 key papers, detailing interactions between neurogenic and myogenic mechanisms in the small and large bowel of several species with remarkable quantitative precision.

Human studies

Marcello had a clear vision on how to translate his research into the clinical world. Live specimens of human

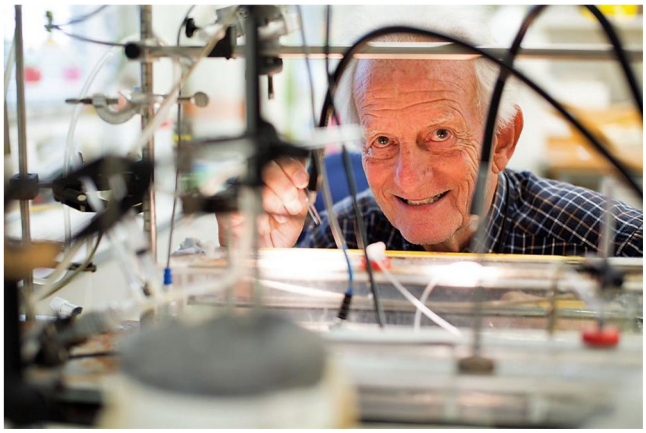

Figure 1. Marcello Costa in the laboratory in 2019 performing an experiment on isolated guinea-pig intestine
The photo includes Marcello's novel method of combining intraluminal pressure changes with electrical recordings and spatio-temporal D-mapping technology.

gut could be obtained (with appropriate permits) from surgeons operating in the same building. This pathway was established by David Wattchow, a colorectal surgeon who did his PhD with Marcello and John Furness. David's efforts made it possible for many studies in animal tissue to be tested in human tissue over ensuing decades. Specimens were taken from the healthy segment of the small or large intestine resected in the treatment of malignancy. In the laboratory they were studied anatomically under the microscope (Wattchow et al., 1995) or physiologically in organ baths (Carbone et al., 2013) in the labs of Simon Brookes and Nick Spencer. Several surgical trainees carried out PhD studies on these specimens, supervised by Marcello.

Marcello was impressed by the work of Dr Anthony Bauer from Pittsburgh, USA, who had shown in animals that anti-inflammatory drugs were candidates to treat post-operative ileus (Bauer & Boeckxstaens, 2004). With David Wattchow and clinical colleagues, a large clinical trial of the use of anti-inflammatories in abdominal surgery was undertaken (Wattchow et al., 2009). Thus, Marcello was involved in study of the human enteric nervous system from the level of the cells, muscle strips and organ bath recordings through to the whole patient and therapeutic applications. He fostered the collaborations that made this happen.

Flinders University

Marcello was extraordinarily well read in non-fiction. He had a collection of several thousand books by contemporary philosophers, mathematicians, modellers and scientists. His study of knowledge itself formed a strong underpinning for his research, and a firm foundation for his humanist beliefs. He was enthusiastic about sharing knowledge and this was evident in his lectures. Throughout his 47 years at Flinders University he held a mixed lecturer/researcher appointment. His lectures to students were eloquent, authoritative and carefully structured. Generations of medical students remember his teaching of neuroscience and physiology, delivered with his distinctive accent. Many young researchers encountered him at scientific meetings and benefited from his perceptive and focused questioning. He supported many junior scientists, going out of his way to provide encouragement and advice. His questions often had a long preamble, but were always followed by an incisive query or comment.

Other contributions

Marcello would be the first to acknowledge that form-filling was not his forte. However, his enthusiasm for good causes more than made up for this. He played a key role in setting up the Centre for Neuroscience at Flinders in 1977 and in 1980−1981 was instrumental in turning the Australian Neuroscience Society into the vigorous formal entity that thrives to this day (renamed the Australasian Neuroscience Society, ANS). In 1994, Marcello served as President of the ANS. He was on the organising committee of 23 research conferences. He also founded the South Australian Neuroscience Institute (SANI) in 2003. Its goal was to unite and coordinate neuroscientific research, education, services and commercialisation. As co-chair, he took on many roles and organised over 20 public forums including several during International Brain Awareness Week. Other talks were held under the title of 'Science outside the Square'. SANI developed links with the Physical and Neurological Council of South Australia, and developed a Graduate Certificate in Neuroscience (Learning) for teachers.

Marcello had a strong belief that leaders should be answerable for their decisions. He had a well-developed sense of fair play and was fearless in university meetings. He was equally outspoken about the misuse of science, especially the promotion of pseudo-science by unscrupulous operators. He was a founding member of Friends of Science in Medicine and openly challenged bogus claims, while championing the value of evidence-based medicine in numerous interviews on radio and television.

Marcello outside the university

In his childhood, Marcello showed a real talent for painting and drawing. This ability was later used in his scientific drawings, some of which have become discipline classics. After moving to Adelaide, he became a keen windsurfer, taking up the sport in its early days. He was noted for some of the long-distance journeys he made; windsurfing to Kangaroo Island, Yorke Peninsula and along much of the 100 km length of the Coorong lagoon. He appreciated art and created a series of YouTube videos on the history of art and perspective. Last, but not least, Marcello was also a family man. He and Daniela have a son, Andre, who is now a successful academic at the University of Adelaide. Marcello was also the father-in-law of Kat, grandfather of Harry, Orlando and Heidi, and brother of Giorgio.

Accolades

Marcello received many awards and accolades during his long career. These included appointment as Fellow of the Australian Academy of Sciences in 1989. In 1992, he was honoured with the title of 'Cavaliere della Repubblica Italiana'. In 2001, he was awarded the Australian Centenary Medal. In 2018, Marcello was

awarded the inaugural Lifetime Achievement Award by the Federation of Neurogastroenterology and Motility Societies and, in 2020, he was appointed as an Officer of the Order of Australia. The latter honour is given by the Governor General of Australia for contributions to Australian society.

However, perhaps his greatest accolade was the respect and affection of the many people who he personally interacted with, in his many areas of interest. In the world of university and science he influenced undergraduates, medical students and many leading scientists in neuroscience and neurogastroenterology. Many of his colleagues referred to him as a 'renaissance man' on the basis of his mastery of multiple fields of knowledge, combined with a deep culture and education. His belief in the value of scientific understanding was unbounded. His own work added enormously to that store of knowledge but, in addition, he encouraged many researchers, junior and senior, in their quest for discovering new knowledge. Marcello was not only a great scientist, ambassador, teacher, public advocate and family man, he was also our friend and inspiration. We miss him deeply.

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Additional information

Competing interests

No competing interests declared.

Author contributions

N.S.: Conception or design of the work; Drafting the work or revising it critically for important intellectual content; Final approval of the version to be published; Agreement to be accountable for all aspects of the work. S.B.: Conception or design of the work; Drafting the work or revising it critically for important intellectual content; Final approval of the version to be published; Agreement to be accountable for all aspects of the work. D.W.: Conception or design of the work; Drafting the work or revising it critically for important intellectual content; Final approval of the version to be published; Agreement to be accountable for all aspects of the work.

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Supporting information

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Peer Review History