

Marcello Costa (1940–2024)

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ABSTRACT

Marcello Costa (1940–2024) was a leading researcher in neuroscience. He was a lecturer in the School of Medicine at Flinders University in Adelaide, Australia for forty-seven years; during this time his research concentrated on the autonomic nervous system, particularly the gastro-intestinal tract and the control of motility. He published many multi-disciplinary studies based on a wide range of highly innovative methods. He played a key role in defining the roles of neuropeptides, in devising methods to characterise different classes of nerve cells, and in the quantitative analysis of intestinal motility. He was also a humanist and a passionate advocate for public education in science.

Keywords: autonomic nervous system, enteric nervous system, gastrointestinal motility, immunohistochemistry, intestinal physiology, neuropeptides, neuroscience, smooth muscle.

Family background

Marcello (Fig. 1) was born on 9 January 1940 in Torino, Italy. He was the second of two children of Verbena and Dalmiro Costa. His family divided their time between the city and their house in Sauze d'Oulx in the High Susa Valley, west of Torino. Now a fashionable ski resort, in the 1940s it was an area of forest and mountains where Marcello and a tribe of local children roamed the countryside. As the smallest and youngest, Marcello was excluded from some of the gang's more ambitious expeditions, and had to entertain himself exploring the wildlife closer to home. Marcello's father was actively anti-fascist and was captured by the Germans in 1944. He survived imprisonment, but tragically died shortly after the liberation of Italy.

Education

In 1949, when he was nine years old, his family (mother Verbena, stepfather Augusto, and older brother Giorgio) moved to Buenos Aires, Argentina. While attending the Italian High School of Buenos Aires, several friends of the family introduced him to diverse aspects of philosophy, an interest that he maintained for the rest of his life. As a child, Marcello was given a small microscope. He was so captivated by the world of tiny objects that he sold his beloved bicycle to purchase a more powerful instrument. The excitement of exploring sectioned material and watching live protozoa fed his imagination; the thrill of seeing new things in the microscope stayed with him for the rest of his life.

Marcello showed a real talent for painting and drawing in his childhood and adolescence. This ability was later used in his scientific diagrams, some of which have become discipline classics. In later years, he created a series of YouTube videos on the history of art and perspective. As an adult he became a keen windsurfer, taking up the sport in its early days. He was noted for some of the long-distance journeys he undertook: windsurfing from the mainland to Kangaroo Island, Yorke peninsula, and along much of the 100 km length of the Coorong lagoon. He was also a guitarist and sang in an Italian folk choir in Adelaide. Marcello was also a family man (see Fig. 2). He and Daniela have a son, Andre, and he was father-in-law of Kat, grandfather of Harry, Orlando, and Heidi, and brother of Giorgio.

Published: 16 September 2025

Cite this: Brookes, S. J. H. and others (2025) Marcello Costa (1940–2024). *Historical Records of Australian Science*, **36**, HR25008. doi:[10.1071/HR25008](https://doi.org/10.1071/HR25008)

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Fig. 1. A formal portrait of Marcello in 2019 (photography by David Summerhayes CC BY-SA 4.0 (<https://creativecommons.org/licenses/by-sa/4.0/>)).



Fig. 2. Marcello, Daniela and their three grandchildren in 2014 enjoying a shared joke (from left: Marcello, Harry, Orlando, Daniela, and Heidi). Family photograph used with permission.

At school in Buenos Aires, Marcello started using his understanding of philosophy to question the religious teaching he had to endure, much to the consternation of his teachers. However, his grades were good and in 1959 he was offered a place at the Università di Torino to study medicine. He finished high school in Buenos Aires and then, in the intervening months, joined a small expedition exploring the remote continental icepacks of Patagonia, venturing into spectacular regions of barely-mapped mountain and glaciers. A few months later, Marcello undertook a second major expedition with his brother Giorgio, climbing mountains in Peru and descending the Ucayali and Amazon rivers. These trips were fitted in between finishing school and setting off for Torino. Marcello returned to Patagonia with his brother, family and friends in 1995, and again

in 2005 and 2006, to re-live some of those remarkable experiences.

At the Università di Torino, Marcello excelled at his academic studies of medicine. However, he also found time to become heavily involved in student politics. He was elected leader of the left-wing Student Radical Party and editor of the student paper, 'Ateneo'. The party and the paper clashed with the conservative university authorities on many matters. In particular, discussion about the Church's position on contraception stirred up considerable controversy, in which Marcello played a significant role. However, when the politics became too factional, Marcello pulled back and concentrated on other interests. He pursued outdoor activities, training in mountain climbing with the Gervasutti School of the Torino Alpine Club. In his spare time, he also played guitar in a jazz band and joined the student choir—a love of music stayed with him for the rest of his life.

Postgraduate research

During his medical studies, Marcello had the opportunity to conduct an original research project. He undertook a research internship in the Department of Anatomy and Histology, under the supervision of Giorgio Gabella. The timing was fortuitous and the project led to a very successful series of studies. A few decades earlier, it had been shown that nerve cells in the periphery release chemical neurotransmitters onto their target cells, rather than making direct electrical connections. Otto Loewi and Henry Dale were awarded the Nobel Prize for this discovery in 1936. The predominance of chemical transmission was later confirmed in the central nervous system too.¹ However, for a long time nobody was able to visualise the actual neurotransmitter chemicals in nerve cells. This was surprising as they were stored in high concentrations in nerve terminals, but finding a selective stain proved a huge challenge.

In 1962 a Swedish group localised some amine neurotransmitters in the light microscope for the first time.² The method was technically complex, requiring exposure of tissue to hot gaseous formaldehyde. Marcello and his supervisor Gabella successfully replicated the 'Falck-Hillarp method' at a time when few laboratories around the world had mastered it. Under fluorescence microscopy, tangles of nerve endings containing catecholamine transmitters emitted an otherworldly green glow, which captivated Marcello's curiosity and aesthetic sense. The technique was new and there were few competitors, so nearly everything they studied was novel and publishable. Marcello surveyed a range of organs and species, describing the distribution and sources of aminergic nerves and their terminals. It was an exhilarating introduction to research, and Marcello published eleven research papers

¹Valenstein (2002).

²Falckh and others (1962).

between 1965 and 1970, before being awarded his MD. During this time, Marcello and his supervisor provided evidence for direct adrenergic innervation of smooth muscle in rat, guinea pig and rabbit³ and thus corrected an oversight by one of the pioneering Swedish groups.

His time studying medicine was notable for another reason. Marcello's mother Verbena had a good friend who bought a house in Lerici on the coast near the Cinque Terre. Marcello was invited for a visit and met the owner's niece who was staying there for a few weeks. Her name was Daniela Tuffanelli. They talked and went their separate ways. A little later Daniela started at Medical School in Torino and one of her tutors in histology was Giorgio Gabella. Inevitably, she and Marcello met again, and their relationship developed in the less-than-romantic setting of the Anatomy Department. When Daniela broke her leg skiing, Marcello borrowed Gabella's car and drove her from the mountains back to Torino. He proposed to her when she was in hospital!

On graduation in 1967, Marcello faced compulsory military service as an army doctor. On one occasion a severe form of gastroenteritis broke out the day before a major NATO exercise, involving over one thousand soldiers. As the doctor on duty, Marcello recommended that the exercise be cancelled. This was not popular with his immediate senior officers. Faced with an intimidating display of authority, Marcello held his ground and the exercise was cancelled, preventing the further spread of the highly contagious infection. He was later thanked by some of the top brass for his intervention, which they recognised as courageous under the circumstances.

The move to Australia

Shortly after completing his service in the Italian army, Marcello presented his data on the localisation of aminergic transmitters at a scientific meeting in Venice. In the audience was Professor Geoffrey Burnstock, whose laboratory at the University of Melbourne was highly regarded for the analysis of neurotransmission to smooth muscle. Marcello and Geoff met and discussed the shortcomings of the classical model of autonomic control by acetylcholine and noradrenaline. With his experience in visualising noradrenaline in nerve terminals, Marcello impressed the Professor. An offer for an eighteen month post-doctoral fellowship in Burnstock's laboratory arrived a month or two later. Marcello and Daniela married in May 1970, and shortly afterwards he set out for Australia; Daniela followed a few months later after completing the next stage of her medical degree.

On arriving at Melbourne University, Marcello met John Furness, a post-doctoral researcher in Burnstock's laboratory.

They shared an enthusiasm for the peripheral nervous system and, as scientists do, quickly dealt with all the matters on which they agreed, then concentrated on their disagreements. In particular, Marcello claimed that there were adrenergic nerve cell bodies in the enteric nervous system of the guinea pig. Furness had looked for such cells and had not found them. Marcello's arrival was the spur to resolve this contradiction. In a matter of a few days (starting almost immediately after Marcello's arrival), they had established that both positions were correct: in several species and regions of gut there were no adrenergic cell bodies. However, in the guinea pig proximal colon, which Marcello had studied, there were occasional bright adrenergic nerve cells. They published that work together⁴ and a mutual respect grew, which turned into a long and highly productive collaboration between two very talented researchers.

Academic position

Marcello's funding ran out in 1973 and he returned to Europe, spending several months in the laboratory of Liisa and Olavi Eränkö in the University of Helsinki.⁵ However, within the year, he was invited back to Melbourne by Professor Burnstock. In 1974 Burnstock announced that he would be moving to a prestigious position at University College, London. Over the next year, several members of the group at Melbourne took up lectureships at other universities. John Furness moved to a lectureship in Flinders University—in the department of Anatomy and Histology. In 1975 Marcello was appointed to a foundation lectureship in Human Physiology at the newly established Flinders University School of Medicine. This position combined research and teaching commitments, and Marcello contributed to both activities for the next forty-seven years. He was given a personal chair as Professor of Neurophysiology in 1986, and made Matthew Flinders Distinguished Professor in 2013. He retired from this role in 2021 at the age of eighty-one, and then became Emeritus Professor. The collaboration between the duo of Marcello Costa and John Furness continued from the mid 1970s, until John moved to the University of Melbourne in 1990.

Flinders University

The new Flinders University School of Medicine was populated by talented young lecturers chosen, in part, for their research talents. The founding Dean of the School, Professor Gus Fraenkel, was a strong proponent of the three pillars of academic medicine—combining research with teaching and

³Gabella and Costa (1969a).

⁴Costa and Furness (1971).

⁵Costa and others (1973).

patient care. Thus it was important that the medical school and hospital were co-located from the earliest stages of planning.

Many of the new lecturers were of a similar age with young families; there was plenty of socialising, holidaying together, and babysitting clubs were part of the fabric. This group of young turks challenged many of the assumptions of established medical schools, breaking down barriers between the departments and teaching by organ systems rather than by discipline. A student perspective on the early days of the School of Medicine has been published recently.⁶ Marcello was actively involved in curriculum design for the early years of the Medical course, coordinating the block on the nervous system. He was also extensively involved in setting up a feeder course for medicine, the Bachelor of Medical Science, which commenced in 1995. Marcello coordinated four topics and taught in six. His commitment to teaching continued until his retirement in early 2022; his load was the same as any other 'balanced' research/teaching academic in the department. In 1986 he was promoted to a personal chair in neurophysiology, then to the prestigious position of Matthew Flinders Distinguished Professorship in 2013.

Early studies; localising amines in nerve

Marcello's first studies used the Falck-Hillarp histochemical method to localise amine transmitters in peripheral nerves of the autonomic nervous system, working with Giorgio Gabella,⁷ then John Furness⁸ and Olavi Eränkö.⁹ His studies were notable for being more than simple descriptions—crushes and lesions were applied to deduce the pathways and projections of aminergic nerves. Marcello was also an early champion of 'stretch preparations' in which gut tissue is dissected into layers, then fixed as thin flat sheets, providing a more 3-dimensional image of ganglia than traditional sections. For the first ten years, most of Marcello's publications were built around studies of aminergic pathways. However, one particularly formative influence occurred during a visit to the laboratory of Antonio Crema in Pisa, where they were studying the physiology and pharmacology of isolated specimens of intestine in an organ bath. Marcello recognised that he had been studying the same nerves and smooth muscle cells as Crema—just from a different perspective. Marcello

became convinced that it was important to link findings made with histology, physiology, pharmacology, and other approaches. From that time on, Marcello became committed to multi-disciplinary neurobiological analysis, and was always trying to reconcile findings made with different methodologies to form a cohesive explanatory schema.

The move to immunohistochemistry of the nervous system

On his move to Flinders University, Marcello branched out into studies of intestinal motor activity in isolated preparations. He combined multi-site force transducer recordings with physiological stimulation, application of agonists and antagonists and photographic recording of movement of colonic peristalsis.¹⁰ This study was a forerunner of many such studies that have teased apart the neural (and non-neuronal) mechanisms underlying intestinal motor behaviour. It showed that multiple interacting mechanisms, largely located in the myenteric plexus, contribute to the propulsion of content.

A new way to study the enteric nervous system came about from discussions with Laurie Geffen and Robert Rush. These two members of the Human Physiology Department, together with Bruce Livett at Monash University, had published one of the first studies using antibodies to localise macromolecules in nerve cells.¹¹ Marcello's interest in localisation of neurotransmitters, and the recent discovery of hypothalamic and opioid neuropeptides,¹² led him and colleagues to obtain an antiserum that bound the neuropeptide somatostatin. Immunohistochemical labelling of flat sheet preparations of gut tissue revealed varicose axons and cell bodies of enteric neurons that were immunoreactive for this neuropeptide.¹³ From the patterns of labelling, they concluded that somatostatin is expressed by a population of interneurons in the enteric nervous system. This was a landmark discovery that was confirmed using other techniques twenty years later.¹⁴

Research on amines continued, boosted by a new method that allowed ultrastructural localisation.¹⁵ However, Marcello and colleagues now started to concentrate on the localisation of neuropeptides (and other molecules) in the enteric nervous system, using immunohistochemical methods. These included studies on Somatostatin, Substance P, VIP, tyrosine hydroxylase and dopamine beta hydroxylase and 5-hydroxytryptamine

⁶Wattchow (2023).

⁷Gabella and Costa (1969a, 1969b).

⁸Costa and Furness (1971, 1973). Costa and others (1971).

⁹Costa and others (1974).

¹⁰Costa and Furness (1976).

¹¹Livett and others (1971).

¹²Hökfelt and others (2000).

¹³Costa and others (1977).

¹⁴Song and others (1997).

¹⁵Furness and others (1977).

enkephalin and GRP and Galanin, calbindin and choline acetyltransferase.¹⁶ Specialised surgical operations devised by John Furness were used to interrupt axonal pathways, allowing the polarity and length of axonal projections to be estimated. A method to optimise immunohistochemical labelling in peeled stretch preparations further improved the analysis.¹⁷ For many antigens, immunohistochemical localisation was supplemented with biochemical quantitation. During this time a gradual shift in thinking developed. While immunohistochemically identified antigens (especially neuropeptides) were interesting for their possible functional roles, they could also be considered as 'markers' to distinguish different functional classes of nerve cells.

Markers and immunohistochemistry

Marcello and colleagues provided early evidence that single enteric neurons could express multiple neuropeptide transmitters or modulators—a revolutionary idea at the time.¹⁸ A review published in 1986 introduced the concept that combinations of markers could be used to distinguish different functional classes of autonomic neurons:¹⁹ '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 (that is, origins, terminations and connections) and well defined functions'. The concept of 'chemical coding' of neurons was established, and it subsequently became highly influential. It has since become a standard approach to distinguish classes of neurons (and other cells) in the central and peripheral nervous systems, and has been used by dozens of laboratories around the world. In recent years it has been confirmed and complemented by single cell transcriptomic studies.

The laboratories of Marcello Costa and John Furness developed an international reputation for their work localising neuropeptides in the enteric nervous system. This was supplemented by studies combining intracellular recordings with dye filling and immunohistochemical analysis—a technical advance at this time led by Joel Bornstein.²⁰ However, the question of the functional role of endogenous neuropeptides remained largely unresolved for a surprisingly long time. Substance P had been discovered in 1921, and was

shown in 1971 to comprise an 11 amino acid peptide. With the discovery of hypothalamic neuropeptides and opioid peptides in the 1970s, there was considerable excitement about this new class of transmitter/modulator molecules. Exogenous neuropeptides had potent effects on putative target cells, however proving a role for the endogenous neuropeptides proved considerably more difficult. Marcello and colleagues had shown the presence and release of substance P in enteric motor neuron axons to gut smooth muscle.²¹ Using Substance P analogues with antagonistic action, Marcello led an elegant study demonstrating that Substance P was a non-cholinergic excitatory transmitter to the external smooth muscle of guinea pig small intestine, which acts via several receptors.²² A role had finally been demonstrated for an endogenous peptide. This was highly significant for the discipline of neuroscience.

A series of innovative studies followed, concentrating on the intrinsic and extrinsic innervation of the gut, mostly in guinea pigs and largely in the small intestine. This preparation was chosen because it had been widely used for pharmacological analysis and intracellular recording studies. Findings included the identification of Substance P and CGRP co-existence in a subset of spinal nociceptors.²³ Sympathetic neurons projecting to the gut were shown to co-express different combinations of neuropeptides depending on their targets and function.²⁴ These approaches were expanded to human tissue obtained from elective surgery in the Flinders Medical Centre by David Wattchow and Janet Keast.²⁵ Later, methods for maintaining intestine for several days *ex vivo* in organ culture were developed by Marcello and his colleague Simon Brookes, facilitating the systematic application of retrograde tracing of neural pathways in the enteric nervous system,²⁶ allowing more precise analysis of projections and pathways of enteric neurons in human and animal intestine.

Over many years a huge amount of information about immunohistochemical markers in enteric neurons accumulated, but the overall picture remained fragmented. Marcello led a major study to define 'chemical coding' in a model preparation: the guinea pig small intestine. This project was based on an antiserum raised against neurokinin B, which appeared to label spuriously all enteric nerve cell bodies in the guinea-pig, but not axons, dendrites, or other cells. Marcello recognised the value of such a marker, and henceforth referred to it as the 'nerve cell body' antiserum.

¹⁶Costa and others (1977, 1984, 1982). Franco and others (1979b). Furness and Costa (1979). Furness and others (1979, 1983a, 1983b, 1987, 1988).

¹⁷Costa and others (1980).

¹⁸Furness and others (1985).

¹⁹Costa and others (1986).

²⁰Bornstein and others (1984, 1989).

²¹Franco and others (1979a, 1979b).

²²Costa and others (1985).

²³Gibbins and others (1985).

²⁴Macrae and others (1986).

²⁵Keast and others (1984). Wattchow and others (1988).

²⁶Brookes and Costa (1990).

Importantly, it allowed accurate quantification of the total proportion of neurons that expressed each marker, paving the way to combine multiple experimental results. In a landmark paper, Marcello distinguished fourteen classes of myenteric neurons, on the basis of co-localisation of nine different markers. These were 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. It provided a foundation for interpretation of many later studies of the enteric nervous system.²⁷

Studies of motility

With this major goal achieved, Marcello turned much of his attention back to the motility patterns of the small intestine, utilising his new understanding of the classes and projections of enteric neurons. With Marcello Tonini from the University of Pavia, he measured smooth muscle activity in *ex vivo* preparations²⁸ with novel watertight partitions, so that drugs could be added selectively to specific parts of motility reflex pathways. Enteric neural pathways were no longer being treated as pharmacological oddities: now their geometry could be taken into account. This method has since been used by a many groups around the world.

In the 1990s, Marcello initiated several studies of peristalsis in the *ex vivo* guinea pig small intestine²⁹ using a preparation modified from the one he had seen in Crema's laboratory many years previously. He added a novel element by combining video recordings to characterise the behaviour in more detail. Grant Hennig, a postgraduate student, measured diameter changes at multiple points along the intestine to quantify the propagation of peristaltic waves. He ran into the same problem as previous studies: frame-by-frame analysis relied on visual memory and was slow and imprecise. Grant had some programming skills and managed to automate the process, converting videos into digital images, then measuring the width of the gut at each point along its length, in successive frames. This method was fast and accurate, but produced impossibly large tables that overwhelmed the observer's ability to identify motility patterns. After many attempts, Grant hit on the idea of compressing the data by converting each measurement into a

grey-scale pixel: large diameters were pale, small diameters were dark. When lined up, these formed a two-dimensional map that captured the complexity of four-dimensional motor activity. Peristaltic waves appeared as oblique pale bands moving in time and space. Marcello saw this image and instantly recognised its potential. The key features of moving images could now be captured as two-dimensional maps and studied as a whole, rather than frame by frame. It was straightforward to write routines to quantify the wave-length, amplitude, rate of propagation, and frequency of motor events,³⁰ and to observe contractions colliding. This was a huge advance over previous descriptive analyses and disjointed series of still-frames,³¹ and it rapidly identified new motor patterns that had been missed in earlier studies. Interestingly, similar spatio-temporal maps of intestinal movements were developed independently at nearly the same time in two other laboratories on the other side of the world.³²

Over the next few years a small series of papers followed, describing neurogenic and myogenic patterns that had not been detected by other techniques in guinea pig proximal and distal colon such as 'ripples' and 'abrupt contractions'.³³ However, spatiotemporal maps entered new territory when they were combined with high resolution manometry (multi-site pressure recordings), which had been pioneered by Phil Dinning and John Arkwright³⁴ at St George's Hospital and CSIRO in Sydney. These two researchers were invited to Flinders to demonstrate their method. As soon as multi-site manometry was time-locked to spatio-temporal maps, the power of this new methodology became apparent. It allowed intestinal movements, propulsion of content, and intraluminal pressure to be correlated during complex motor behaviour for the first time.³⁵ Later studies combined measurements of longitudinal contraction and application of a wide range of pharmacological agonists and antagonists. Recordings were made in 5 species: mice, rats, guinea pigs, rabbits, and humans, identifying common mechanisms and significant inter-species differences, especially in the interplay between myogenic mechanisms and neurogenic control.

Working closely with Phil Dinning, Lukasz Wiklendt, and Nick Spencer, Marcello combined intraluminal pressure maps with spatio-temporal maps of wall movements and focal recordings of smooth muscle electrical activity.³⁶ The multi-colour maps combined measurements of diameter,

²⁷Costa and others (1996).

²⁸Tonini and Costa (1990, 1992, 1996).

²⁹Waterman and others (1992, 1994a, 1994b).

³⁰Hennig and others (1999).

³¹Cannon (1902).

³²Bouchoucha and others (1999). Berčík and others (2000).

³³D'Antona and others (2001). Hennig and others (2010).

³⁴Arkwright and others (2009).

³⁵Dinning and others (2011).

³⁶Dinning and others (2014). Costa and others (2021b).

length, pressure, and muscle electrical activity together with measurements of flow. Complex behaviour could be reduced to a few neurogenic and myogenic patterns that interacted spatially and temporally. Marcello and colleagues produced a series of more than thirty papers, from 2011 to 2024, detailing interactions between neurogenic and myogenic mechanisms in the small and large bowel of multiple species with remarkable quantitative precision.

Several of these papers stand out. In 2013 a study of rabbit colon plotted local pressure vs local intestinal diameter (Diameter/Pressure maps or DPmaps) at each point along the gut, creating two-dimensional orbit plots.³⁷ Orbits reflected states of the muscle. For example, a region with increasing pressure, but no change in diameter, was interpreted as undergoing an isometric contraction. Combinations of contraction/dilation with increases and decreases in local pressure described twelve such states which accounted for the whole Diameter/Pressure map. These orbits can be understood as describing changes in muscle compliance during active contraction and relaxation. By combining areas where active contraction was occurring and comparing them to areas where active relaxation was occurring, the patterning of the underlying enteric neuronal circuits could be deduced. This showed that waves of contraction were preceded by downstream areas of relaxation, adding to the pioneering account of Bayliss and Starling in 1899.³⁸ Of particular importance was the observation that movement of content fed back into the circuitry to play a key role in the coordination of motility patterns. This gave rise to the concept of neuromechanical loops that make behaviour more than the output of neural circuits.³⁹

This methodology has since been applied to interpret manometric recordings from the oesophagus of conscious humans.⁴⁰ Manometry studies in isolated specimens of bowel have also been compared with manometric recordings from live human patients.⁴¹ In one of his later studies Marcello addressed the question of how semi-liquid content in the proximal colon is converted, within a short distance of the colonic flexure, into faecal pellets of very consistent dimensions. He showed that this was not due to rapid reabsorption of water, but rather was associated with a distinctive myogenic motor pattern unique to the flexure.⁴² It was an elegant demonstration that gut motility is driven by a limited repertoire of common mechanisms, neurogenic

and myogenic, which show species-specific and region-specific adaptation for their roles in digestion, mixing, and propulsion.

Human studies

The bulk of Marcello's research was carried out in isolated preparations from small laboratory animals: guinea pigs, rabbits, mice and rats. However, he was very aware of species' differences and was keen to test whether his findings applied to our own species. A special opportunity was provided by the School of Medicine being co-located within a busy hospital—Flinders Medical Centre. With the assistance of senior surgeons, it was possible to obtain specimens of live human bowel (with ethics permits and patient consent), and apply the same techniques that had been optimised in animal preparations. This pathway was established by Dr David Wattchow, during his PhD with John Furness and Marcello, and who published several studies on immunohistochemical labelling of human enteric neurons.⁴³ After completing his PhD, Dr Wattchow retained his links with Marcello for the next three decades and a series of papers on human tissue was published. As well as immunohistochemical staining, studies included retrograde tracing,⁴⁴ and human tissue physiology in organ baths.⁴⁵ These studies showed remarkable similarities between the human enteric nervous system and those of widely-studied laboratory animals, validating many of the earlier studies in non-human mammals. Marcello was also involved in clinical studies in patients. He brought to the attention of David Wattchow the discovery that anti-inflammatory drugs reduced post-operative ileus in several laboratory animals.⁴⁶ This led to a clinical trial⁴⁷ that showed that one of the drugs reduced the development of ileus without affecting its time-course. This collaboration led to Marcello's involvement as a supervisor of clinicians undertaking PhDs with David Wattchow.

Research students

During his career Marcello was primary supervisor of ten PhD students, including James Vickers, who is now Distinguished Professor and Director of the Wicking Dementia Research and Education Centre at the University

³⁷Costa and others (2013).

³⁸Bayliss and Starling (1899).

³⁹Dinning and others (2014). Costa and others (2015).

⁴⁰Omari and others (2014, 2016).

⁴¹Dinning and others (2016). Rosli and others (2020).

⁴²Costa and others (2021a).

⁴³Wattchow and others (1987, 1988).

⁴⁴Wattchow and others (1997). Porter and others (2002).

⁴⁵Carbone and others (2013). Kuizenga and others (2015).

⁴⁶Bauer and Boeckstaens (2004).

⁴⁷Wattchow and others (2009).

of Tasmania, and Janet Keast, President (2024) of the Australasian Neuroscience Society. He was also primary supervisor of seven Honours students. Arguably, his largest impact was on research students at numerous Australian and international meetings who benefited from his perceptive 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.

Engagement with the discipline

In the late 1960s, when Marcello's career was taking off, neuroscience was just becoming established as a discipline in its own right. The Society for Neuroscience was founded in 1969. Until that time, study of the nervous system was fragmented between physiology, anatomy, histology, pharmacology, and biochemistry. Marcello developed a strong opinion that the nervous system should be studied in its own right, and that disciplinary siloes were an unhelpful distraction. In 1977, Marcello was one of a small group who set up the Centre for Neuroscience (CNS) at Flinders University. It cut across the disciplines and ran a regular series of weekly seminars from members, interstate visitors, and overseas guests, who gave talks ranging from social psychology to molecular pharmacology. The membership was young and committed; attendance at seminars was high, and question time had a reputation for being intense. Marcello was Convenor of the CNS from 1986 to 1989, and was awarded honorary life membership in 2008. The CNS also supported members by running practice interviews, providing feedback on grant applications, and organising funding and purchase of common-service research equipment. For most of its existence it was funded solely by annual voluntary subscriptions of its members. In 1981 members of the CNS hosted the 10th meeting of the Australian Neuroscience Society (ANS—later changed to the Australasian Neuroscience Society) at Flinders; Marcello was part of a group that lobbied successfully for the formal establishment of the ANS with a constitution. Marcello served as President of the ANS from 1994 to 1995.

In local contributions, Marcello knew his limitations; bureaucracy was not a personal favourite. However, this did not stop him from taking on a major role as a member of the Animal Ethics Review Sub-Committee at Flinders University. He was a member for twenty-six years, many of them as Chairperson. The name 'Sub-Committee' belies the importance of its work. The Sub-Committee vetted every animal ethics request and provided rapid feedback to applicants, before their submissions reached the Animal Welfare Committee, where the final decision was made. The Sub-Committee streamlined the ethics process and ensured that time was not wasted on minor errors. This was a big contribution to research over many years.

Membership of societies

Marcello was an active member of many research societies relevant to his interests. Starting with discipline-based societies, he later joined several neuroscience societies and then, as the field grew, he joined sub-speciality groupings such as the International Society for Autonomic Neuroscience (ISAN) of which he was a founding member.

- Member- Australian Physiological and Pharmacological Society 1972–1990
- Member- Australian/Australasian Neuroscience Society 1981–2023
- Member- Societa Italiana di Neuroscienze (SIN) 1988
- Member- Societa Italiana di Farmacologia (SIF) 1988
- Member- Gastroenterological Society of Australia 1990–2000
- Member- Australian Physiological Society 1990–2020
- Member- International Steering Committee of ISAN (International Society of Autonomic Neuroscience) 1994–7
- Member- European Neuroscience Society 1990–2000
- Member- International Society for Neurochemistry (ISN) 1994–6
- Member- International Neural Network Society (INNS) 1994–7
- Member- International Neuropeptide Society (INS) 1994–7
- Member- International Society for Autonomic Neuroscience 1994–2023

Journal contributions

Marcello reviewed papers for over twenty journals, including:

1. Neuroscience
2. Gastroenterology
3. Journal of Neuroscience
4. Journal of Physiology
5. Neurogastroenterology and Motility
6. Gut
7. British Journal of Pharmacology
8. American Journal of Physiology
9. PLOS
10. Acta Physiologica
11. Frontiers journals

and was an editorial board member of 9 journals:

1. Medical Biology 1976–1985
2. Neuroscience 1980–2000
3. Regulatory Peptides 1986–2002
4. News in Physiological Sciences 1988–1992
5. Journal of Chemical Neuroanatomy 1990–1994
6. Life Sciences 1990–2001

7. Neurogastroenterology and Motility 1995–2000
8. Techniques in Proctology 1997–2000
9. Frontiers journals in Neuroscience 2020–2024

Contributions to meetings

Between 1980 and 2021 Marcello was invited to speak at nearly one hundred international conferences about his early work on Substance P and other neuropeptides and neurotransmission, then later on many aspects of the enteric nervous system, its neurotransmitters and neurotransmission and cellular organisation, the nature and control of motility, peristalsis, neurogenic and myogenic mechanisms in the gut. He was on the organising committee of twenty-three research conferences over the years (Fig. 3). He was one of the founders of 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 twenty public forums, including several during International Brain Awareness Week. Other talks were held under the title of 'Science outside the Square' (Fig. 4). SANI developed links with the Physical and Neurological Council of South Australia, and

developed a Graduate Certificate in Neuroscience (Learning) for teachers. Marcello also gave up many weekends to contribute to 'Science Alive' demonstrations of research methods to the public.



Fig. 4. Marcello was founder and co-Chair of the South Australian Neuroscience Institute (SANI), set up to promote public awareness of neuroscience. Here, Marcello is seen speaking at a SANI public event in 2005. Photograph provided by Simon Brookes.



Fig. 3. In 1983 Marcello Costa and John Furness organised a meeting of investigators of the enteric nervous system (ENS) from round the world. The meeting was held at Flinders University. In 2014 Marcello organised a follow-up meeting 'ENS II' in Adelaide. It was attended by many current opinion leaders, some of whom had been at the original meeting.

Major honours and awards

1. Elected Fellow of the Australian Academy of Science in 1989
2. Awarded the title 'Cavaliere della Repubblica Italiana' in 1992
3. Recipient of inaugural international prize 'Piedmontese of the Year' in 1994
4. Elected honorary member of the Golden Key Honour Society in May 1997
5. Awarded the Centenary Medal of Australia in 2003
6. Awarded life membership of the Centre of Neuroscience Flinders University in 2008
7. Awarded life membership of the Australian Neuroscience Society in 2010
8. Appointed Matthew Flinders Distinguished Professor of Flinders University in 2012
9. 'Skeptic of the Year' award (2012) to the Friends of Science in Medicine (FSM) was received by Marcello Costa as one of the 4 co-founders
10. Lifetime achievement award at the Federation of the Neurogastroenterology and Motility Societies conference, Amsterdam in August 2018
11. Officer of the Order of Australia (AO) in 2020
12. Higher Education hot list; 50 Top Australian Educators in 2020
13. Elected Fellow of the Academy of the International Union of the Physiological Societies (IUPS) in May 2022.

Final years

In 2006 Marcello reduced his working time from full time to 0.75, with the free quarter of the year set aside for travel to Italy and elsewhere in Europe. He carefully timed this break each year so that he could continue to deliver his full teaching load and exam marking—a gesture that was greatly appreciated by his peers. In 2018 he reduced his work time to 0.5, again keeping on most of his teaching commitments. He persuaded the university to divert this salary saving to employ a part-time research assistant for him in the lab. During this whole period, Marcello spent a considerable time in the laboratory, guiding experiments and analysing data. Much of his writing was done at home. He retired from his position of Matthew Flinders Distinguished Professor at the beginning of 2022, and was appointed as Distinguished Professor Emeritus, maintaining regular links with the laboratories, giving and attending seminars, and making irregular visits to meet his colleagues. Marcello had been diagnosed with mesothelioma, and passed away on Sunday 14 April 2024 at his home in Seacliff, Adelaide, surrounded by his family. A memorial service was held on 24 April 2024

in Centennial Park, Adelaide, with speakers from Marcello's family and colleagues.

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 pseudoscience 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

Marcello had many interests which he pursued enthusiastically, but he was also very much a people-person. He was devoted to his family including his son Andre and daughter-in-law, Kat, his grandchildren Harry, Orlando, and Heidi, and his brother Giorgio in Argentina, with whom he conversed regularly. He often spoke of young researchers at meetings and seminars who had impressed him. His colleagues at Flinders will remember him as a generous host at the celebrations that he held on his balcony overlooking the beach at Seacliff several times a year. He would serve slices of home-made pizza and offer cups of impossibly strong espresso that he made on a small stove-top pot. The conversation was always lively and stimulating.

In the last years of his life, Marcello wrote a significant essay entitled 'One Physics For World and Mind—A framework for understanding the physical nature of the mind', in which he brought together his deep understanding of neuroscience, ranging from the simple circuits of the gut through to the highest functions of the brain. He wove into this the conviction that all natural phenomena are four-dimensional structures with a physical basis, and explained his rejection of dualism. This is a highly original work, extensively edited by his colleague Ian Gibbins, which is commended to anyone with an interest in neuroscience and a curiosity about the nature of mind. It is available, in full, online.⁴⁸

Conclusion

Marcello was a deeply cultured man and a great neuroscientist. He had many interests in life that he explored with tremendous energy and commitment. These are well documented in his autobiography.⁴⁹ They ranged from his professional work as a researcher, to reading and discussing philosophy, his love of painting, art and music of all types, through to the physical pursuits of long-distance windsurfing, mountain climbing, and exploration. He had an extraordinary

⁴⁸Costa (2024).

⁴⁹Costa (2023).

intellect which he focussed on many challenging areas of neuroscience. He was best known for highly innovative studies of the enteric nervous system and its controls of motility of the gastrointestinal tract, but his findings influenced many other areas of neuroscience. A list of his publications is available in the Supplementary Material (see below). He encouraged talented students to take up the challenge of research and shared advice and experience selflessly. He was also deeply committed to the promotion of science especially public education, which he saw as a way to fight the dangers of misinformation, pseudoscience and denialism. To many of us who knew him, he was a charming, eloquent and thoughtful man who would always share a minute (or an hour) to discuss whatever seemed important, always coming up with a sprinkling of new, well-informed perspectives. He was generous and had a strong humanist streak.

Supplementary material

Supplementary material is available [online](#).

References

- Arkwright, J. W., Underhill, I. D., Maunder, S. A., Blenman, N., Szczesniak, M. M., Wiklendt, L., Cook, I. J., Lubowski, D. Z., and Dinning, P. G. (2009) Design of a high-sensor count fibre optic manometry catheter for in-vivo colonic diagnostics, *Optics Express*, **17**(25), 22423–22431. doi:10.1364/OE.17.022423
- Bauer, A. J., and Boeckstaens, G. E. (2004) Mechanisms of postoperative ileus, *16*(Suppl 2), 54–60. doi:10.1111/j.1743-3150.2004.00558.x
- Bayliss, W. M., and Starling, E. H. (1899) The movements and innervation of the small intestine, *The Journal of Physiology*, **24**, 99–143. doi:10.1113/jphysiol.1899.sp000752
- Berčák, P., Bouley, L., Dutoit, P., Blum, A. L., and Kucera, P. (2000) Quantitative analysis of intestinal motor patterns: spatiotemporal organization of nonneural pacemaker sites in the rat ileum, *Gastroenterology*, **119**(2), 386–394. doi:10.1053/gast.2000.9306
- Bornstein, J. C., Costa, M., Furness, J. B., and Lees, G. M. (1984) Electrophysiology and enkephalin immunoreactivity of identified myenteric plexus neurones of guinea-pig small intestine, *The Journal of Physiology*, **351**, 313–325. doi:10.1113/jphysiol.1984.sp015247
- Bornstein, J. C., Furness, J. B., and Costa, M. (1989) An electrophysiological comparison of substance P-immunoreactive neurons with other neurons in the guinea-pig submucous plexus, *Journal of the Autonomic Nervous System*, **26**(2), 113–120. doi:10.1016/0165-1838(89)90159-8
- Bouchoucha, M., Benard, T., and Dupres, M. (1999) Temporal and spatial rhythmicity of jejunal wall motion in rats, *Neurogastroenterology & Motility*, **11**(5), 339–346. doi:10.1046/j.1365-2982.1999.00162.x
- Brookes, S. J., and Costa, M. (1990) Identification of enteric motor neurones which innervate the circular muscle of the guinea pig small intestine, *Neuroscience Letters*, **118**(2), 227–230. doi:10.1016/0304-3940(90)90633-K
- Cannon, W. B. (1902) The movements of the intestines studied by means of the Röntgen rays, *American Journal of Physiology*, **6**, 251–277. doi:10.1152/ajplegacy.1902.6.5.251
- Carbone, S. E., Dinning, P. G., Costa, M., Spencer, N. J., Brookes, S. J., and Wattchow, D. A. (2013) Ascending excitatory neural pathways modulate slow phasic myogenic contractions in the isolated human colon, *Neurogastroenterology & Motility*, **25**(8), 670–676. doi:10.1111/nmo.12129
- Costa, M. (2023) *Adventures in Gut Neuroscience*. Wakefield Press, Adelaide, Australia.
- Costa, M. (2024) One Physics For World and Mind - A framework for understanding the physical nature of the mind. <https://marcellocosta.au/wp/from-molecules-to-mind/>
- Costa, M., and Furness, J. B. (1971) Storage, uptake and synthesis of catecholamines in the intrinsic adrenergic neurones in the proximal colon of the guinea-pig, *Zellforschung und mikroskopische Anatomie (Vienna, Austria)*, **120**(3), 364–385. doi:10.1007/BF00324898
- Costa, M., and Furness, J. B. (1973) The origins of the adrenergic fibres which innervate the internal anal sphincter, the rectum, and other tissues of the pelvic region in the guinea-pig, *Zeitschrift für Anatomie und Entwicklungsgeschichte*, **140**(2), 129–142. doi:10.1007/BF00520326
- Costa, M., and Furness, J. B. (1976) The peristaltic reflex: an analysis of the nerve pathways and their pharmacology, *Naunyn-Schmiedeberg's Archives of Pharmacology*, **294**(1), 47–60. doi:10.1007/BF00692784
- Costa, M., Furness, J. B., and Gabella, G. (1971) Catecholamine containing nerve cells in the mammalian myenteric plexus, *Histochemie*, **25**(2), 103–106. doi:10.1007/BF00279108
- Costa, M., Eränkő, L., and Eränkő, O. (1973) Effect of hydrocortisone on the extra-adrenal intensely fluorescent chromaffin and non-chromaffin cells in stretch preparations of the newborn rat, *Ptschrift Fur Zellforschung Und Mikroskopische Anatomielexus*, **146**(4), 565–578. doi:10.1007/BF02347184
- Costa, M., Ernkő, O., and Eränkő, L. (1974) Hydrocortisone-induced increase in the histochemically demonstrable catecholamine content of sympathetic neurons of the newborn rat, *Brain Research*, **67**(3), 457–466. doi:10.1016/0006-8993(74)90494-6
- Costa, M., Patel, Y., Furness, J. B., and Arimura, A. (1977) Evidence that some intrinsic neurons of the intestine contain somatostatin, *Neuroscience Letters*, **6**(2–3), 215–222. doi:10.1016/0304-3940(77)90021-0
- Costa, M., Buffa, R., Furness, J. B., and Solcia, E. (1980) Immunohistochemical localization of polypeptides in peripheral autonomic nerves using whole mount preparations, *Histochemistry*, **65**(2), 157–165. doi:10.1007/BF00493164
- Costa, M., Furness, J. B., Cuello, A. C., Verhofstad, A. A., Steinbusch, H. W., and Elde, R. P. (1982) Neurons with 5-hydroxytryptamine-like immunoreactivity in the enteric nervous system: their visualization and reactions to drug treatment, *Neuroscience*, **7**(2), 351–363. doi:10.1016/0306-4522(82)90272-X
- Costa, M., Furness, J. B., Yanaihara, N., Yanaihara, C., and Moody, T. W. (1984) Distribution and projections of neurons with immunoreactivity for both gastrin-releasing peptide and bombesin in the guinea-pig small intestine, *Cell & Tissue Research*, **235**(2), 285–293. doi:10.1007/BF00217852
- Costa, M., Furness, J. B., Pullin, C. O., and Bornstein, J. (1985) Substance P enteric neurons mediate non-cholinergic transmission to the circular muscle of the guinea-pig intestine, *Naunyn-Schmiedeberg's Archives of Pharmacology*, **328**(4), 446–453. doi:10.1007/BF00692914
- Costa, M., Furness, J. B., and Gibbins, I. L. (1986) Chemical coding of enteric neurons, *Progress in Brain Research*, **68**, 217–239. doi:10.1016/s0079-6123(08)60241-1
- Costa, M., Brookes, S. J., Steele, P. A., Gibbins, I., Burcher, E., and Kandiah, C. J. (1996) Neurochemical classification of myenteric neurons in the guinea-pig ileum, *Neuroscience*, **75**(3), 949–967. doi:10.1016/0306-4522(96)00275-8
- Costa, M., Wiklendt, L., Arkwright, J. W., Spencer, N. J., Omari, T., Brookes, S. J., and Dinning, P. G. (2013) An experimental method to identify neurogenic and myogenic active mechanical states of intestinal motility, *Frontiers in Systems Neuroscience*, **7**, 7. doi:10.3389/fnsys.2013.00007
- Costa, M., Wiklendt, L., Simpson, P., Spencer, N. J., Brookes, S. J., and Dinning, P. G. (2015) Neuromechanical factors involved in the formation and propulsion of fecal pellets in the guinea-pig colon, *Neurogastroenterology & Motility*, **27**(10), 1466–1477. doi:10.1111/nmo.12646
- Costa, M., Hibberd, T. J., Keightley, L. J., Wiklendt, L., Kyloh, M. A., Dinning, P. G., Brookes, S. J. H., and Spencer, N. J. (2021a) Novel intrinsic neurogenic and myogenic mechanisms underlying the formation of faecal pellets along the large intestine of guinea-pigs, *Journal of Physiology*, **599**(20), 4561–4579. doi:10.1113/JP282069
- Costa, M., Keightley, L. J., Hibberd, T. J., Wiklendt, L., Dinning, P. G., Brookes, S. J., and Spencer, N. J. (2021b) Motor patterns in the proximal and distal mouse colon which underlie formation and propulsion of feces, *Neurogastroenterology & Motility*, **33**(7), e14098.

- D'Antona, G., Hennig, G. W., Costa, M., Humphreys, C. M., and Brookes, S. J. (2001) Analysis of motor patterns in the isolated guinea-pig large intestine by spatio-temporal maps, *Neurogastroenterology & Motility*, **13**(5), 483–492. doi:10.1046/j.1365-2982.2001.00282.x
- Dinning, P. G., Arkwright, J. W., Costa, M., Wiklendt, L., Hennig, G., Brookes, S. J., and Spencer, N. J. (2011) Temporal relationships between wall motion, intraluminal pressure, and flow in the isolated rabbit small intestine, *American Journal of Physiology - Gastrointestinal & Liver Physiology*, **300**(4), G577–G585. doi:10.1152/ajpgi.00532.2010
- Dinning, P. G., Wiklendt, L., Omari, T., Arkwright, J. W., Spencer, N. J., Brookes, S. J., and Costa, M. (2014) Neural mechanisms of peristalsis in the isolated rabbit distal colon: a neuromechanical loop hypothesis, *Frontiers in Neuroscience*, **8**, 75. doi:10.3389/fnins.2014.00075
- Dinning, P. G., Sia, T. C., Kumar, R., Mohd Rosli, R., Kyloh, M., Wattchow, D. A., Wiklendt, L., Brookes, S. J., Costa, M., and Spencer, N. J. (2016) High-resolution colonic motility recordings in vivo compared with ex vivo recordings after colectomy, in patients with slow transit constipation, *Neurogastroenterology & Motility*, **28**(12), 1824–1835. doi:10.1111/nmo.12884
- Falckh, B., Hillarp, N., Thieme, G., and Torp, A. (1962) Fluorescence of catecholamines and related compounds condensed with formaldehyde, *Journal of Histochemistry & Cytochemistry*, **10**, 348–354. doi:10.1177/10.3.348
- Franco, R., Costa, M., and Furness, J. B. (1979a) Evidence for the release of endogenous substance P from intestinal nerves, *Naunyn-Schmiedeberg's Archives of Pharmacology*, **306**(3), 195–201. doi:10.1007/BF00507103
- Franco, R., Costa, M., and Furness, J. B. (1979b) Evidence that axons containing substance P in the guinea-pig ileum are of intrinsic origin, *Naunyn-Schmiedeberg's Archives of Pharmacology*, **307**(1), 57–63. doi:10.1007/BF00506552
- Furness, J. B., and Costa, M. (1979) Projections of intestinal neurons showing immunoreactivity for vasoactive intestinal polypeptide are consistent with these neurons being the enteric inhibitory neurons, *Neuroscience Letters*, **15**(2–3), 199–204. doi:10.1016/0304-3940(79)96113-5
- Furness, J. B., Costa, M., and Blessing, W. W. (1977) Simultaneous fixation and production of catecholamine fluorescence in central nervous tissue by perfusion with aldehydes, *Histochemical Journal*, **9**(6), 745–750. doi:10.1007/BF01003068
- Furness, J. B., Costa, M., and Freeman, C. G. (1979) Absence of tyrosine hydroxylase activity and dopamine beta-hydroxylase immunoreactivity in intrinsic nerves of the guinea-pig ileum, *Neuroscience*, **4**(2), 305–310. doi:10.1016/0306-4522(79)90091-5
- Furness, J. B., Costa, M., and Eckenstein, F. (1983a) Neurones localized with antibodies against choline acetyltransferase in the enteric nervous system, *Neuroscience Letters*, **40**(2), 105–109. doi:10.1016/0304-3940(83)90287-2
- Furness, J. B., Costa, M., and Miller, R. J. (1983b) Distribution and projections of nerves with enkephalin-like immunoreactivity in the guinea-pig small intestine, *Neuroscience*, **8**(4), 653–664. doi:10.1016/0306-4522(83)90001-5
- Furness, J. B., Costa, M., Gibbins, I. L., Llewellyn-Smith, I. J., and Oliver, J. R. (1985) Neurochemically similar myenteric and submucous neurons directly traced to the mucosa of the small intestine, *Cell & Tissue Research*, **241**(1), 155–163. doi:10.1007/BF00214637
- Furness, J. B., Costa, M., Rökaeus, A., McDonald, T. J., and Brooks, B. (1987) Galanin-immunoreactive neurons in the guinea-pig small intestine: their projections and relationships to other enteric neurons, *Cell & Tissue Research*, **250**(3), 607–615. doi:10.1007/BF00218954
- Furness, J. B., Keast, J. R., Pompolo, S., Bornstein, J. C., Costa, M., Emson, P. C., and Lawson, D. E. (1988) Immunohistochemical evidence for the presence of calcium-binding proteins in enteric neurons, *Cell & Tissue Research*, **252**(1), 79–87. doi:10.1007/BF00213828
- Gabella, G., and Costa, M. (1969a) Adrenergic innervation of the intestinal smooth musculature, *Experientia*, **25**(4), 395–396. doi:10.1007/BF01899944
- Gabella, G., and Costa, M. (1969b) Distribution of adrenergic fibres in the small intestine of the newborn guinea pig, *Panminerva Medica*, **11**(9), 407–409.
- Gibbins, I. L., Furness, J. B., Costa, M., MacIntyre, I., Hillyard, C. J., and Girgis, S. (1985) Co-localization of calcitonin gene-related peptide-like immunoreactivity with substance P in cutaneous, vascular and visceral sensory neurons of guinea pigs, *Neuroscience Letters*, **57**(2), 125–130. doi:10.1016/0304-3940(85)90050-3
- Hennig, G. W., Costa, M., Chen, B. N., and Brookes, S. J. (1999) Quantitative analysis of peristalsis in the guinea-pig small intestine using spatio-temporal maps, *The Journal of Physiology*, **517**(Pt 2), 575–590. doi:10.1111/j.1469-7793.1999.0575t.x
- Hennig, G. W., Gregory, S., Brookes, S. J., and Costa, M. (2010) Non-peristaltic patterns of motor activity in the guinea-pig proximal colon, *Neurogastroenterology & Motility*, **22**(6), e207–e217. doi:10.1111/j.1365-2982.2009.01453.x
- Hökfelt, T., Broberger, C., Xu, Z. Q., Sergeev, V., Ubink, R., and Diez, M. (2000) Neuropeptides — an overview, *Neuropharmacology*, **39**(8), 1337–1356. doi:10.1016/S0028-3908(00)00010-1
- Keast, J. R., Furness, J. B., and Costa, M. (1984) Somatostatin in human enteric nerves. Distribution and characterization, *Cell & Tissue Research*, **237**(2), 299–308. doi:10.1007/BF00217149
- Kuizenga, M. H., Sia, T. C., Dodds, K. N., Wiklendt, L., Arkwright, J. W., Thomas, A., Brookes, S. J., Spencer, N. J., Wattchow, D. A., Dinning, P. G., and Costa, M. (2015) Neurally mediated propagating discrete clustered contractions superimposed on myogenic ripples in ex vivo segments of human ileum, *American Journal of Physiology - Gastrointestinal & Liver Physiology*, **308**(1), G1–G11. doi:10.1152/ajpgi.00230.2014
- Livett, B. G., Geffen, L. B., and Rush, R. A. (1971) Immunochemical methods for demonstrating macromolecules in sympathetic neurons, *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, **261**(liv839), 359–361. doi:10.1098/rstb.1971.0065
- Macrae, I. M., Furness, J. B., and Costa, M. (1986) Distribution of subgroups of noradrenaline neurons in the coeliac ganglion of the guinea-pig, *Cell & Tissue Research*, **244**(1), 173–180. doi:10.1007/BF00218395
- Omari, T. I., Wiklendt, L., Dinning, P., Costa, M., Rommel, N., and Cock, C. (2014) Upper esophageal sphincter mechanical states analysis: a novel methodology to describe UES relaxation and opening, *Frontiers in Systems Neuroscience*, **8**, 241. doi:10.3389/fnsys.2014.00241
- Omari, T. I., Jones, C. A., Hammer, M. J., Cock, C., Dinning, P., Wiklendt, L., Costa, M., and McCulloch, T. M. (2016) Predicting the activation states of the muscles governing upper esophageal sphincter relaxation and opening, *American Journal of Physiology - Gastrointestinal & Liver Physiology*, **310**(6), 359–366. doi:10.1152/ajpgi.00388.2015
- Porter, A. J., Wattchow, D. A., Brookes, S. J., and Costa, M. (2002) Cholinergic and nitrergic interneurons in the myenteric plexus of the human colon, *Gut*, **51**(1), 70–75. doi:10.1136/gut.51.1.70
- Rosli, R. M., Heitmann, P. T., Kumar, R., Hibberd, T. J., Costa, M., Wiklendt, L., Wattchow, D. A., Arkwright, J., de Fontgalland, D., Brookes, S. J. H., Spencer, N. J., and Dinning, P. G. (2020) Distinct patterns of myogenic motor activity identified in isolated human distal colon with high-resolution manometry, *Neurogastroenterology & Motility*, **32**(10), e13871. doi:10.1111/nmo.13871
- Song, Z. M., Brookes, S. J., Ramsay, G. A., and Costa, M. (1997) Characterization of myenteric interneurons with somatostatin immunoreactivity in the guinea-pig small intestine, *Neuroscience*, **80**(3), 907–923. doi:10.1016/S0306-4522(96)00605-7
- Tonini, M., and Costa, M. (1990) A pharmacological analysis of the neuronal circuitry involved in distension-evoked enteric excitatory reflex, *Neuroscience*, **38**(3), 787–795. doi:10.1016/0306-4522(90)90071-B
- Tonini, M., Waterman, S. A., Candura, S. M., Coccini, T., and Costa, M. (1992) Sites of action of morphine on the ascending excitatory reflex in the guinea-pig small intestine, *Neuroscience Letters*, **144**(1–2), 195–198. doi:10.1016/0304-3940(92)90748-V
- Tonini, M., Costa, M., Brookes, S. J., and Humphreys, C. M. (1996) Dissociation of the ascending excitatory reflex from peristalsis in the guinea-pig small intestine, *Neuroscience*, **73**(1), 287–297. doi:10.1016/0306-4522(96)00040-1
- Valenstein, E. S. (2002) The discovery of chemical neurotransmitters, *Brain and Cognition*, **49**(1), 73–95. doi:10.1006/brcg.2001.1487
- Waterman, S. A., Costa, M., and Tonini, M. (1992) Modulation of peristalsis in the guinea-pig isolated small intestine by exogenous and endogenous opioids, *British Journal of Pharmacology*, **106**(4), 1004–1010. doi:10.1111/j.1476-5381.1992.tb14448.x
- Waterman, S. A., Costa, M., and Tonini, M. (1994a) Accommodation mediated by enteric inhibitory reflexes in the isolated guinea-pig small intestine, *Journal of Physiology*, **474**(3), 539–546. doi:10.1113/jphysiol.1994.sp020043

- Waterman, S. A., Tonini, M., and Costa, M. (1994b) The role of ascending excitatory and descending inhibitory pathways in peristalsis in the isolated guinea-pig small intestine, *Journal of Physiology*, **481**(Pt 1), 223–232. doi:[10.1113/jphysiol.1994.sp020433](https://doi.org/10.1113/jphysiol.1994.sp020433)
- Wattchow, D. A. (2023) *As the Twig is Bent, so Grows the Tree*. A personal history of medicine at Flinders Green Hill Publishing, Adelaide, Australia.
- Wattchow, D. A., Furness, J. B., Costa, M., O'Brien, P. E., and Peacock, M. (1987) Distributions of neuropeptides in the human esophagus, *Gastroenterology*, **93**(6), 1363–1371. doi:[10.1016/0016-5085\(87\)90267-8](https://doi.org/10.1016/0016-5085(87)90267-8)
- Wattchow, D. A., Furness, J. B., and Costa, M. (1988) Distribution and coexistence of peptides in nerve fibers of the external muscle of the human gastrointestinal tract, *Gastroenterology*, **95**(1), 32–41. doi:[10.1016/0016-5085\(88\)90287-9](https://doi.org/10.1016/0016-5085(88)90287-9)
- Wattchow, D. A., Porter, A. J., Brookes, S. J., and Costa, M. (1997) The polarity of neurochemically defined myenteric neurons in the human colon, *Gastroenterology*, **113**(2), 497–506. doi:[10.1053/gast.1997.v113.pm9247469](https://doi.org/10.1053/gast.1997.v113.pm9247469)
- Wattchow, D. A., De Fontgalland, D., Bampton, P. A., Leach, P. L., McLaughlin, K., and Costa, M. (2009) Clinical trial: the impact of cyclooxygenase inhibitors on gastrointestinal recovery after major surgery - a randomized double blind controlled trial of celecoxib or diclofenac vs. placebo, *Alimentary Pharmacology & Therapeutics*, **30**(10), 987–998. doi:[10.1111/j.1365-2036.2009.04126.x](https://doi.org/10.1111/j.1365-2036.2009.04126.x)

Conflicts of interest. None of the authors declares a conflict of interest.

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