PATRICK DAVID WALL
5 April 1925 — 8 August 2001
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Elected FRS 1989

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Patrick (Pat) Wall was a neurophysiologist and true pioneer in the science of pain. He discovered that the sensory information arising from receptors in our body, such as those for touch and heat, could be modified, or ‘gated’, in the spinal cord by other sensory inputs and also by information descending from the brain; this meant, as is now well recognized, that the final sensory experience is not necessarily predictable from the original pain-eliciting sensory input. He used this to explain the poor relationship between injury and pain, and to illustrate the fallacy of judging what someone ‘should’ be feeling from the sensory input alone. In 1969, together with his colleague, Ron Melzack, Pat proposed the ‘gate control theory of pain’ and the circuit diagram that summarized how central spinal cord circuits can modulate sensory inputs. Later on, he began to regret that ‘goddamned diagram’, which had come to dominate his life and work, but, like all great models, it paved the way for the future. Now, over 50 years after it was first published, molecular genetic dissection of dorsal horn neuronal circuitry has indisputably confirmed that sensory inputs are indeed ‘gated’ in the spinal cord dorsal horn. Through a career that started with a medical degree in Oxford, followed by almost 20 years at Yale and MIT in the USA, and continued at University College London, Pat Wall was a highly influential, critical, creative and original thinker who revolutionized our understanding of the relationship between injury and pain, and who also became a champion for all who suffered from chronic pain.

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**INTRODUCTION**

Patrick (Pat) Wall was born in 1925 in Nottingham. He remembered his father Thomas Wall, a director of education, as lively, social and adventurous but his mother Ruth, nee Cresswell, as a loner, coolly disapproving and cynical. As a boy, he was entertained, and shielded from his mother, by his older brother, Robert (35)* (figure 1).

While a scholarship student at St Paul’s School in London, Pat was evacuated during the Second World War, which gave him his first sense of freedom and independence, something that he came to value above all things. He later won a scholarship to study medicine at Oxford, but found medicine uninspiring and so, taking advantage of the disarray caused by the war, struck out on an independent career as a research scientist. This step was made possible by Paul Glees, a neuroanatomist at Oxford who offered Pat the opportunity to work in his lab while completing his medical degree. Together they improved techniques to study degenerating nerve fibres, leading to Pat’s first publications while still a medical student (1, 2).

**EARLY RESEARCH CAREER: YALE, CHICAGO AND MIT**

Pat Wall’s research career was established in the United States over almost 20 formative years in the 1950s and ‘60s. No doubt because of his promising start at Oxford, he was offered a job in the Physiology department at Yale under John Fulton, whose early primate work had triggered the practice of frontal lobotomy across the world. The Yale Frontal Lobe Project aimed to provide basic physiological data on brain function, but in practice the members pursued their own interests. Here, Pat was fortunate to interact with H. T. Chang (Zhang Xiangtong), the pioneering electrophysiologist who returned to China in 1956 to become one of the founders of China’s neuroscience. Chang taught him how to stimulate local areas of the brain and the fundamentals of working with excitable tissues, which shaped his future career as a neurophysiologist exploring functional neuronal connections in the living nervous system.

Moving on from Yale to the University of Chicago and Massachusetts Institute of Technology (MIT), Pat worked with Jerry Lettvin, Warren McCullough and Walter Pitts, three ‘geniuses’ and intellectual liberators who had new ideas that the nervous system was not fixed and could be controlled by different inputs. This was a key time in Pat’s scientific life and, together with these colleagues, he exploited the then new technique of single-unit recording of neurons in central sensory pathways (3) (figure 2).

Although Pat was to become a specialist in spinal cord physiology, the original motive for applying these new techniques to the spinal cord was a desire to excite brain cells, which was quite difficult, while spinal dorsal horn cells are easily excited by touch and pinch stimulation of the skin. At the time that he began these experiments, the senses of touch and pain were classically described in terms of simple lines of information from the skin (via primary afferents) up to the spinal cord dorsal horn and subsequently on up to the brain, with specific ‘lines’ for each modality (see Moayedi & Davis 2013). The synaptic connections along the route from skin to brain were viewed as relays, where sensory information passed, more or less unchanged, from one section of the nervous system to the next. Since the spinal dorsal horn is the first site of sensory synapses in the central nervous system (CNS), Pat naturally expected that individual neurons in this region would faithfully relay information from specialized primary afferents in the skin. But ‘it was instantly apparent that the classically

* Numbers in this form refer to the bibliography at the end of the text.
predicted specialized stable units simply did not exist. In fact, almost all of the cells responding to noxious stimuli also responded to innocuous touch stimuli, later named wide dynamic range cells’ (38). These early experiments led him to propose that sensory information in the spinal cord was not the result of simple relayed information, but of active control by signals from the periphery (presynaptic control) and that, although spinal cord neurons detected the characteristics of the sensation, the circuitry in which they operated was not fixed and could be ‘gated’ by controlling their peripheral sensory nerve inputs (4–6).

The excitement of presenting these new data and ideas at an international meeting was tempered by being summoned to the office of the great Wilder Penfield FRS, where John Eccles FRS, the leading spinal cord physiologist of the time, dismissed the discovery as heresy based on experimental artefact. This event may have triggered Pat’s lifelong loathing for scientific conservatism and the suppression of new ideas; he warned all who worked with him of the dangers of scientists who continue to preserve myths and refuse to countenance new ideas. This iconoclasm, combined with true enjoyment of laboratory experiments and critical scientific discussion, defined Pat’s career.

**Sensory neuron properties in the spinal cord dorsal horn**

The evidence for Pat’s proposals began at MIT in the early 1960s, when he published two seminal studies on the properties of individual neurons in the cat dorsal horn that responded to touch, temperature and noxious stimulation of the skin (6, 7) (figure 3).
Figure 2. Top: Pat Wall (left) at MIT holding a photograph of a histological section through the cat spinal cord. The vertical lines show where he had placed his electrodes to record dorsal horn sensory neuron activity. Bottom: a figure (6) showing the spinal cord recording set-up and plots of activity following stimulation of the foot of a cat (under anaesthetic). Each white dot represents an action potential evoked by pressure, pinch or heating the skin. Used with permission from the American Physiological Society.

The first compared the cutaneous receptive fields (areas of skin that, when stimulated, excite a neuron) of dorsal horn cells with those of the primary sensory afferents, leading Pat to deduce that each dorsal horn neuron receives convergent input from many primary afferents. Furthermore, many cells responded to several stimulus modalities: light touch, changes of temperature and noxious pressure of the skin, each modality evoking different patterns of discharge. These data suggested that there are not separate neurons for each sensory modality in the spinal cord (6).

The second study (the first Wall paper with ‘pain’ in the title) focused more specifically on the convergence of specific modalities of input onto dorsal horn cells and importantly reported an interaction between these modalities. The experiments showed that ‘damage to the receptive field of a cell or the application of an itch-producing substance, cowhage, produces a characteristic bursting discharge of the cells’ but that this pattern of discharge could be altered by simultaneous stimulation of another modality. Thus ‘the unusual pattern of afferent
Figure 3. The gate control theory of pain (10, 28). The dorsal horn of the spinal cord is represented by individual neurons forming a circuit, with inputs from large-diameter (L) touch receptors and small-diameter (S) nociceptors. The excitatory (+) and inhibitory (−) connections illustrate how gate (G) neurons can control the input from primary afferent fibres and alter the output of the transmitting (T) cell, which in turn, drives a sense of pain in the brain. The output response (pain) is therefore not predictable from the nociceptor input alone, but from the balance of nociceptor and touch inputs. Descending fibres from the brain (Central Control) can also modulate the output response. (Online version in colour.)

impulses, set up by light vibration of the skin, interferes with the response of these cells to touch, damage, itching compounds, and temperature’ (7).

A third important paper in this series demonstrated the convergence of large, myelinated A fibres (touch and vibration receptors) and small unmyelinated C fibre afferents (nociceptors) onto dorsal horn neurons, but emphasized the different effects of these two inputs (9). While the A fibres induce a short intense burst of activity and then ‘turn the cell off’, the C fibres ‘turn the cell on’, leading to repetitive discharge and a ‘wind-up’ of activation upon repeated stimulation. Since most sensory inputs are from a mix of myelinated and unmyelinated afferents, with fast and slow conduction of impulses respectively, the overall pattern of activity in the spinal cord will depend on the balance between the two (9). These insights into the interaction between sensory inputs in the spinal cord cast aside the simple view of the spinal cord relaying ‘touch’, ‘pain’ and ‘temperature’ from the periphery up to the brain in separate channels, and opened a new understanding of neural networks that compare, contrast, predict and control the senses. The discoveries laid the neurophysiological groundwork for the gate control theory of pain.

THE GATE CONTROL THEORY OF PAIN

The basis of modern pain assessment and treatment emerged from the gate control theory of pain, the product of a collaboration between Pat Wall, now a young MIT professor of biology,
and his Canadian colleague, Ronald Melzack, who had been appointed as assistant professor of psychology at MIT in 1959.

Melzack, whose research advisor was Donald O. Hebb (FRS 1966), had already worked on the challenging problem of pain. He had discovered that young puppies raised in social isolation were not behaviourally reactive to pain when they grew up and apparently had difficulty in discriminating between sensory stimuli (Melzack & Scott 1957). He proposed that, without the advantage of prior learning, all information ascended to the brain of the restricted dogs, without any inhibition occurring at lower levels of the CNS, particularly below the brainstem reticular formation. This introduced Pat to the idea of descending instructions from the brain playing a role controlling sensory processing in the spinal cord. As Melzack recalled, ‘we both had ideas that we shared: pain is due to patterns of nerve impulses rather than straight-line transmission of modality-specific impulses to a pain center; information that arrives at the spinal cord is filtered and selected on the basis of the total pattern of activity in stimulated fibers as well as by descending information from the brain’ (Melzack 1996).

Thus, Wall and Melzack began a perfect collaboration between spinal cord neurophysiologist and neuropsychologist. Together they wrote a paper on general cutaneous sensation that was published in *Brain* in 1962 (8), and then decided to write a paper specifically on pain, entitled ‘Pain mechanisms: a new theory’, published in *Science* in 1965 (10). The gate control theory had two great strengths: primarily it was the first theory of pain that incorporated central control processes both from other sensory modalities and descending from the brain, and secondly it was drawn as a circuit diagram that scientists could follow and test (see figure 3). The theory underwent a number of iterations and is best explained in their 1982 book, *The challenge of pain* (28). It was based on the following propositions:

1. The transmission of nerve impulses from afferent fibres to spinal cord transmission (T) cells is modulated by a spinal gating mechanism in the dorsal horn.
2. The spinal gating mechanism is influenced by the relative amount of activity in large-diameter (L) and small-diameter (S) fibres: activity in large fibres tends to inhibit transmission (close the gate), while small-fibre activity tends to facilitate transmission (open the gate).
3. The spinal gating mechanism is influenced by nerve impulses that descend from the brain.
4. A specialized system of large-diameter, rapidly conducting fibres (the central control trigger) activates selective cognitive processes that then influence, by way of descending fibres, the modulating properties of the spinal gating mechanism.
5. When the output of the spinal cord transmission (T) cells exceeds a critical level, it activates the action system—those neural areas that underlie the complex, sequential patterns of behaviour and experience characteristic of pain.

Evidence for descending control of dorsal horn activity from the brain and the balance of inhibitory and excitatory factors determining the receptive fields of dorsal horn cells soon followed (12, 13).

The impact of the gate theory was enormous, and remains so to this day. It explained for the first time numerous clinical observations that pain could be unrelated to the severity of an injury, from accident victims who felt no pain upon severe injury to those individuals
where gentle touch was agony (28). It explained how individuals may endure self-inflicted wounds during a religious ceremony but find an injection needle unbearable. The theory exposed the inadequacies of classic sensory physiology where the emphasis lay on ‘labelled’ pain pathways from the peripheral receptors directly activating a ‘pain centre’ in the brain, which did not explain the complexity of pain. It forced scientists and clinicians to accept the brain as an active system that filters, selects and modulates inputs. Its emphasis on central neural mechanisms meant that psychological factors, which had previously been dismissed as ‘reactions to pain’, were now seen to be an integral part of pain processing. The power of these factors was exemplified in a remarkable survey of acute trauma pain in the emergency clinic, where 37% of patients stated that they did not feel pain at the time of injury, with onset of pain beginning up to 9 hours or more later—the predominant emotions previously being embarrassment at appearing careless or concern about loss of wages (29).

Simplistic medical procedures for pain relief, based on labelled line theories of pain such as surgical sectioning of nerves and pathways, were gradually replaced by methods to modulate the sensory input by pharmacological and other therapeutic means. The theory predicted that cutaneous stimulation of the painful area, through fast-conducting large fibres, should be able suppress pain. Support came from clinical colleagues Peter Nathan and Bill Sweet, who had long been intrigued by the complexity of pain. With them, Pat showed that large-fibre stimulation could reduce pain in humans (11, 15), leading to the rapid expansion of TENS (transcutaneous electrical nerve stimulation), which is still used today as a non-invasive treatment, supported by evidence from functional brain imaging (Peng et al. 2019). The success and enthusiastic reception of the gate theory by the clinical community pioneered the concept that spinal nociceptive processing depends upon the context. The subsequent discovery of the existence of control systems in the brain that modulate pain perception, accompanied by a focus on new molecular mechanisms of pain, has led to the exciting possibility of new targets for analgesia.

But the gate theory was also controversial. The details of the circuit, particularly the selective presynaptic control, were hard to prove, and it lacked a simple specific pain pathway that could be easily targeted. It was followed by a number of what Pat called ‘ill-judged attacks’ largely because it was indeed a theory, albeit with a circuit diagram that was not strictly correct. While accepting that the spinal circuitry is more complex than that originally proposed, Pat always felt that being wrong was not the problem, being unimaginative was. These criticisms can be assigned to history; more than 50 years of advances in pain research attest to the importance of the theory (Mendell 2014; Treede 2016), and molecular genetic techniques that allow identification and selective manipulation of specific sub-populations of spinal cord inhibitory and excitatory interneurons have confirmed many of its components (Koch et al. 2018). But, for Pat, the gate theory remained both a blessing and a curse. Towards the end of his life he wrote ‘while some version of the gate theory is now generally accepted ... I am still not happy with what has been accepted. Most still write of the spinal gate as an elaborate gain control system affecting a one-way, input-output, pain-producing mechanism. I think of it as the tip of a distributed and integrated feedback mechanism, one of whose functions is to produce pain as an output state’ (38). This idea of pain as an awareness of a need-state rather than as a sensation was a concept that he had proposed more than 20 years earlier (23) and was a theme of his 1999 book The science of suffering (37).
Biographical Memoirs

The Cerebral Functions Group at University College London (UCL)

Pat left the USA to return to London in 1967, to take up a chair in the Department of Anatomy at UCL, then run by J. Z. Young FRS and later Geoffrey Burnstock (FRS 1986). His return to the UK was triggered by an increasing discomfort with US politics and the political fallout from the Vietnam war. In the Cerebral Functions Group, on the fourth floor of the UCL Anatomy building in 1960s London, Pat created the perfect environment for his innovative thinking and experimental flair and consolidated his position as not only one of the leading neuroscientists in the world but also the ‘king’ of the new science of pain.

Numerous visitors and research fellows joined Pat in the Cerebral Functions Group through the 1970s, ’80s and ’90s, including Ron Dubner, Allan Basbaum (FRS 2006), Steve Waxman, Tony Yaksh, Howard Fields, Jonathan Dostrovsky, Lorne Mendell, Marshall Devor, Stephen McMahon, Clifford Woolf, Terence Coderre, Karen Berkley, Maria Fitzgerald (FRS 2016), Martin Koltzenberg and others, many going on to become leading pain scientists themselves. The Cerebral Functions Group also encompassed outstanding independent neuroscientists in other fields, notably the future Nobel Prize winner John O’Keefe (FRS 1992), recording from the first place cells in the hippocampus, and Semir Zeki (FRS 1990), recording from the first colour coding cells in the visual cortex. Valuing links with other pioneering neuroscientists, Pat was a founding member of the British Neuroscience Association, which started as a London based discussion group at the Black Horse pub in Rathbone Place, with colleagues such as Stephen Rose and Colin Blakemore (FRS 1992).

It was a tremendously productive period for Pat. The scientists in the Cerebral Functions Group (figure 4) were free of teaching, administration and committees. Grant funding was flexible, but costs were low and university support was a given. Pat did his own experiments together with visitors and students who joined him in the shabby labs overlooking the rooftops at UCL. His day began with paperwork, and then mid morning he would go into the lab, with an obligatory cup of coffee, and lean over the electrophysiology rig (a converted lathe with ashtray attached) to record spike activity from individual dorsal horn neurons and meticulously record his data in a heavy leather-bound ledger. When colleagues took over the recording, he would sit, stroking his beard and smoking roll-ups, discussing the brain, sensory processing and above all pain and its clinical importance, peppered with a good dose of politics, people, successes and failures. The experiment terminated promptly at the end of the working day, because ‘no science should be done after 6.00 pm’, and anyway it was time for a beer. As a mentor and colleague, he was second to none, as eloquently described in his obituaries (Devor 2001a, b; Fields 2001; McMahon et al. 2001).

Plasticity of sensory connections following injury

Scientifically, Pat had spread his wings. While continuing to explore the dorsal horn mechanisms that gate sensory inputs, particularly in substantia gelatinosa neurons of the dorsal horn (24), he was intrigued by a series of findings on the plasticity (changeability) of somatosensory maps in the thalamus, dorsal column nuclei and dorsal horn.

The results of lesions of the sensory nerve inputs extended his understanding from short term modulation of sensory inputs, such as a gentle rubbing of a bruise, to lasting neuroplasticity where nerve injury could alter somatotopic maps in the CNS for months rather
Figure 4. The Cerebral Functions Group in the Department of Anatomy at UCL. Top: Pat Wall by his famous recording rig, made from an old lathe. He always wore a white coat during the working day, even in his office, perhaps because of his clinical training. Bottom: the group in 1984, discussing data together in one of the labs. From left to right: Stephen McMahon, Pat Wall, Clifford Woolf and Maria Fitzgerald. (Online version in colour.)
than minutes (18, 21). Thus he began to think about pain on a completely different time scale (22). The rapidity with which adjustments in synaptic connections could occur following nerve injury ruled out sprouting and new growth within the spinal cord, and Pat proposed (and provided evidence for) the concept of ‘relatively ineffective’ or ‘silent’ synapses that are normally quiescent, but which become functionally strengthened following removal of inputs, or deafferentation (19) (figure 5). This idea of activity dependent modulation of intrinsic synaptic strength, as opposed to pre- or post-synaptic inhibition, was novel and underappreciated at the time, but is now known to be a central mechanism for a wide range of CNS functions, from memory to pain (Ji et al. 2003).

Mechanisms underlying chronic pain

Pat began to think about the relationship between the plasticity of sensory connections in the spinal cord and the problem of chronic pain; this led him to be the first scientist to question why some pain lasts so long, beyond any initial injury. The resistance of some pain to treatment, particularly the neuropathic (very unpleasant burning) pain that follows nerve injury, prompted him to explore the concept that chronic pain and brief, acute pain have different mechanisms and to explore whether chronic pain is linked to neuroplasticity.

These ideas were stimulated by his interactions with clinicians and pain patients, including a survey of military amputees during and after the Yom Kippur war (20), facilitated by a close association with the Hebrew University of Jerusalem, first as a visiting professor in the early 1970s later then helping to establish their Center for Research on Pain in 1977. His laboratory in the Institute of Life Sciences (Russian Compound) at the Hebrew University was home to many well-known pain investigators, including Michael Gutnick, Peter Carlen, Marshall Devor and Ze’ev Seltzer. Together they described the physiological changes that occur at the cut end of an injured peripheral nerve and the exquisite sensitivity of the resulting neuromas (14, 17). Over the following years Pat and his colleagues discovered that the excessive or
aberrant sensory inputs from damaged nerves had the potential to alter the central circuitry to which they are connected, reorganizing central somatotopic maps (21, 25), and inducing lasting hypersensitivity (33), a process discovered by his colleague Clifford Woolf and now referred to as central sensitization (Woolf 1983). Changes in dorsal horn connectivity and excitability could also be induced experimentally by altering the pattern or activation of afferent inputs (26, 27, 32, 33), or by pharmacological disinhibition (31), suggesting an underlying plasticity of the system that could underlie chronic pain (34, 36). The clinical implications of this work were considerable, shifting the emphasis of chronic pain from the original injury to the consequent central plasticity (Ji et al. 2003; Kuner & Flor 2016).

Legacy

Pat was first and foremost a neuroscientist, but his clinical background led him to apply his discoveries to the wider problems of pain and suffering. His lasting legacy is that the complexity of pain experience can be understood through systematic analysis of neuronal receptive fields, interconnections and the balance of excitation and inhibitory mechanisms within the central nervous system. He identified that pain had been neglected and misunderstood by the clinical community and that chronic pain is not a ‘symptom’ but a condition in its own right that requires a deep understanding of the underlying neural circuits that generate it.

Over his career, he became a powerful advocate for the relief of pain, pushing for more investigation, more understanding and more recognition of its importance. One of his last published commentaries, on the study of spinal injury pain, was challenging investigators to think mechanistically: ‘I hope we do not have to wait another century before the dynamics of pain mechanisms and the role of both ascending and descending mechanisms is recognized from the examination of the consequences of spinal cord injury’ (39).
COMMUNICATION, CONTROVERSY AND PERSONAL LIFE

Pat was an outstanding communicator both in writing and in public speaking (figure 6). In addition to many reviews, he wrote two excellent books that should still be read today (14, 28). Following the formation of the International Association for the Study of Pain (IASP), he helped to establish the journal Pain in 1975, which he edited for 25 years and which remains
the leading journal in the field of pain research (16). He negotiated with the publisher Churchill Livingstone to publish the first comprehensive textbook of pain in 1984, which he co-edited with Ron Melzack (30). Now called Wall & Melzack's textbook of pain, it is currently in its sixth edition (McMahon et al. 2013).

He was a hugely popular speaker with a conversational style of communication that challenged his audience to stand back and question the easily taught doctrines and the science of prominent figures who opposed his views. As a man of vision, with little time for scientific conservatism, Pat was seen by some as a controversial figure who cared little for civility. ‘I have been enthralled by my progress of good luck and discovery’, he said towards the end of his life, ‘and my only regret has been the tedious dullness of the opposition’ (38).

His certainty about the role of neuronal plasticity and the importance of altered patterns of neural activity in generating pain did not allow for a ‘labelled line’ for pain, which he considered a Cartesian view. This led to frequent clashes with classical sensory physiologists and anatomists of the time, who focused upon the properties of peripheral nociceptors and specific nociceptive connections in the spinal cord. He was right, of course, but his method of using mockery as a critical tool created enemies. Perhaps this was why he was not elected as Fellow of the Royal Society until 1989, something that irked him and convinced him that he had been blackballed by his competitors. His pride when he was finally elected was evident, and even more so upon his award of the Royal Society Royal Medal in 1999.

The fact was that Pat thrived on open scientific and political discussion and welcomed visitors from all walks of life. He was a left-wing raconteur and wit, widely read and admired across the world, with numerous friends in the arts and sciences, but a man who did not suffer fools gladly.

He was guarded about his private life and never spoke of his personal feelings or domestic matters. Married three times and with many lovers in between, he never had any children. He claimed that his first wife ‘was a child herself’ while the other two had children of their own when he married them, but in truth he was a fiercely independent and private man who did not see his life as a family affair, but rather as an adventure, an intellectual challenge and, ultimately, a quest for relief for those who suffer pain.

Following his retirement from UCL, Pat took up an emeritus position in Stephen McMahon’s unit at Kings College London, continuing experiments on the mechanisms underlying spinal cord excitability and writing his critically acclaimed book, The science of suffering (37). He was diagnosed with cancer in 1999 and was in much pain himself at that time. He died in the flat that he shared with his third wife Mary Helton and their much-loved dog (figure 7), overlooking Hampstead Heath, one of the most beautiful places in London.

Pat’s list of awards can be found in his autobiography (38).

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The frontispiece photograph shows Patrick Wall in 2000, in a typical pose, enjoying scientific discussion with cigarette and lighter in hand. All photographs, including the frontispiece photograph, were provided to the author by the Wall family. The copyright status is unknown.
Maria Fitzgerald studies the developmental physiology and neurobiology of pain circuits in the brain and spinal cord. Her work has had a major impact on our understanding of how pain perception emerges in childhood and how early pain experience can shape pain sensitivity for life.

Maria studied physiological sciences at University of Oxford and trained in pain physiology and neuroscience with Patrick Wall at UCL, who taught her to love science and never to be afraid of asking questions. She was elected a Fellow of the Academy of Medical Sciences in 2000 and a Fellow of the Royal Society in 2016. She was awarded Honorary Membership of IASP in 2018 and the Feldburg Prize 2021. Her research has shown that, while basic nociception is functional at birth, the systems in the spinal cord and brain that determine pain perception and central pain control develop later in childhood and are vulnerable to stress and trauma in early life. Her research has changed clinical perception by showing that pain in children requires appropriate measurement and treatment, which should be tailored to the developmental stage of the child. Maria is currently professor of developmental neurobiology at University College London.

A podcast of an interview with Professor Maria Fitzgerald about her early career, including her training with Pat Wall, called ‘Being brave and asking questions’ can be found at https://www.painresearchforum.org/forums/interview/153682-being-brave-and-asking-questions-podcast-maria-fitzgerald.

**REFERENCES TO OTHER AUTHORS**

Devor, M. 2001a Obituary: Patrick David Wall 1925–2001. *Pain* 94, 125–129. (doi:10.1016/S0304-3959(01)00415-8)

Devor, M. 2001b The life and science of Patrick David Wall 1925–2001. Jerusalem, Israel: Center for Research on Pain, Hebrew University of Jerusalem (https://paincenter.huji.ac.il/life-and-science-patrick-david-wall-1925-2001).

Fields, H. 2001 *Patrick D. Wall, DM, FRS 1925–2001: a remembrance*. San Francisco, CA: Center for Integrative Neuroscience, University of California, San Francisco.

Ji, R. R., Kohno, T., Moore, K. A. & Woolf, C. J. 2003 Central sensitization and LTP: do pain and memory share similar mechanisms? *Trends Neurosci.* 26, 696–705. (doi:10.1016/j.tins.2003.09.017)

Koch, S. C., Acton, D. & Goulding, M. 2018 Spinal circuits for touch, pain and itch. *Annu. Rev. Physiol.* 80, 189–217. (doi:10.1146/annurev-physiol-022516-034303)

Kuner, R. & Flor, H. 2016 Structural plasticity and reorganisation in chronic pain. *Nat. Rev. Neurosci.* 18, 20–30. (doi:10.1038/nrn.2016.162)

McMahon, S., Fitzgerald, M. & Rose, S. 2001 Patrick Wall 1925–2001: a tribute. *Br. Neurosci. Assoc. News.* 40, 2–3.

McMahon, S. B., Koltzenburg, M., Tracey, I. & Turk, D. (eds). 2013 *Wall and Melzack’s textbook of pain*, 6th edn. Philadelphia, PA: Elsevier.

Melzack, R. 1996 Gate control theory: on the evolution of pain concepts. *Pain Forum* 5, 128–138. (doi:10.1016/S1082-3174(96)80050-X)

Melzack, R. & Scott, T. H. 1957 The effects of early experience on the response to pain. *J. Comp. Physiol. Psychol.* 50, 155–161. (doi:10.1037/h0047770)

Mendell, L. M. 2014 Constructing and deconstructing the gate theory of pain. *Pain* 155, 210–216. (doi:10.1016/j.pain.2013.12.010)

Moayedi, M. & Davis, K. D. 2013 Theories of pain: from specificity to gate control. *J. Neurophysiol.* 109, 5–12. (doi:10.1152/jn.00457.2012)

Peng, W. W., Tang, Z. Y., Zhang, F. R., Li, H., Kong, Y. Z., Iannetti, G. D. & Hu, L. 2019 Neurobiological mechanisms of TENS-induced analgesia. *Neuroimage* 195, 396–408. (doi:10.1016/j.neuroimage.2019.03.077)

Treede, R.-D. 2016 Gain control mechanisms in the nociceptive system. *Pain* 157, 1199–1204. (doi:10.1097/j.pain.000000000000499)

Woolf, C. J. 1983 Evidence for a central component of post-injury pain hypersensitivity. *Nature* 306, 686–688. (doi:10.1038/306686a0)
The following publications are those referred to directly in the text. A full bibliography is available as electronic supplementary material at https://doi.org/10.6084/m9.figshare.c.5725876.

(1) 1946 (With P. Glees) Fibre connections of the subthalamic region and the centro-median nucleus of the thalamus. *Brain* 69, 195–208. (doi:10.1093/brain/69.3.195)

(2) 1947 (With P. Glees & T. A. Wright) An ensheathed rotating knife for causing brain lesions. *Nature* 160, 365–366. (doi:10.1038/160365a0)

(3) 1953 (With B. Howland, J. Y. Lettvin, W. S. McCulloch & W. Pitts) On microelectrodes for plotting currents in nervous tissue. *J. Physiol.* 122(Suppl.), 24P–25P.

(4) 1958 Excitability changes in afferent fibre terminations and their relation to slow potentials. *J. Physiol.* 142, 1–21. (doi:10.1113/jphysiol.1958.sp005997)

(5) 1959 Repetitive discharge of neurons. *J. Neurophysiol.* 22, 305–320. (doi:10.1152/jn.1959.22.3.305)

(6) 1960 Cord cells responding to touch, damage, and temperature of skin. *J. Neurophysiol.* 23, 197–210. (doi:10.1152/jn.1960.23.2.197)

(7) (With J. R. Cronly-Dillon) Pain, itch, and vibration. *Arch. Neurol.* 2, 365–375. (doi:10.1001/archneur.1960.03840100003002)

(8) 1962 (With R. Melzack) On the nature of cutaneous sensory mechanisms. *Brain* 85, 331–356. (doi:10.1093/brain/85.2.331)

(9) 1965 (With L. M. Mendell) Responses of single dorsal cord cells to peripheral cutaneous unmyelinated fibres. *Nature* 206, 97–99. (doi:10.1038/206097a0)

(10) (With R. Melzack) Pain mechanisms: a new theory. *Science* 150, 971–979. (doi:10.1126/science.150.3699.971)

(11) 1967 (With W. H. Sweet) Temporary abolition of pain in man. *Science* 155, 108–109. (doi:10.1126/science.155.3699.108)

(12) The laminar organization of dorsal horn and effects of descending impulses. *J. Physiol.* 188, 403–423. (doi:10.1113/jphysiol.1967.sp008146)

(13) 1969 (With P. Hillman) Inhibitory and excitatory factors influencing the receptive fields of lamina 5 spinal cord cells. *Exp. Brain Res.* 9, 284–306. (doi:10.1007/BF00235240)

(14) 1974 (With M. Gutnick) Properties of afferent nerve impulses originating from a neuroma. *Nature* 248, 740–743. (doi:10.1038/248740a0)

(15) (With P. W. Nathan) Treatment of post-herpetic neuralgia by prolonged electric stimulation. *Br. Med. J.* 3, 645–647. (doi:10.1136/bmj.3.5932.645)

(16) 1975 Editorial. *Pain* 1, 1–2. (doi:10.1016/0304-3959(75)90002-0)

(17) 1976 (With M. Devor) Type of sensory nerve fibre sprouting to form a neuroma. *Nature* 262, 705–708. (doi:10.1038/262705a0)

(18) (With A. I. Basbaum) Chronic changes in the response of cells in adult cat dorsal horn following partial deafferentation: the appearance of responding cells in a previously non-responsive region. *Brain Res.* 116, 181–204. (doi:10.1016/0006-8993(76)90899-4)

(19) 1977 (With B. Barlow & R. M. Gaze) The presence of ineffective synapses and the circumstances which unmask them. *Phil. Trans. R. Soc. Lond. B* 278, 361–372. (doi:10.1098/rstb.1977.0048)

(20) 1978 (With P. L. Carlen, H. Nadvorna & T. Steinbach) Phantom limbs and related phenomena in recent traumatic amputations. *Neurology* 28, 211–217. (doi:10.1212/wnl.28.3.211)

(21) (With M. Devor) Reorganisation of spinal cord sensory map after peripheral nerve injury. *Nature* 276, 75–76. (doi:10.1038/276075a0)

(22) 1979 Three phases of evil: the relation of injury to pain. *Ciba Found. Symp.* 69, 293–304. (doi:10.1002/9780470720523.ch17)

(23) On the relation of injury to pain: the John J. Bonica Lecture. *Pain* 6, 253–264. (doi:10.1016/0304-3959(79)90047-2)

(24) 1980 The role of substantia gelatinosa as a gate control. *Res. Publ. Assoc. Res. Nerv. Ment. Dis.* 58, 205–231.
(25) 1981 (With M. Devor) Plasticity in the spinal cord sensory map following peripheral nerve injury in rats. *J. Neurosci.* 1, 679–684. (doi:10.1523/JNEUROSCI.01-07-00679.1981)

(26) 1982 (With M. Fitzgerald, J. C. Nussbaumer, H. Van Der Loos & M. Devor) Somatotopic maps are disorganized in adult rodents treated neonatally with capsaicin. *Nature* 295, 691–693. (doi:10.1038/295691a0)

(27) (With C. J. Woolf) Chronic peripheral nerve section diminishes the primary afferent A-fibre mediated inhibition of rat dorsal horn neurones. *Brain Res.* 242, 77–85. (doi:10.1016/0006-8993(82)90497-8)

(28) (With R. Melzack) *The challenge of pain*, rev. edn. London, UK: Penguin Books. (First published as *The puzzle of pain*, 1973, Penguin Education).

(29) (With R. Melzack) Acute pain in an emergency clinic: latency of onset and descriptor patterns related to different injuries. *Pain* 14, 33–43. (doi:10.1016/0304-3959(82)90078-1)

(30) 1984 (Editor, with R. Melzack) *The textbook of pain*. Edinburgh, UK: Churchill Livingstone.

(31) 1985 (With N. Saadé & S. J. Jabbur) Effects of 4-aminopyridine, GABA and bicuculline on cutaneous receptive fields of cat dorsal horn neurons. *Brain Res.* 344, 356–359. (doi:10.1016/0006-8993(85)90814-5)

(32) 1986 (With C. J. Woolf) Relative effectiveness of C primary afferent fibers of different origins in evoking a prolonged facilitation of the flexor reflex in the rat. *J. Neurosci.* 6, 1433–1442. (doi:10.1523/JNEUROSCI.06-05-01433.1986)

(33) 1987 (With A. J. Cook, C. J. Woolf & S. B. McMahon) Dynamic receptive field plasticity in rat spinal cord dorsal horn following C-primary afferent input. *Nature* 325, 151–153. (doi:10.1038/325151a0)

(34) 1988 Recruitment of ineffective synapses after injury. *Adv. Neurol.* 47, 387–400.

(35) 1989 Personal Records of the Royal Society.

(36) 1991 Neuropathic pain and injured nerve: central mechanisms. *Br. Med. Bull.* 47, 631–643. (doi:10.1093/oxfordjournals.bmb.a072497)

(37) 1999 *The science of suffering*. London, UK: Weidenfeld & Nicolson.

(38) 2001 *The history of neuroscience in autobiography*, vol. 3 (ed. L. L. Squires). New York, NY: Academic Press.

(39) Letter to the Editor. *Pain* 93, 197–198. (doi:10.1016/S0304-3959(01)00310-4)