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Anne A. Gershon
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Herpes Zoster: Postherpetic Neuralgia and Other Complications

Focus on Treatment and Prevention

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Illustration page iii: Composition of coronal section of the spinal cord at T7 showing no difference in dorsal horn substance P staining and dorsal horn atrophy on the right side of the image using immunocytohistochemistry superimposed on a monarch butterfly.

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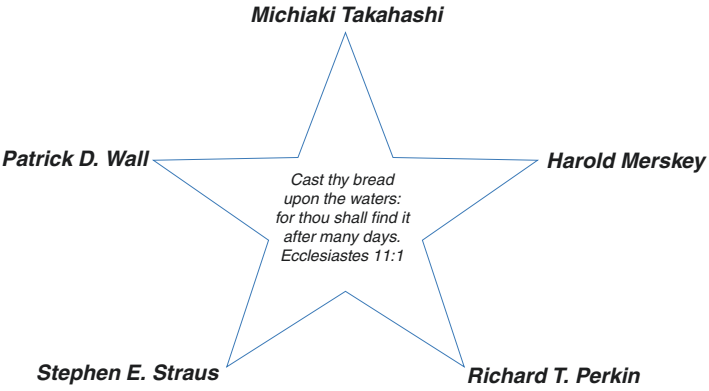
"If I have seen further it is by standing on the shoulders of giants."
(Sir Isaac Newton 1643–1727)



This book is dedicated to individuals who have played important roles in modern times in preventing, treating, and understanding the varicella zoster virus (VZV) and its complications:

Michiaki Takahashi (1928–2013):
Dr. Takahashi's vision and courage inspired him to attenuate VZV over 40 years ago, in order to prepare a live vaccine against this virus. Guided by his experience with live attenuated measles and polio vaccines, he isolated VZV from a child with varicella and attenuated it by serial passage in human and guinea pig cells at reduced temperature. When first developed, the live attenuated VZV vaccine was highly criticized by many scientists. However, Dr. Takahashi and his colleagues persevered, demonstrating the vaccine's safety and efficacy in preventing varicella in healthy children exposed to VZV at home and in school, in children hospitalized with a variety of illnesses, and, finally, in children with leukemia in whom varicella is associated with significant mortality. Dr. Takahashi and his colleagues also demonstrated the vaccine's safety and immunogenicity in older adults already latently infected with VZV, an important preamble to its use to prevent herpes zoster.

Reassured by Dr. Takahashi's pioneering studies in Japan and aided by Dr. Takahashi's extraordinary generosity, physicians in the United States and throughout the world began to study the live attenuated Oka VZV vaccine, which has proven to be one of the safest and most effective vaccines in use today. It has saved millions of individuals worldwide from morbidity and mortality due to VZV. Its success in preventing herpes zoster and postherpetic neuralgia has served as a model for the development of newer VZV vaccines and encouraged investigators attempting to develop therapeutic vaccines for latent and persisting infections by other human herpesviruses. At this writing, VZV remains the only human herpesvirus for which there are licensed vaccines. Dr. Takahashi was an inspiring colleague and a warm friend.

Dr. Stephen E. Straus (1946–2007) *was a consummate physician-scientist whose career was devoted to innovative research on the molecular biology, pathogenesis, treatment, and prevention of human viral infections and immunological diseases. His research extended from the bedside to the laboratory bench and back to the bedside. He was a leading contributor to our understanding of VZV and the diseases it causes. Steve Straus and his colleagues cloned and mapped the complete VZV genome and constructed a detailed map of VZV's transcripts. He was the first to prove by molecular techniques that the viruses causing varicella and a subsequent episode of herpes zoster in the same individual were identical. His studies of VZV latency in human sensory ganglia characterized the cells that were latently infected, determined the VZV copy number in individual neurons, mapped the VZV transcripts expressed during latency, and demonstrated fundamental differences between HSV and VZV latency. Steve played a leading role in the planning and execution of the Shingles*

Prevention Study, which demonstrated the safety and efficacy of live attenuated Oka VZV vaccine in reducing the incidence and severity of herpes zoster and postherpetic neuralgia, and led to licensure of zoster vaccine in 2006. He served on the study's planning and executive committees, the writing committee, and the clinical evaluation committee, which adjudicated every suspected case of herpes zoster, and he was the initial principal investigator of the National Institutes of Health study site. In 1999, Steve was appointed the first director of the National Center for Complementary and Alternative Medicine, where he established the primacy of rigorous scientific research to ensure that therapies in this challenging area were evidence based. Steve was diagnosed with a brain tumor in November 2004; yet, despite his illness, he continued to make major contributions to both basic and clinical research until his death in 2007. Steve was a wise mentor, a sterling role model, and a dear friend to scores of fellows, students, and colleagues, many of whom pursued successful careers in medical research inspired by his example.

Harold Merskey (1929–) *Harold is an inspiration and source of wisdom for his many friends, students, and colleagues because of the breadth of his scholastic ability, leadership, generosity, courage, feisty defense of the vulnerable, ongoing sage advice, and friendships over many decades. He collaborated on the original identification by randomized controlled trial of the independent analgesic effect of the antidepressant amitriptyline in postherpetic neuralgia. He has published as well 10 books and over 400 articles on various aspects of pain. The following quotation from Virgil is reminiscent of Harold: "It was his part to learn the powers of medicine and the practice of healing, and careless of fame, to exercise the quiet art."*

Richard T. Perkin (1931–2003): *Dick Perkin was well known to many of the authors of this volume. The eldest son of an American entrepreneur who co-founded the company Perkin-Elmer in 1937, Dick like his father had a deep interest in science. A crater of the moon was named after his father. A graduate of Harvard College in 1954, Dick was also passionate about music, and he was strongly motivated to heal the world and make it a better place. After retiring from various executive positions, he devoted his life to philanthropic causes, particularly through Rockefeller University, the Wildlife Conservation Society, and the Juilliard School of Music. In 1991, at the age of 60, when his elderly mother developed vision-threatening severe ophthalmic zoster with PHN, he decided to establish a research group dedicated to developing means to prevent zoster, through research and education. He assembled a group of internationally recognized academic physician-investigators with a similar interest and called it the Varicella Zoster*

Virus (VZV) Research Foundation, which he successfully directed for the next 12 years, until his death. This group conducted international research meetings, raised and discussed questions about VZV, and supported the research of highly qualified young investigators with an interest in the virus. The Foundation, which met in such venues as Paris, Osaka, New York, La Jolla, and Washington, was instrumental in supporting universal vaccination against varicella and played a critical role in the development and testing of the first vaccine to prevent zoster, which was Dick Perkin's dream. In addition to his intellectual side, Dick had a quick wit and an abiding interest in people, and he deeply loved the members of his family. He was beloved by his office staff, the VZV Board of Directors, and the many and diverse scientists involved in VZV research. Reflecting his modesty, the VZV Research Foundation that Dick established did not bear his name, but it will forever evoke his memory and remind us all of his good works and dedication.

Patrick Wall (1925–2001) *An early and memorable grand rounds by Professor Wall was on postherpetic neuralgia when he was a visiting professor in Toronto. It must have been surprising for clinicians that a basic scientist would discuss this condition with such knowledge of the clinical manifestations of the disease. Dr. Wall felt strongly that his postdoctoral basic science students should attend the pain clinic and see patients with intractable neuropathic pain such as postherpetic neuralgia. It was from the nerve fiber spectrum from four nerve biopsies of postherpetic neuralgia by the neurosurgeon William Noordenbos that Patrick Wall and Ronald Melzack suggested the gate control theory of pain. They thought from the preponderance of small slowly conducting fibers (pain excitatory) and reduction in large fibers (inhibition) that "fast blocks slow." Pat Wall continued to be a world leader and an inspiration for his many*

students and colleagues over many years via fellowships and his editorship of the journal PAIN.

C. Peter N. Watson,
Anne A. Gershon,
Michael N. Oxman

The Patients Speak in Poetry, Art, and Prose

This book begins and ends with patients' perceptions first with Elizabeth MacCallum with poetry and last with Susan Telling's drawings. In between, Chap. 3 is a narrative by Anne Tuzi regarding the impact of postherpetic neuralgia on her life.

My Constant Companion

By Elizabeth MacCallum

Before the first rays of light
Warning of the day to come
My friend is here.
The darkness in the light
Snickering
My constant companion.
The devil incarnate
Burrowing, gnawing, snarling
My sine qua non.
The claws in the caress
Needling the would-be bliss
My most faithful servant.
But at the last I will escape.
Promising the world to come
Grace is here
Unsullied kindly light.

Preface

A quarter of a century has passed since the publication of Peter Watson's first volume *Herpes Zoster and Postherpetic Neuralgia* [9]. During this interval, there have been numerous advances in pain science and medicine, including in our *understanding* of the causes of chronic pain, in *treatment modalities* and in *attitudes* about what pain is, and how we should relate to it. The most dramatic change has been in the basic sciences, where we know a great deal more than we did in 1993 about the biological mechanisms that underlie chronic pain. Then, almost every journal article and book chapter on neuropathic pain (and there were plenty in the early 1990s) opened with the statement that pain following nerve injury is fundamentally a mystery. Today this is no longer the case, albeit much still needs to be learned. On the clinical front, advances have been modest in comparison, but some new treatment modalities have come online (e.g., the lidocaine patch for postherpetic neuralgia) while others have faded away. Substantial advances have also occurred in the realm of changed attitudes. The public campaign launched by EFIC at the European Parliament in Brussels in October 2001 declared that chronic pain needs to be viewed not as a symptom, but as a disease, a major biomedical problem, and a healthcare priority in its own right [7]. A Google search today for "Chronic pain is a disease" turned up over 300,000 web pages referring to this phrase. Perhaps there is a little hyperbole here, but the slogan and the concept have resonated broadly. This, together with related campaigns promoting pain monitoring as the "fifth vital sign" and the need to overcome the fear of using opiates for palliative care and beyond, has significantly changed attitudes among pain professionals and the public [2]. Increasingly it is held that when pain relief can be achieved, it constitutes a human right.

But despite progress, painful conditions continue to rank high among the contributors to the global burden of disease. Pain is also big business. Pain relieving drugs are among the most prescribed (and lucrative) in the pharmacopeia [5, 8], http://www.medscape.com/viewarticle/844317. Yet several large members of BigPharma have closed down their research programs on analgesic drugs in the past few years. This is after failures of vastly expensive development efforts such as tachykinin receptor antagonists and COX-2 inhibitors. In the specific niche of drugs

approved for neuropathic pain, today's most widely used compounds provide only fractional pain relief for a small minority of the patients who take them (e.g., for gabapentin NNT = 7 [4]). Their effect is mostly placebo. Indeed, whole sectors of widely used pain remedies are based entirely on the placebo effect, homeopathy being a prime example. The placebo effect and more broadly, context-related modulation of pain, is a powerful analgesic modality that some investigators feel should be introduced knowingly into pain practice [6]. Our general failure to crack the problem of chronic pain, including pain in shingles and postherpetic neuralgia, has led some opinion leaders to conclude that reducing the intensity of pain is not even the endpoint we should be shooting for. Rather, we should focus more on the psychosocial factors that exacerbate pain [1].

Personally, I remain optimistic. Historically speaking, it is not so long ago that pain was taken for granted as a normal part of life including in the most enlightened parts of the world. Temporal and religious leaders saw pain, and even torture, as legitimate means of seeking truth (e.g., trial by ordeal), educating children, entertaining the public, and redeeming souls. Today, gladiatorial sport, public burning of nonbelievers, and the like have been eradicated from most of the planet. Indeed, in many countries large fortunes are spent, by public demand, to minimize suffering even in farm animals and laboratory rodents. Standing back, the distance we have travelled in the realm of attitudinal change regarding pain is stupendous [3].

Taking the long view, there are also successes in the realm of treatment modalities. We have four broad-spectrum, tried-and-true drugs that are so good that we almost take them for granted. First are opiates which, with all their side effects and abuse potential, are a gift from the Gods of antiquity. Second is aspirin and the related over-the-counter NSAID and non-anti-inflammatory pain relievers. They are cheap, safe enough for short-term use without a doctor's prescription, and they work well for pain of modest intensity. Third is lidocaine and the other local anesthetics. Safe, pretty easy to use, and for short-term nerve and regional blocks, they work dramatically almost every time (no NNT = 7 for lidocaine!). Fourth are general anesthetics. Until their introduction, limbs were sawed off with the patient only a shot of whiskey away from being wide awake. The advent of ether and chloroform heralded today's essentially pain-free surgery. Anesthesia was hailed at the time, and quite correctly, as "the conquest of pain." But we now take it so much for granted that, despite the fact that we have virtually no idea how propofol and the other anesthetics eliminate pain (and consciousness), it is rare to see even a single lecture addressing this subject at major international pain conferences. Over the years, these four modalities have steadily improved as new agents, e.g., anticonvulsants and antidepressants, have come on line. Perhaps further down the road, when Peter Watson once again gathers his troops to review herpes zoster and postherpetic neuralgia, some of the remarkable discoveries currently coming out of basic science laboratories will already have been translated into new families of drugs and procedures that really work in the clinic.

Marshall Devor
Israel

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Preface and Acknowledgments

> "Life is short and the Art is long; the occasion fleeting; experience fallacious; and judgment difficult. The physician must not only do what is right himself, but also to make ….the externals cooperate" – attributed to Hippocrates, the first aphorism

All of the above is true of herpes zoster (and life). Although the evidence base for this disease is increasing, treatment remains very much an Art (sic). Herpes zoster has been known since antiquity [1]. The *occasion* suggested for effective treatment of zoster with antivirals is indeed *fleeting* (72 h). Favorable *experience* with the treatment of herpes zoster and postherpetic neuralgia based on the many early uncontrolled interventions is often *fallacious* because of the natural history of resolution that occurs in many patients. *Judgment*, for example, regarding the use of opioids for intractable postherpetic neuralgia is indeed *difficult*. The last sentence of the aphorism refers to a variety of "externals" but includes prevention [2] of herpes zoster by vaccination.

Herpes zoster, overall, is the most common neurological disease. Postherpetic neuralgia is its most feared and common complication with its potential accompaniment of visual loss and facial disfigurement, which can completely change functioning and quality of life. Progress regarding this virus has been slow in the prevention of postherpetic neuralgia at the acute stage of the painful rash and also in the treatment of established postherpetic neuralgia. An important advance is the promise of prevention by the current live attenuated zoster vaccine and the possibility of other new, more effective, and more broadly applicable vaccines. New information is available regarding epidemiology, pathophysiology, neuropathology, antiviral drugs for treatment of acute zoster, and pharmacotherapy of postherpetic neuralgia. The evidence for viral persistence supports the important role of this virus in vascular diseases, such as stroke, myocardial infarction, and temporal arteritis (granulomatous angiitis).

This book has been written for a wide readership. There is a broad interest in herpes zoster and its complications, not only from infectious disease and pain specialists but also among general internists, general practitioners, neurologists, oncologists, public health departments, the pharmaceutical industry, clinical trial experts, and the general public.

The book has been organized into five parts. After the introduction, a chapter on varicella is followed by a section on the acute illness of herpes zoster with its complications and management. Part III focuses on the assessment, pathology, and pathophysiology of postherpetic neuralgia. This is important because postherpetic neuralgia has been one of the main neuropathic pain conditions targeted by clinical research in neuropathic pain (together with painful diabetic neuropathy) and ideas about its pathophysiology have broader ramifications for neuropathic pain in general. Part IV on the treatment of postherpetic neuralgia is comprehensive and also cautionary because once the disease is established, treatment is difficult. The chapter on improving clinical trial design is critical in looking for new and more effective treatments for this terrible neuropathic pain. Part V focuses on methods for preventing the disease in the first place which is our best hope of dealing with this virus and its complications. Prevention will hopefully occur chiefly by means of the currently licensed live attenuated zoster vaccine and the promise of new, more effective, and more widely applicable recombinant varicella-zoster virus glycoprotein vaccines.

I have been very fortunate in eliciting the collaboration of two senior world authorities on infectious diseases, particularly diseases caused by varicella-zoster virus. Dr. Anne Gershon was invaluable as coeditor of my previous volume on this topic. Dr. Michael Oxman was the first author of a seminal article on the first vaccine to prevent herpes zoster. Together we have been fortunate to assemble an exceptional group of chapter authors in various fields who are at the cutting edge of the many different facets of the varicella-zoster virus.

As well as these coeditors, I want to acknowledge the invaluable assistance and generosity of the many and eminent chapter authors who have contributed to this book. Further, the support of my family, Dr. Judy Watt Watson, and our children, Simon and Emily, has been vital.

Toronto, ON, Canada C. Peter N. Watson

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Patrick D. Wall (1925–2001): An Appreciation

One of the dedications of this book is to the memory of Professor Patrick D. Wall FRS (1925–2001). It is timely since 2015 the time of this writing, marks not only the 90th anniversary of his birth but also the 50th anniversary of the publication of his seminal collaborative paper with Ronald Melzack on the "gate control theory of pain" [1]. It is a testament to Pat Wall's (and Ron Melzack's) capability as insightful thinkers that this theory continues to resonate and inspire despite 50 years of intense scientific scrutiny. Many scientific competitors attacked specific aspects of the hypothesis in the first few years after its publication, and Wall relished engaging in the resulting debates. With the perspective of time, however, the overall influence of the gate control theory on the landscape of pain science and medicine is undeniable.

It is also pertinent to recall Pat Wall's life and scientific contributions at this time since there is now a whole generation engaged in pain research and clinical management who never witnessed this great man in action and never directly benefited from his wisdom, critical advice, and encouragement. Hopefully, this dedication will draw attention to Wall's fundamental contributions to current pain research.

Pat Wall was born in Nottingham, United Kingdom. His father Thomas was a schoolteacher who went on to become a school inspector. Thomas Wall was a Cambridge University graduate who had served as a decorated artillery officer in the First World War [2]. Pat was also physically active as a young man, a fact which may come as a surprise to many who knew him in later years. His father Thomas was an athlete who participated in international competition in field and track and in soccer. Wall described his childhood thus: "I was brought up in a family full of adventure. My father's extrovert character effectively submerged my mother's [Ruth] covert Puritanism. My older brother's obsession with cars and airplanes so successfully distracted my parents that I grew up in a wonderful calm*"* [3]. Pat was educated at St. Paul's School, London, where one particularly influential teacher, Tony Barnett, was fundamental in sowing the seeds of Pat's iconoclastic character, including the often fierce and usually gladiatorial deployment of reasoned argument to seek out and challenge ill-founded authoritarian pronouncements, scientific "facts," and seeming paradoxes. These early influences were also reflected in his left-wing politics. As one of his obituaries noted: "Although he possessed immense

charm, he could be intolerant and critical of scientists who made statements which he considered unjustified, and often ruffled feathers by challenging 'received wisdom'."

Wall studied medicine at Oxford University and the Middlesex Hospital, qualifying in 1948. During this time, he spent a summer working in the laboratory of Sir Alexander Fleming at St. Mary's Hospital. Like many London medical students of that generation, he volunteered to go to Europe and assist in caring for surviving Holocaust victims. While he rarely spoke of this experience, it undoubtedly shaped his humanitarian and his political views later in life. Although he never practiced clinical medicine for any length of time, the ethos of guiding his laboratory research by lessons learned from careful clinical observation of patients was one that he carried through his scientific career. His first two scientific papers, one on brain connectivity and one on a novel experimental method, were published in *Brain and Nature* when he was only 21. After graduating, he moved to the United States and passed through a number of major universities including Yale, Chicago, and Harvard before ending up at the Massachusetts Institute of Technology. It was when he was at MIT that he met his collaborator, the Canadian psychologist Ronald Melzack. Together they set about developing the gate control theory published in *Science* in 1965 [1]. This seminal paper is a masterpiece of scientific reasoning which leaned heavily on clinical observations in chronic pain patients. It elaborated the concept of sensory-sensory modulation of pain at the level of the spinal dorsal horn and laid the foundations for the study of spinal gating by pathways descending from the brain. The clinical community embraced the idea of gate control quickly, encouraged by a productive collaboration between Pat and the well-known neurosurgeon Bill Sweet which yielded the methods of TENS (transcutaneous electrical nerve stimulation) and spinal cord stimulation. The embrace by clinicians still endures half a century later. In time the research community also came on board. Today, spinal modulation and descending control are central themes in the neuroscience of pain.

In 1967 Wall returned to the United Kingdom to a Chair in the Anatomy Department at University College London, where he remained until his retirement. In his early days at UCL, he was heavily influenced by the then head of department, the great neuroanatomist JZ Young.

From his base in London, Pat continued to contribute to the understanding of pain. His oft-quoted advice to those embarking on a scientific career was "One has to choose an important subject that no one else is working on, write a book about it and start a journal for it." His own career followed such a path. His life's work revolved around elucidating the mechanisms of pain, a largely ignored topic at the time. He co-edited what remains the major textbook in the field *Wall & Melzack's Textbook of Pain* (Elsevier), now in its sixth edition. And he founded and edited *PAIN*, still the premier journal in the field. One of the likely reasons for the success of the journal and of the textbook is that they both provided a welcoming forum for the views of laboratory scientists, clinical researchers, and practitioners from a wide range of disciplines. In 1973, Pat also played a key role in the establishment of the

International Association for the Study of Pain (IASP), in the "guise" of its scientific study officer.

One of Wall's major contributions while at UCL was to change the one-dimensional way that pain was then viewed. He argued strongly that "pathological" pain, which had no physiological or survival benefit to the organism, had to be viewed differently from acute pain. This approach drew attention to the fundamental importance of plasticity in the nervous system. He was particularly angered by pain from the prostate cancer which, in the end, took his life. This was pain which, in the pre-medical world at least, served no purpose. He pioneered research on aberrant responses of peripheral nerves and of the central nervous system (CNS) to nerve injury. Such responses, he argued, underlie neuropathic pain. Characteristically, his views that there are dramatic alterations in the CNS in response to peripheral nerve injury or inflammation were fiercely attacked at the time. Again, he relished the debate. Equally characteristically, in the fullness of time, his forward thinking and challenging ideas on neuroplasticity in the pain system came to form a central focus of current day pain research. Were he here with us today, Wall would probably still be raising challenges and fighting dragons.

As noted, throughout his life, Pat's ideas were fomented by observations in patients. For much of his early time at UCL, he had an honorary appointment at the Hebrew University of Jerusalem, Israel, where he made frequent scientific trips and developed a number of collaborations. The development of his ideas concerning neuropathic pain was strongly influenced by clinical observations of post-amputation pain in Yom Kippur war veterans. This led to his work on experimental neuromas and the publication of the first animal model of neuropathic pain [4]. While full-thickness sciatic nerve axotomy has since been largely succeeded by more refined partial nerve injury models, this paper remains important, perhaps mostly for what was in it, but has been forgotten and is only now being rediscovered. We refer to the recognition that neuropathy is often characterized by spontaneous pain in the presence of sensory loss, "anesthesia dolorosa." It is now becoming apparent from the increasing number of sensory profiling studies of neuropathic pain patients that sensory loss (hypesthesia) accompanied by ongoing pain is a far more frequent clinical presentation in neuropathic pain patients than sensory gain phenomena (e.g., allodynia and hyperalgesia). The partial exceptions are postherpetic neuralgia, CRPS, and traumatic nerve injury, where sensory gain is frequent. Sensory gain is also the endpoint that has been most commonly used in animal models for the past decades as we struggle to find ways of assessing ongoing pain.

The sciatic nerve neuroma model in rodents also drew attention to the importance of measuring ethologically appropriate complex behavioral responses in animals, as opposed to altered thresholds for reflexive responses to simple sensory stimuli, the endpoint of convenience that dominates the field today. In his 1979 paper, Wall highlighted a complex self-mutilation behavior that developed following nerve injury that he termed "autotomy." He believed that autotomy behavior reflects ongoing pain perceived by the animal, akin to phantom limb pain or anesthesia dolorosa. The precise relevance of autotomy behavior to clinical pain is still debated; indeed the authors of this appreciation chapter do not fully agree on its

interpretation. The debate about autotomy was relished and encouraged by Wall, and it is still going on today. Wall stressed the importance of understanding the normal behavior of an animal as a framework for interpreting pathological responses. He sometimes had a laboratory rat freely roaming in his office at UCL. This was both to learn firsthand about his experimental subjects and to make the point among his scientific colleagues. Pat's insights concerning spontaneous *versus* evoked pain are currently being rediscovered, decades after he first drew attention to them.

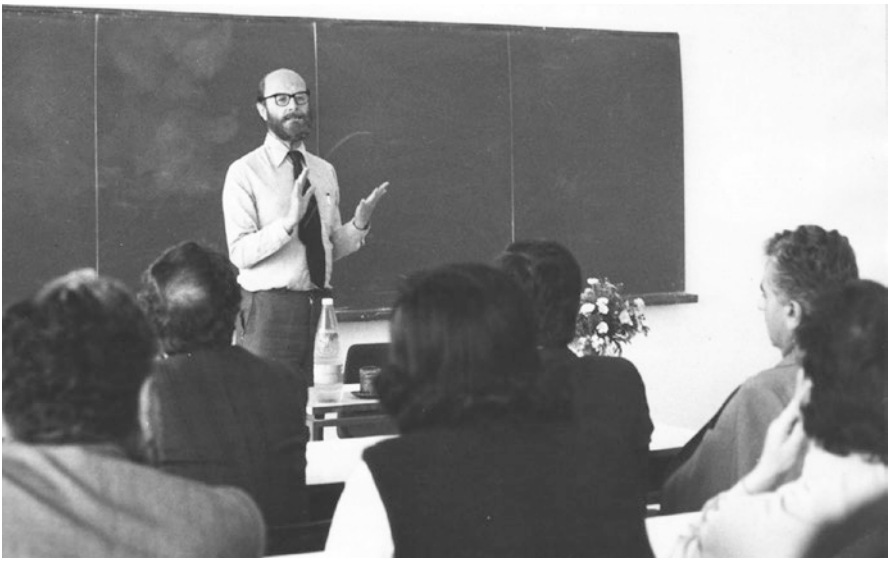
Wall remained active in pain research in his retirement, moving his laboratory from UCL to St. Thomas' Hospital London, adjacent to the laboratory of his protégé Steve McMahon. He continued to conduct his own electrophysiological recordings and produced new and important work right up to the time of his death.

A testament to his remarkable abilities as a teacher and mentor is the legacy of his students and associates, many of whom have gone on to become world-leading researchers in the field of pain. Examples include Howard Fields, Allan Basbaum, Jonathan Dostrovsky, Steve McMahon, Marshall Devor, Maria Fitzgerald, and Clifford Woolf. He also profoundly influenced others who worked in different aspects of neuroscience, such as the 2014 Nobel laureate John O'Keefe. Many, including the authors of this volume, continue to directly and indirectly benefit from the downward dissemination of his influence through his many academic offspring.

Andrew SC Rice

Marshall Devor

Patrick Wall characteristically engaging an audience



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