Clifford J. Woolf, M.B., B.Ch., Ph.D.

Recipient of the 2004 Excellence in Research Award

IN a corner of the Boston Public Garden, Boston, Massachusetts, stands a tall, neo-Gothic monument commemorating the demonstration at Massachusetts General Hospital on October 16, 1846, by William T. G. Morton, M.D., that inhaling ether produces a reversible state of insensibility during surgery. The monument carries a quotation from the Book of Revelations, “Neither shall there be any more pain.” Unfortunately, that dream was not realized in 1846 and remains a dream to this day. Dr. Clifford Woolf has dedicated his professional career to dissecting the physiologic and biochemical mechanisms of pain sensation in what he passionately maintains is the essential first step in promoting a rational basis for the effective management of pain. He has done this with persistence, flair, imagination, and innovation. A measure of Woolf’s success is that he is the recipient of the 2004 American Society of Anesthesiologists Excellence in Research Award.

A medical student in Johannesburg, South Africa, in the early 1970s, Dr. Woolf was first confronted with the limitations of our empirical approach to analgesia. Coming across a surgical resident applying electrodes to the abdomen of a patient with postoperative pain, Dr. Woolf had the temerity to ask, “Why are you doing that?” and “How does it work?”—a habit he has never lost. The resident, who was dutifully applying the new therapy of transcutaneous electrical nerve stimulation, replied that the reason he was doing it was simple: to control the patient’s pain. As for how it worked, “Don’t know, don’t care, doesn’t matter.” This was one of those seminal moments that help to define a career. As Dr. Woolf was pondering that response, he also was influenced by a world captivated by all things oriental, particularly acupuncture (remember Nixon’s ping-pong diplomacy?). Into that mix, he added the discovery by Hans Kosterlitz and J. Hughes of pentapeptides from the brain with potent opiate agonist activity, the enkephalins. This potent combination led Dr. Woolf to question whether transcutaneous electrical nerve stimulation worked not by simply closing a gate to pain transmission, as proposed by Drs. Melzack and Wall, but instead by means of endogenous opioid activity induced by the electrical stimulation, which would also account for the analgesic effect of acupuncture.

Dr. Woolf committed himself to an unconventional, unplanned and informal M.D.–Ph.D. program. While a medical student, he sought to prove his hypothesis, working at the bench nights, weekends, and vacations. He somehow managed between patients to write his Ph.D. thesis while completing his internship at the Johannesburg General Hospital, Johannesburg, South Africa. Disproving his hypothesis, Dr. Woolf demonstrated that transcutaneous electrical nerve stimulation had only limited analgesic efficacy in rodent models and did not work *via* enkephalin release. This coincided with publication of several controlled studies that indicated no superior action for acupuncture analgesia over a placebo.

It was this disappointing but educational experience that even the sexiest of hypotheses can prove wrong that persuaded Dr. Woolf that starting with anecdotal clinical experiences and attempting to derive a biologic explanation was the wrong way to go about the study of pain. It was time to turn the approach on its head and attempt to let the comprehension of science drive clinical treatment. This professional realization coincided with another personal one. This was the height of the apartheid regime in South Africa, immediately after the Soweto riots, when the army, including conscripts, was being used to suppress “local disturbances” and fight a civil war in Angola. Dr. Woolf, due to be called up for army service a week after his internship ended, decided with his wife, Fredia, that they must leave South Africa—even if they could never return.

In early 1979, Dr. Woolf arrived in London, England, during what became know as the Winter of Discontent as the Labor Government collapsed as a result of uncontrollable strikes, garbage was not collected, bodies were not buried, and supermarkets were stripped bare—not an auspicious beginning for an immigrant. Looking for a postdoctoral position, he unexpectedly managed to get a lectureship at the Middlesex Hospital Medical School.
The Middlesex was the smallest of what was then the fragmented London University Medical School system. Contrary to his expectations of moving from a scientific backwater in Johannesburg to the cutting edge of modern science, he found the Department of Physiology at Middlesex trapped in a 1940s space war, with unmodernized laboratories, little active research, and few research staff or students, only endless lectures to bored students in the midst of the first round of heavy cuts in University funding by Thatcher. The atmosphere was sufficiently deadly that Woolf considered, instead of suicide, returning to internal medicine and obtained his membership of the Royal College of Medicine in preparation for this.

Rescue came late in 1979 when Dr. Woolf submitted a manuscript based on his Ph.D. studies to the journal Pain, which was then edited by Professor Patrick Wall. Wall was based at University College London, the largest constituent of the University of London and justly famous for the quality of its research. Dr. Wall was the indisputable giant of the pain field, a world-class neurophysiologist and the discoverer of the Spinal Gate Control Theory, which he had made with Ron Melzack when they were based at Massachusetts Institute of Technology. Dr. Woolf had written to Dr. Wall from South Africa but had received the all-too-familiar reply, “No postdoctorate positions available.” Nevertheless, on receipt of the manuscript, Dr. Wall invited Dr. Woolf to the University College London for a chat, and on discovering the difficulties Dr. Woolf would face in conducting any reasonable research project at the Middlesex, Dr. Wall asked Dr. Woolf on a sudden whim to join his research team. This resulted in an immediate profound transformation of Dr. Woolf’s research activities and prospects by Dr. Wall’s extraordinary mentorship. Suddenly, he found himself in the most active and innovative pain research laboratory in the world, led by one of the most effective, if somewhat eccentric, of postwar English intellectuals, and began active collaborative research projects with the other postdoctorate students in the laboratory, Tony Dickenson, Maria Fitzgerald, and Steve McMahon, each of whom have gone on to become leaders of pain research.

After learning the tools of electrophysiology, Dr. Woolf began at University College of London his first completely independent study. He decided that one way to understand the processing of sensory information in the spinal cord was to look at its output. He began recording from individual motor axons teased from the nerves to flexor muscles to study systematically the stimulus-response characteristics of the flexion withdrawal reflex as a surrogate for nociception or pain. This necessitated a preparation with no anesthetic, because general anesthesia itself induces loss of the flexion reflex. Borrowing from Sherrington’s classic work on cats, Dr. Woolf managed for the first time to produce a decerebrate-spinal rat preparation. During a short-acting anesthetic, the entire brain was removed, and the spinal cord was transected. The animal was then legally and clinically “dead,” but the spinal cord below the transection remained fully functional. Not surprisingly, Dr. Woolf learned that flexor α motor neurons showed minimal spontaneous activity and were activated only by noxious mechanical or thermal stimuli applied to the skin. The advantage of this preparation was that unlike recordings from uncharacterized cells in the dorsal horn (known in the Wall laboratory as ADCs, “any damn cell”), the neuronal activity in flexor motor units leads to a clear physiologic change, contraction of a flexor muscle, and represented the consequence of the integration of sensory input into the spinal cord and the activation of multiple polysynaptic circuits. During the course of these experiments, Dr. Woolf noticed that motor units recorded at the end of a day’s experimentation had much larger receptive fields and more vigorous responses than those he recorded at the beginning. By recording units continuously for many hours, Dr. Woolf discovered that this was not a sampling issue but the consequence of an evolving change in the properties of the neurons resulting from the repeated noxious stimulation of the periphery. He recognized immediately what this meant: an activity-dependent plasticity in the spinal cord increasing its responsiveness. This important phenomenon has become known as central sensitization. Although he managed to get a single-author manuscript accepted in Nature on this discovery in 1983,1 it took many years to persuade neuroscientists and clinicians that the phenomenon represented a major new insight into understanding the mechanisms of postinjury pain hypersensitivity. During this time, Dr. Woolf worked hard to show that the phenomenon could be detected in dorsal horn neurons,2 involved activation of N-methyl-D-aspartate receptors, was reduced by opiates, and contributed to tactile allodynia and secondary hyperalgesia. Nevertheless, he continued to face skepticism about its clinical significance, which stimulated him to collaborate in clinical trials on the relative merits of morphine analgesia given before or after surgery in an attempt to prevent or preempt central sensitization.3 It now seems difficult to believe, but at that time, there was enormous resistance from anesthesiologists and surgeons to administering an analgesic until a patient reported severe pain. It is one of Dr. Woolf’s major achievements that many now recognize that treating pain early is both scientifically valid and ethically essential.

Central sensitization, apart from contributing to postoperative and posttraumatic pain, has been shown to play a major role in neuropathic pain, migraine, functional bowel disorders, and fibromyalgia. We now recognize that pain may not always have a detectable peripheral trigger but can be the expression of a change in the function of the central nervous system and that
much of the tenderness we feel in clinical conditions is due to heightened sensitivity to normal sensory inputs, including those that would normally never produce pain. Expanding our understanding of plasticity in the spinal cord, he demonstrated that there is both a physical rearrangement of synaptic connections in the dorsal horn after peripheral nerve injury and a phenotypic switch in primary sensory neurons. Not only does the software of the system change, so does its hardware. Dr. Woolf eventually became a Professor of Neurobiology at University College of London and an Honorary Consultant at University College London Hospital.

In 1997, I recruited Dr. Woolf from a chilly lab in London, England, to Boston, Massachusetts, to become the first incumbent of the Richard J. Kitz Chair of Anaesthesia Research at Harvard Medical School and Director of the Neural Plasticity Research Group in the Department of Anesthesia and Critical Care at Massachusetts General Hospital. The attraction was twofold: an opportunity to retool his laboratory in a much more molecular biologic direction and to be part of Massachusetts General Hospital’s ongoing commitment to translating science from bench to bedside. During the time that Dr. Woolf has been at Massachusetts General Hospital, he has consolidated his new laboratory into one of the major centers of pain research in the United States. His research team has exploited subtractive hybridization and microarrays to reveal that hundreds of genes are regulated in pain-related conditions in dorsal root ganglion and dorsal horn neurons and has shown that some of these genes are likely to be the targets for completely new classes of analgesics. His laboratory has participated in the cloning of a novel nociceptor sensory neuron-specific sodium channel, defined the intracellular signaling pathways and ion channel/receptors that mediate central sensitization, and revealed that cyclooxygenase 2 is induced in the spinal cord after peripheral inflammation and that this is a major target for the analgesic action of cyclooxygenase inhibitors. Complementing this, Dr. Woolf has expanded the scope of his research to include an analysis of why the central nervous system does not regenerate and how neurons survive or die after injury.

On a personal level, Dr. Woolf’s devotion to his laboratory and fellows is exceeded only by his unwavering devotion to his family—his wife, Fredia, and two sons, Matthew and Alexander. To all, he is a Pied Piper leading to intermingle well. We hear stories about laboratory parties becoming overnight affairs in his home, with bodies littering his living room floor into the wee hours of the weekend.

Dr. Woolf also has a keen eye for style. Returning from London with a completely shaved head, we realized he was no frumpy Harvard professor.

Now that Dr. Woolf’s large multidisciplinary laboratory has gotten into its stride, we can confidently expect many more exciting discoveries to change the way we understand and treat pain. To exploit the increased insight that he and others have made into pain mechanisms, he has actively pushed for a new mechanistic approach to the diagnosis and treatment of pain and has taken the lead in trying to establish clinical tools for determining in patients what drives their pain and how likely they are to respond to particular treatments. Recognizing that abuse of slow-release opiates is a major societal problem, Dr. Woolf has dreamed up the ingenious idea of adding capsaicin, the pungent ingredient in chili pepper, to such formulations as a way to deter abuse by snorting, chewing, or injections.

Perhaps echoing the synaptic mechanisms underlying central sensitization, Dr. Woolf runs his laboratory as a facilitator, maximizing and increasing the efficacy of the activities of his talented, highly motivated and loyal research staff, including Andrew Alchorne, Gary Brenner, Jason Campagna, Mike Costigan, Joachim Scholz, and Tarek Samad, who have and continue to include many anesthesiologists working near the site of the first clinical demonstration of ether anesthesia in the Etherdome at Massachusetts General Hospital.

Dr. Morton showed in 1846 that sensation could be interrupted, which was a major breakthrough but obviously of limited use for nonsurgical pain. We need a means to control pain selectively, without resorting to a state of anesthesia or producing undesirable side effects or dependency. Dr. Woolf’s inspiring work indicates that this is surely not a pipe dream: Unraveling the molecular determinants of pain holds great promise for leading us to a means to make the dream a reality. It is certainly very exciting for Massachusetts General Hospital, which took the lead 158 yr ago, to again be taking the lead in the noble effort to control pain.

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References


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