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Topics in pain management: part 2 in a series

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## Postherpetic neuralgia (PHN): pain mechanisms and pathologies

A discussion with Dr Clifford J. Woolf

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### Clifford J. Woolf, MD, PhD

Dr Woolf is the Richard Kitz Chair of Anesthesia Research at Harvard Medical School and the Massachusetts General Hospital. Dr Woolf has made fundamental contributions to our understanding of pain mechanisms. Most notable among these contributions is a definition of pain hypersensitivity as a result of abnormal excitability of central nervous system neurons, also known as the phenomenon of central sensitization. Central sensitization was first described in a seminal study by Dr Woolf published in *Nature* in 1983. The identification of central sensitization has since led to new therapeutic approaches to pain management, including the concept of preemptive analgesia. Dr Woolf's work has also established new analgesic drugs such as NMDA receptor antagonists.

In addition to the discovery of central sensitization, Dr Woolf has spearheaded the discovery of several other key pain mechanisms, such as the reorganization of synaptic architecture in the spinal cord after peripheral nerve injury (central sprouting), transcriptional changes in sensory and spinal neurons (phenotypic switches), and loss of inhibitory interneurons (disinhibition). These findings collectively provide a basis for a mechanistic understanding of pain. Currently, Dr Woolf is leading a new mechanism-based approach to the diagnosis and treatment of pain.

Dr Woolf's work reveals that some forms of chronic pain, most notably, neuropathic pain, represent the development of a nervous system pathology and that optimal therapy should be aimed at treating the underlying causes of pain (disease management) rather than symptom control alone.

After training for his MD and PhD at the University of the Witwatersrand in Johannesburg, South Africa, Dr Woolf worked at University College London for nearly 20 years, latterly as a professor of neurobiology and as an honorary consultant at University College London Hospital.

In 1997, Dr Woolf established the Neural Plasticity Research Group based in the Department of Anesthesia and Critical Care at the Massachusetts General Hospital, affiliated with the Neuroscience Program at Harvard Medical School.

Dr Woolf has received many awards for his work in pain and regeneration research, including the Distinguished Young Investigator Award from the International Association for the Study of Pain, a Spine Society of Europe Medal, and a Bonica Medal from the Eastern Pain Association; he is the 2004 recipient of the American Society for Anesthesia Excellence in Research Award. Dr Woolf is the author of more than 300 publications.

## PHN pain mechanisms and pathologies

### A discussion with Dr Clifford J. Woolf

**Known for his pioneering work in neurobiology, Dr Woolf has made several pivotal discoveries in the areas of neural plasticity, central sensitization, and in elucidating the pathophysiology of chronic pain, among others. Here he shares his knowledge of PHN pain mechanisms and their critical role in selecting targeted treatment for chronic pain patients.**

#### How would you define localized pain?

"Some physicians think of localized pain as cutaneous or skin-generated pain. But localized pain just means localized to one part of the body, it doesn't necessarily mean it's restricted to the surface. Localized pain can also be felt as deep pain and is not exclusive to one particular pain state."

#### What role does localized pain play in postherpetic neuralgia?

"Postherpetic neuralgia is a peripheral neuropathic pain involving damage to restricted regions of the peripheral nervous system. PHN is, therefore, a type of neuropathic pain that has a regional topographic restriction—so localized pain is generally a prominent feature in this syndrome."

#### What is meant by the terms "peripheral" and "central sensitization," and is there a relationship between them?

"Peripheral sensitization is a reduction in nociceptor threshold. Usually, this occurs in response to inflammatory mediators and is restricted to the site of tissue damage. When the threshold is reduced, these nociceptors can be activated by stimuli that would normally feel innocuous. In PHN, a similar phenomenon can occur in the absence of inflammation, with a reduction of heat pain threshold.

"Central sensitization is an abnormal state of excitability within the central nervous system triggered by inputs from nociceptors, whereby normal innocuous inputs now generate pain.

"The connection between peripheral and central

sensitization is that high-threshold sensory fibers that have been affected by peripheral sensitization are more easily activated by peripheral stimuli, providing a bigger nociceptor input to the CNS, thus triggering the induction of central sensitization. Once central sensitization is produced, normally innocuous stimuli such as touch, vibration, and pressure are perceived as painful sensations. For example, peripheral input (such as ectopic input from injured nerves) can trigger a change in the function of the nervous system making it hyperexcitable and hyperresponsive. Think of central sensitization as the radio volume control of the sensory pathways of the nervous system. The peripheral input acts as the trigger that sets the volume dial. In a normal state the volume would be set at a tolerable level, but in the case of PHN, the volume is set at an uncomfortably high level."

#### What is the "wind-up" phenomenon, and how does it manifest clinically?

"'Wind-up' refers to the fact that a repeated stimulus with a steady intensity can produce a progressively increasing response in a patient. Testing for wind-up in a clinical setting can detect central sensitization. If a physician applies a repeated tactile stimulus to skin once every 2 seconds, and it produces more and more pain, almost to the point of being unbearable, that response would indicate an abnormal gain of the pain system, thereby resulting in the manifestation of central sensitization."

#### Should pain mechanisms guide treatment approaches?

"Identifying the mechanisms responsible for a patient's pain provides the starting point for selecting proper treatment. In the past, the standard treatment approach was trial and error, which was reflected by the clinical view that 'pain is pain.' Now we know there are quite distinct pain syndromes with different underlying mechanisms. We know that the most rational treatment strategy is to first identify what is causing the pain, and then target therapy to that specific mechanism."

#### Can addressing peripheral sensitization help dampen central sensitization?

"Addressing peripheral sensitization can be useful in 2 ways: it can reduce the nociceptor input that produces pain in its own right, which triggers central sensitization, and it can also reduce the low-threshold sensory input that, after central sensitization, is interpreted as painful. In the case of PHN, there are 2 elements that factor into

this differentiation. The first involves an abnormal sensitivity of the nociceptor in some patients, making them hypersensitive to stimuli. In the same way that someone who is sunburned responds to temperature in a heightened way, the affected nociceptors respond to normally innocuous stimuli with a heightened response. In this case, blocking peripheral activity can reduce the abnormal input to the nervous system, thus reducing pain generated by the nociceptors, and can also dampen the generation of central sensitization. The second element involves tactile allodynia. By reducing the input generated by light touch, you can reduce pain without necessarily affecting central sensitization."

#### How do Na+ channels factor into the development and maintenance of pain?

"Sodium channels are responsible for the excitability of neuronal membranes. Once a noxious stimulus such as a pinch or heat is converted by specific sensory transducer proteins into electrical activity in nociceptor terminals, the activity then generates, via sodium channels, action potentials that convey the information about the peripheral stimulus to the spinal cord. When peripheral nerve damage occurs, however, there is abnormal excitability in the nerve fibers, which generates abnormal, or ectopic, action potentials. Action potentials, whether normal or ectopic, can be interrupted by drugs such as local anesthetics that block voltage-gated sodium channels."

#### What is the rationale for early intervention in PHN?

"Early intervention in PHN makes sense for the patient, but its preemptive effect in aborting the development of the disease is difficult to prove. Ultimately we may be able not only to reduce symptoms but also the progression of the disease."

Although Dr Woolf received compensation for his participation, the opinions expressed herein are his own.

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**Inside** PHN pain mechanisms and pathologies:  
a discussion with pioneering neurobiologist Dr Clifford J. Woolf — Part 2 in a series

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