



## The Search for the Killer Painkiller

By **ANDREW POLLACK**

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**D**espite all the advances of modern medicine, the main drugs used to fight pain today are essentially the same as those used in ancient times.






Hippocrates wrote about the pain-soothing effects of willow bark and leaves as early as 400 B.C. Opium was cultivated long before that. Aspirin and morphine, based on the active ingredients in these traditional remedies, were isolated in the 1800's and helped form the foundation of the modern pharmaceutical industry.

But scientists are now trying to find new ways of fighting pain. The effort has been given new impetus by the recent withdrawal of Vioxx and the questions surrounding the safety of similar pills like Celebrex and Bextra. Those concerns come on top of the problems of abuse of narcotic painkillers like OxyContin. "There's a huge void, and no one is filling it," said Remi Barbier, chief executive of Pain Therapeutics, a company in South San Francisco, Calif.

But Dr. Barbier's company and dozens of others are trying. And some new treatments may come from things in nature that soothe or sting, like marijuana, hot chili peppers, nicotine and deadly toxins of snails and fish.

While the withdrawal of Vioxx leaves more room for newcomers, it also makes their challenge harder. Not only have opioids and aspirin been hard to beat, but the Food and Drug Administration is now expected to demand more evidence that drugs are safe before approving them.

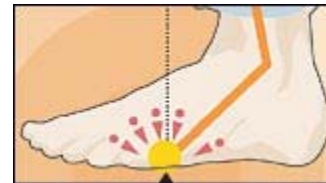
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But what scientists have going for them now is a more detailed, though still not complete, understanding of the molecular mechanisms by which pain is perceived. The goal is to create drugs that block specific parts of the mechanism while avoiding the side effects that have plagued opioids and anti-inflammatory drugs like aspirin.

Tens of millions of Americans suffer from chronic pain, according to various surveys, and millions more suffer acute pain from an illness or injury each year. Specialists say pain has received inadequate attention and treatment.

"Pain has historically been viewed as a symptom of other things that are more important," said Dr. Russell Portenoy, chairman of pain management and palliative care at Beth Israel Medical Center in New York. But now, he said, there is a growing realization that "chronic pain is itself an illness, and it's a complex illness."

Normal pain - from touching a hot stove, for example - is a beneficial warning system. After an injury nerves can become extra sensitive to pain. A warm shower can be painful on a sunburned back. That, too, is protective, said Dr. Clifford J. Woolf, a professor of anesthesia research at Harvard and Massachusetts General Hospital. The sensitivity forces a person to protect an injured area so it can heal.

But in some cases this nerve hypersensitivity continues well after the stimulus is gone, like an alarm frozen in the "on" position. The pain takes on a life of its own.

"Persistent pain is not just long-term acute pain," said Dr. Allan I. Basbaum, a professor of anatomy at the University of California, San Francisco and editor of the journal *Pain*. "The nervous system has changed."

Doctors classify pain into various categories, but there are two main types of persistent pain. One, sometimes called nociceptive pain, results from damage to tissues, as from arthritis or a burn. The other, called neuropathic pain, results from damage to the nerves themselves and is often set off by diseases like diabetes or shingles.

Opioids, like morphine or OxyContin, are used for more severe tissue-type pain. But the drugs have side effects, including constipation and a slowdown in breathing. Users can become tolerant, meaning that they need increasingly higher doses, or they become addicted to the drugs.

Aspirin and similar drugs like naproxen (sold under names like Aleve and Naprosyn) and ibuprofen (Advil and Motrin) are called nonsteroidal anti-inflammatory drugs or Nsaid's and are used for less serious pain. They block certain chemicals that contribute to inflammation, but they can also cause stomach ulcers and bleeding.

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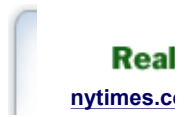
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