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THE EDITOR'S CORNER

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Take Two Aspirin (Part 2)

Patients and doctors often think of inflammation as a simple symptom, but it frequently becomes an integral and active feature of disease and, in a vicious cycle, perpetuates the ailment that it is signaling. This is why treating rheumatoid arthritis is so difficult, and why patients so often risk serious side effects from medications to get even temporary relief.

Ancient Egyptians used concoctions of myrtle leaves to treat joint pain and other discomforts. Hippocrates advocated using the sap of willow bark for similar complaints, as well as for fever reduction. The active ingredient in these timeless remedies is salicylic acid. In 1897, the Bayer Company in Germany developed a similar but more effective drug: acetylsalicylic acid, commonly known as aspirin. This simple, safe, and inexpensive remedy was the mainstay for treating pain and fever for decades, but we had to wait until the 1970s for Sir John Vane of England to explain exactly how it worked. He won the Nobel Prize for demonstrating that aspirin interferes with the formation of prostaglandins at injury sites by blocking an enzyme essential to their creation: cyclo-oxygenase, or COX. Although newer drugs such as ibuprofen, phenylbutazone, and indomethacin are chemically different from acetylsalicylic acid, they also act at the cyclo-oxygenase site in the cascade of prostaglandin synthesis. These drugs have become known generically as non-steroidal anti-inflammatory agents (NSAIAs).

NSAIAs clearly have limited ability to control pain, and they also have some fairly serious side effects. Yet they form a large part of the therapeutic foundation of modern medicine. In 1997, more than 77 million prescriptions were written for NSAIAs, and an equal amount of these drugs were bought over the counter. In the United States alone, this amounted to $8 billion. No one has figured out the cost of the side effects of NSAIAs, but 80,000 people are hospitalized each year, and about 8,000 of them die due to misuse of these drugs. The alternatives to NSAIAs, such as gold shots, immunosuppressants, and cortisone, have proven no more effective and,in many cases, so dangerous that they can be used for only short periods of time.

Phillip Needleman, chief scientist at Monsanto Company, is about to change forever the way we treat pain and inflammation. Dr. Needleman, a pioneer in prostaglandin research, became convinced a few years ago that inflamed cells produce a different kind of prostaglandin than normal cells do. That intuition yielded spectacular results when he discovered two distinct types of cyclo-oxygenase enzymes–COX-1, whose prostaglandins keep the stomach, platelets, kidneys, and other organs functioning properly, and COX-2, which is produced only when tissue is injured or inflamed.

G.D. Searle, Monsanto's pharmaceutical division, permitted Dr. Needleman to organize a large research team in a search for drugs that would have an affinity for COX-2 while sparing COX-1. Five years after the first publication of the two-enzyme theory, Monsanto treated its first patient with a new drug that did exactly this, appropriately named Celebra. Celebra has now been used in more than 10,000 patients in clinical trials for dental pain, rheumatoid arthritis, and osteoarthritis and has given spectacular relief without any side effects.

Evidence is also mounting that a significant reduction in inflammation over a long period will allow joints to heal permanently. Should this prove true, COX-2 inhibitors will represent far more than

symptomatic relief. They would impede the progress of the underlying disease itself. I hope a dental researcher somewhere is considering a test of the effect of these enzyme repressors on the chronic gingivitis often seen in orthodontic patients. COX-2 inhibitors also hold the potential to eliminate the need for addictive narcotics, such as codeine, Percodan, and Demerol, which are used to control severe pain. Imagine their utility for the pain commonly associated with orthodontic appliances, now usually treated with NSAIAs.

Cancer researchers are equally excited by COX-2 inhibitors, because the cellular mutations that occur prior to the onset of colon cancer are accompanied by huge levels of COX-2 enzymes. Test animals who received Celebra never developed the precancerous polyps that precede frank cancerous lesions. There is good evidence that other cancers, such as breast tumors, also involve high COX-2 enzyme levels. Alzheimer's disease is an affliction characterized by neuronal inflammation, which is lessened by NSAIAs. Celebra promises to slow the cognitive degeneration of Alzheimer's patients by at least 50%.

The economic potential for a drug this potent, this widely applicable, and apparently this safe is almost unlimited. I read a few months ago that had aspirin been developed recently, it would have taken 15 years of work and regulatory review before it would have been released, and the added expense of federal nitpicking would have made it cost $5 a pill. Clearly, something like that is occurring with Celebra, because I have seen a forecast price of $7 per pill. With the stakes so high, of course, Searle is not alone in the quest for a commercial product. Merck is developing its own COX-2 inhibitor, Vioxx, and the competition might bring the price down a bit. Nevertheless, for people who suffer horrific chronic pain and have received only modest relief and a lot of bothersome side effects from current remedies, a more expensive but effective and safe alternative such as Celebra or Vioxx might look like a real bargain.

COX-2 inhibitors promise to be the greatest advancement in the health sciences since the introduction of antibiotics, and could not be more timely for a growing population of elderly people beset with chronic inflammatory ailments. We can only hope the FDA doesn't drag its feet on this one, because our available therapies aren't getting the job done. □