Pain Management and End-of-Life Care CME Program

Module 2

Registration: The registration page and test questions are at the end of this article. The ten questions must be answered and submitted to the CSA in order to receive the CME credit. The full text of each module of this CME program, along with references, also will be accessible through the CSA Web Site, **www.csahq.org**.

Fees: This is a free service for CSA members. Non-members will be charged $25 per CME credit hour.

Availability: This program is available from June 30, 2004 until June 30, 2007.

Target Audience: California law now requires that every licensed physician complete 12 credit hours in pain management and end-of-life care by the end of 2006. This module fulfills one credit hour of CME toward that requirement. This program is intended for all licensed physicians, including anesthesiologists, residents, and physicians with an interest in pain management.

Faculty and Disclosures for Module 2:

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Dr. Prager has numerous consulting agreements with medical equipment and pharmaceutical companies, none of which represent a conflict with regard to the content of this article.

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The California Society of Anesthesiologists Educational Programs Division designates this educational activity for a maximum of 1 credit hour toward the AMA Physician's Recognition Award.

Your CME certificate will be mailed from the CSA office.

Evaluation: An evaluation of Module 2 of this series is offered after the test questions. Please fill in your responses to the questions and return them to the CSA office.

Objectives: Untreated pain produces many secondary effects that create changes in the overall health of the patient. This CME program enumerates some of the changes to allow the reader to understand how earlier intervention can be more beneficial than merely reducing a patient's pain.

Resources: To complete this program for CME credit, please refer to the figures that accompany the program. A PDF file of these slides is available for viewing on the CSA Web Site, **www.csahq.org**, on the page for the CSA Online CME Program, Module 2. If you do not wish to use the online file, you may contact the CSA office at (800) 345-3691 and request a fax copy of the slides.

Is Untreated Pain a Disease?

By Joshua Prager, M.D., M.S.

Assembly Bill 487 mandates that physicians in California complete 12 educational hours of pain management and end-of-life care in order to be relicensed. This legislation was passed as a result of a lawsuit that reached a verdict in June of 2001. In this suit, a family sued a physician in a pain management-related case and was awarded $1.5 million. MICRA protects physicians from verdicts of more than $250,000 for pain and suffering in malpractice cases in California. In this case, the family of the deceased patient sued for elder abuse and was awarded sixfold the MICRA limit. Brad Stuart, M.D., Director of Hospice for Northern California, indicated, "The fact that a physician was found guilty of elder abuse is a terrible thing … it is a serious wake-up call to physicians that we must begin treating pain the way we treat disease."[1]

Although pain is not considered by most physicians to be a disease in a classic sense, untreated pain produces many secondary effects that create changes in the overall health of the patient. This article enumerates some of the changes to allow the reader to understand how earlier intervention can be more beneficial than merely reducing a patient's pain.

In order to understand the changes that occur as a consequence of untreated pain, we will first briefly review pathways of pain transmission. The first author to connect a peripheral pain sensation to a pain pathway was Descartes in 1664 (Figure 1).[2] He likened the transmission of pain to the pulling of a delicate thread to a bell that hangs at the other end in the brain. In the intervening centuries, considerable progress has been made in understanding these pathways, especially with the more frequent use of functional magnetic resonance imaging (fMRI) during the last decade.

There are four distinct neurophysiologic processes involved in the pain experience: transduction, transmission, modulation, and perception.

- **Transduction** is the process in which a painful stimulus is converted to a neurophysiologic signal in sensory nerve endings.

- **Transmission** is the process of conduction of the impulses that are generated by the painful stimulus along the nerves to the central nervous system; the major synapses for these nerves are located in the dorsal horn of the spinal cord and in the thalamus. There are projections to cingulate, insular, and somatosensory cortices. Earlier thinking only described the projections to the somatosensory cortex.

- **Modulation** is the process in which pain transmission can be altered. Impulse transmission in both the peripheral nervous system and in the central nervous system can be modulated in an inhibitory fashion by a descending pathway from the brain. The pathway is directed to synapses in the dorsal horn to inhibit pain signals from leaving the horn and ascending up the spinal cord. More recent information describes excitatory mechanisms that can increase nociceptive impulse transmission as well.

- **Pain perception** probably lies at the level of the thalamus. The cerebral cortex is essential for the discrimination of specific sensory experiences.

Complete discussions of pain transmission can be found elsewhere and are not the intent of this article. What follows is a discussion of some of the changes in the pain pathway that occur as a consequence of untreated pain.[3]

Change #1: Genetic induction and protein production in the spinal cord.

In one study in rats, epidural catheters were placed prior to burning the rats' tails. Half of the rats were administered bupivacaine in their epidural space prior to burning their tails. The rats were sacrificed and their spinal cords were examined. The rats that were not administered any local anesthetic in their epidural catheter demonstrated production of C-FOS in the dorsal horn of the cord. (Figure 2.) Those rats that were administered bupivacaine did not demonstrate this. The fact that the rats that had the pain signal to the cord blocked by bupivacaine did not produce C-FOS demonstrates that pain stimuli can induce a gene that then produces the synthesis of C-FOS in the cord. Although the exact significance of the C-FOS is not understood, the fact that its action can be inhibited by blocking the signal is profoundly important.

Change #2: True structural changes occur in the spinal cord in neuropathic pain.

Allodynia is defined as an innocuous stimulus producing a severe pain. Until the work of Clifford Woolf,[4] we did not have an anatomic model for allodynia. Woolf's classic work explaining allodynia describes the changes that occur in the dorsal horn of the cord. C-fibers, also called the polymodal nociceptors, carry chronic pain information from the periphery to the spinal cord. A-fibers carry normal sensations to the cord. C-fibers synapse in the substantia gelatinosa, that is lamina II of the dorsal horn. Nonpainful sensations synapse elsewhere. Readers are urged to read Woolf's landmark article in which he suggests that with allodynia communication occurs, that is, interneurons grow into lamina II, such that normal sensation is brought to that section of the cord that receives pain information. This information is then transmitted cephalad as pain information although its origin was not pain. (Figures 3, 4 and 5.)

Change #3: Loss of pain inhibition.

The descending pathway for pain from the brain descends through the spinal cord to activate neurons in the dorsal horn. These neurons inhibit transmission of pain information from the periphery to the dorsal horn. Animal models suggest that neuropathic pain induces apoptosis (death) of these inhibitory cells

in the spinal dorsal horn.[5] (Figure 6. The white areas represent cell death.) The significance of loss of inhibitory neurons is profound. Without the ability to inhibit information, due to cell death, pain signals are not attenuated and essentially we lose our ability to ignore pain signals. We are consistently presented with a plethora of information which our nervous system must interpret. Inhibition is one aspect of processing this information.

Change #4: Peripheral nerve injury can produce sprouting of sympathetic nervous tissue producing communication between the autonomic nervous system and the somatic nervous system.

Paravertebral sympathetic ganglia contain fibers that arise both from the intermediate lateral cell column of the spinal cord (preganglionic fibers) and the cell bodies of fibers that extend efferently to target organs (grey communicating ramus). McClelland[6] demonstrated that eleven days after sciatic nerve ligation in rats neuromas formed, and subsequently, perivascular axons formed a ring around the dorsal root ganglion. Figure 7 shows sympathetic nervous tissue sprouting from the dorsal root ganglion associated with the sciatic nerve. Dorsal root ganglia immediately above (not associated with the sciatic nerve) did not demonstrate sprouting of sympathetic nervous tissue. Similarly, dorsal root ganglia associated with the sciatic nerve on the contralateral side did not demonstrate sprouting of sympathetic nervous tissue. Fine sprouts increase in density in a period of 30 days following injury. These data support the role of the sympathetic nervous system in hyperalgesia by creating aberrant innervation of the dorsal root by sympathetic terminals. Chemical sympathetic blockade can alleviate stimulus induced responses. In many neuropathic pain syndromes, sympathetically mediated phenomena occur subsequent to the nerve injury. This information provides an explanation for this phenomenon by demonstrating the anatomic changes that occur following the nerve injury.

Change #5: Receptive field changes in the brain occur as a consequence of untreated pain.

The classic model of pain transmission suggests that pain information is transmitted from the periphery through the cord with an eventual projection to the contralateral somatosensory cortex. More recently, fMRI has also demonstrated increased activity in the limbic system, in particular, in the anterior cingulate cortex.[7] (Figure 8). This has a particular importance because the limbic system is responsible for affect and may explain the suffering component of pain. In addition, the limbic system contributes to depression,

anxiety, sleep, appetite and libido. With the demonstrated connection to this area of the brain we now have an explanation for the behavioral changes that occur in pain patients that represent far more than merely a physical response to a painful stimulus.

Other areas in the brain with demonstrated changes by fMRI are the dorsolateral prefrontal cortex (DLPFC). This area in the brain is important in cognitive and attentional roles. In addition, the DLPFC plays an important role in the descending inhibitory influence on the medial thalamus and mid-brain pain-related structures that influence the remaining aspects of the descending pathway for pain -and hence, a role in pain modulation.

Furthermore, preliminary data suggest decreased contralateral thalamic activity with chronic pain. Thus, there are marked receptive field changes in the brain that have global impact on a person's well being.

In 1864 Silas Weir Mitchell, a Civil War physician, described what we now term complex regional pain syndrome, in vivid words, "We met with a small number of men who were suffering from a pain which they described as a burning or mustard red-hot or as a red-hot file rasping the skin.… The part itself is not alone subject to an intense burning sensation but becomes exquisitely hyperesthetic so that a touch or a tap of the fingers increases the pain. Exposure to the air is avoided with a care which seems almost absurd.… The seat of burning pain is very various.… Its intensity varies from a most trivial burning to a state of torture which hardly can be credited but which reacts on the whole economy until **the general health is seriously affected**."[8] Thus we see that 140 years ago Mitchell wrote about a pain syndrome that affected the general health. In the intervening years medical education has barely noted this concept in its teachings.

Disease is defined as an interruption, cessation, or disorder of bodily function, system, or organs; or an identifiable group of signs and symptoms, or consistent anatomical alteration.[9] With this definition, changes that are enumerated above meet the definition of disease. Clearly, untreated pain causes a variety of changes that can affect the general well being of the individual. Thus, as physicians, we should attempt to prevent pain from progressing from being a noxious stimulus to becoming a constellation of phenomena affecting the entire being.

References

1. *Los Angeles Times*, June 15, 2001

2. Melzack R, Wall PD. Pain mechanism: a new theory. *Science*. 150:971, 1965
3. Galer B, Gammaitoni A, Alverez N. Pain in American College of Physicians, *Medicine*, 2004.
4. Woolf CJ, Mannion RJ. Neuropathic Pain Aetiology Symptoms, Mechanisms, and Management. *Blanchett*, Volume 353, June 5, 1999.
5. Schotz J, Broom DC, Lekan H A, Coggeshall RE, Woolf CG. Animal Models of Neuropathic Pain Induce Apoptosis in Spinal Dorsal Horn. International Association for the Study of Pain Annual Meeting, San Diego, August 2002.
6. McLachlanem Janig W, Devor M, Michaelis M. Peripheral Nerve Injury Triggers, Noradrenergic Sprouting Within Dorsal Root Ganglia. *Nature* 1993, 363:543-546.
7. Rezai A, Stanton-Hicks M. Imaging the Brain and CRPS. North American Neuromodulation Society Annual Meeting, Orlando, Florida, May 2004.
8. Mitchell SW, Moorehouse GR, and Keen WW. *Gunshot Wounds and Other Injuries of Nerves.* Philadelphia, J.B. Lippencott, 1864.
9. Stedman's Medical Dictionary

To complete Module 2 for CME credit, please fill out the registration form on page 55, answer the test questions and the evaluation questions on pages 56 and 57, and send copies of all these pages to the CSA office by fax or mail.

Registration

To register for the CSA CME Course in Pain Management and End-of-Life Care, Module 2, fill out this form. Then make copies of the test and evaluation. Once you have answered the questions, **mail or fax** the form, the test answers and the evaluation to the CSA office at:

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Is Untreated Pain a Disease?-Cont'd

Questions

1. The substantia gelatinosa is

    a) Part of the dorsal root ganglion
    b) Lamina V of the dorsal horn of the spinal cord
    c) Part of the somatosensory cortex of the brain
    d) Lamina II of the dorsal horn of the spinal cord
    e) Part of the thalamus

2. Pain perception is predominantly at the level of

    a) The spinal cord
    b) The thalamus
    c) The peripheral nerve
    d) None of the above

3. The descending pathway for pain can

    a) Inhibit pain
    b) Amplify pain
    c) Both A and B
    d) None of the above

4. All of the below are distinct neurophysiological processes involved in the pain experience except

    a) Transduction
    b) Reaction formation
    c) Transmission
    d) Modulation
    e) Perception

5. The fact that bupivacaine administered to rats in the epidural space inhibited the development of C-FOS when the rats were provided painful stimuli suggests

    a) Bupivacaine is a C-FOS inhibitor
    b) By inhibiting pain signals, bupivacaine inhibited genetic induction
    c) There is no relationship between bupivacaine and C-FOS
    d) C-FOS causes neuron growth

6. When the sciatic nerve was ligated in the study cited, sympathetic fibers were seen at

    a) The ipsilateral dorsal root ganglion
    b) Bilaterally at the dorsal root ganglion
    c) Ipsilaterally at levels above and below the dorsal root ganglion
    d) At the contralateral dorsal root ganglion

7. Weir Mitchell was the first to comment about pain as a disease

Is Untreated Pain a Disease?-Cont'd

a) at the turn of the 20th Century
b) in the l860s
c) in the l950s
d) in the l980s
e) in the year 2000

8. With neuropathic pain, interneurons can grow in the dorsal horn of the spinal cord

a) True
b) False

9. With neuropathic pain there can be death of inhibitory neurons in the dorsal horn of the spinal cord

a) True
b) False

10. On functional MRI, changes of perfusion can be seen in

a) The somatosensory cortex
b) The prefrontal cortex
c) The thalamus
d) The anterior cingulate cortex
e) All of the above

Evaluation

As part of the CSA Educational Programs Division's ongoing efforts to offer continuing medical education, the following evaluation of this program is requested. This is a useful tool for the EPD in preparing future CME programs.

1. How well were the learning objectives of this program met?

Very Well	5	Above Average	4
Average	3	Below Average	2
Not Well at All	1		

2. How relevant was the information in this program to your clinical practice?

Very Well	5	Above Average	4
Average	3	Below Average	2
Not Well at All	1		

3. How would you rate this program overall?

Very Well	5	Above Average	4
Average	3	Below Average	2
Not Well at All	1		