

**Highlights of
the NIH Pain Consortium
5th Annual Symposium on Advances in Pain Research
NIH Lipsett Auditorium, Clinical Center
May 5, 2010**

This symposium focused on moving towards personalized pain management through development of tools for individualized pain management, translation of research into tailored clinical practice, and examination of emerging therapies for individualized pain management.

Introduction and Welcome

Lawrence Tabak, D.D.S., Ph.D., Director, National Institute of Dental and Craniofacial Research and Pain Consortium Co-Chair

Dr. Tabak reviewed the mission, history, and goals of the Pain Consortium since its founding in 1996. The Consortium's mission is to support and expand pain research and promote collaboration across the NIH institutes and centers (ICs) that participate. Its current goals are to (1) develop a comprehensive, forward-thinking pain research agenda for NIH, (2) identify key opportunities in pain research that provide multidisciplinary and trans-NIH participation, (3) increase visibility for pain research supported by NIH through intramural and extramural programs and (4) pursue pain research through public-private partnerships whenever applicable.

Key research areas include basic mechanisms of pain, effective pain management, individual differences in pain sensitivity and therapeutic response, and biobehavioral aspects of pain perception. In fiscal year 2009, NIH allotted \$333 million for pain research; the estimated figure for FY 2010 is \$341M. In addition, the American Reinvestment and Recovery Act of 2009 (ARRA) funding for pain research in FY 09 was \$53M, and is estimated to be \$31M this year.

Dr. Tabak provided examples of NIH research supported by special programs such as the Roadmap Transformative R01 Program, ARRA Challenge Grants, and recent Funding Opportunity Announcements issued by ICs participating in the Pain Consortium and the Blueprint Grand Challenge Program.

A component of health-care reform legislation relevant to the Pain Consortium includes a plan for an Institute of Medicine Conference on Pain, requirement that the Pain Consortium submit annual recommendations to the NIH Common Fund for pain research initiatives, improved coordination of pain related by establishment of an Interagency Pain Research Coordinating Committee and health-care education and training.

The Pain Consortium website (<http://painconsortium.nih.gov/>) has information on research funding opportunities, contact information for Consortium representatives, and activities related to pain research. Dr. Tabak closed by thanking the members of the symposium's organizing committee .

Message from the American Pain Society (APS) Representative

Ronald Dubner, D.D.S., Ph.D., Professor and Chair of the Department of Biomedical

Sciences at University of Maryland Dental School and Past-President, American Pain Society

On behalf of the APS, Dr. Dubner related the mission and vision of APS. The society's mission is to bring together a diverse multidisciplinary group of scientists, physicians, and other professionals to increase the knowledge of pain and transform public policy and clinical practice to reduce pain-related suffering. APS's vision is of a world where pain prevention and relief are available to all people.

The strongest area of interest of the APS membership, which includes physicians, basic scientists, psychologists, and nurses, is chronic pain. The APS addresses issues related to research, education, treatment, and advocacy. Among its programs and services are an annual scientific meeting, the *Journal of Pain*, evidence-based guidelines for treatment, APS e-news, clinical centers of excellence program, advocacy for increased funding and federal legislation for pain research, a small grants program, and a pain research award. Dr. Dubner stated that the need for funding advocacy is demonstrated by the fact that only 0.53% of the NIH budget in fiscal year 2008 was allotted for pain research.

APS accomplishments in 2009-2010 include receipt of training award for young investigators to attend the annual meeting, continuation of small research grant awards, partnering with the Rita Allen Foundation on two grants (\$50,000 per year for 3 years); advocating for increased NIH funding for basic pain research and educating about available NIH resources (e.g., transformative R01s, the Challenge Grant Initiative of the NIH Blueprint for Neuroscience Research); encouraging volunteers to serve on NIH study sections; educating individuals at APS annual scientific meetings, publishing in three areas for an evidence-based clinical guidelines program as well as the 6th edition of *Principles of Analgesic Use*, and advocating for a National Pain Care Policy Act (which was included in the recently passed health-care bill),.

Future APS goals in partnership with the NIH Consortium are to obtain trans-NIH recognition of persistent pain as a problem, to enhance awareness of co-existing factors of chronic pain disease, such as sensory, psychosocial, and digestive conditions (as in fibromyalgia and irritable bowel syndrome), and to encourage a trans-NIH initiative on nonpharmacological supplements for chronic pain management.

Session 1: Developing tools for Individualized Pain Management

Moderator: *Linda Porter, Ph.D., National Institute of Neurological Disorders and Stroke*

Assessment Tools To Characterize Individual Pain Phenotypes

Clifford J. Woolf, M.B., B.Ch., Ph.D., Children's Hospital, Boston

Dr. Woolf described his research as a translational project to define pain phenotypes in patients. Contributing factors to a pain phenotype could include the type of disease (nature, duration, location, extent), psychosocial and economic factors associated with pain (affecting the individual family, culture, society), genotype (including polymorphic genes), and neurobiological mechanisms of pain. As a tool for identifying a pain fingerprint, Dr. Woolf devised a list of 85 items to collect during a standardized interview and physical exam. The multidimensional information that is collected is entered into datasets for correlation of data points with pain presentation. Among 187 patients, Dr. Woolf identified

groups with four types of pain that were not disease based. Dr. Woolf and colleagues then looked further at the relative frequency of pain-related symptoms (e.g., patients' complaints, deep pain, warmth- or cold-evoked pain, numbness) to create a classification tree analysis of the results. They conducted a follow-up study that applied the 85 item approach to low back pain patients, which showed greater diagnostic sensitivity than an MRI.

The researchers do not know yet whether this new approach can identify responders to different treatments, whether the pain phenotype can change in response to treatment, or whether individuals at risk of pain chronicity can be identified.

Developing Imaging Biomarkers of Analgesic Effects

David Borsook, M.D., Ph.D., McLean Hospital, Harvard University

Dr. Borsook spoke about defining pain phenotypes by using imaging technology to identify and measure changes in brain structure and function in response to chronic pain. Imaging may provide a useful tool for identifying biomarkers of chronic pain in certain disease states and to identify the affects of analgesic medications on pain induced altered brain function. Altered brain activity in response to chronic pain maps to particular parts of the brain. In addition, structural changes such as reduction of gray matter is detected in chronic pain states. The potential reversal of the structural and functional changes, by analgesic drugs such as morphine is of particular interest.

When trying to use imaging to differentiate drugs by their effects on brain activity, Dr. Borsook found that some drugs were distinguishable from one another, but not as applied to specific pain conditions. It looks as if biomarkers will have to be determined with multiple criteria. Future research in this area may be aided by a new imaging consortium for drug development as well as by FDA interest in this topic. Such future work may look at use of brain imaging of metabolites and brain arrays (patterns of activation) for drugs and diseases, and also for presymptomatic changes in brain structure in patients with chronic diseases.

Methodology for Adaptive Treatment Strategies for Chronic Disorders: Focus on Pain

Susan A. Murphy, Ph.D., University of Michigan

Dr. Murphy stated that optimal treatment strategies for chronic pain can be designed based on on high-quality, but inexpensive measures of patient responses to treatments. "Adaptive" refers not only to the initial personalization of treatment type and dosage, but to continue to adapt and readapt the treatment strategy as the patient progresses over time, a process that requires sequential decisions.

An important part of the adaptive strategy is determining the best sequences of treatments, the best timing for changes in treatments, and the information needed make these decisions. One approach is to use sequential multiple assignment randomized trials (SMART), in which crucial decisions are coupled with subject randomization at each of multiple stages of the clinical trial. Sample size is important for ensuring enough statistical power to get useful results.

The SMART approach is helpful in identifying positive synergies with combined treatment strategies. For example, treatment A may not appear best initially but may have enhanced long-term effectiveness when followed by maintenance treatment B. SMART is also useful in identifying negative synergies, such as increased side effects. For example, treatment A may produce a high proportion of early responders but also cause side effects that reduce the options for subsequent treatments for those who did not respond initially to treatment A. In other words, the burden imposed by treatment A may be sufficiently high so that early non-responders are not likely to adhere to subsequent treatments.

SMART design success depends on choosing primary hypotheses of scientific importance that aid in developing the adaptive treatment strategy and choosing secondary hypotheses that further develop the adaptive treatment strategy. The approach is simple, and randomization eliminates confounding. SMART allows for collection and examination of intermediate outcomes. Dr. Murphy provided several examples of theoretical and actual SMART studies, noting that secondary analyses of pretreatment variables and outcomes can provide evidence for more deeply individualized adaptive treatment strategies.

Moving from the Means to the Standard Deviations in Pain Research: Novel Approaches To Characterize Pain Phenotypes

Christine Miaskowski, R.N., Ph.D., FAAN, University of California, San Francisco

Dr. Miaskowski presented novel methods to evaluate intra- and inter-individual differences in disease symptomology and to identify subgroups of patients with different response patterns to interventions. One was from a study at UCSF; “Evaluation of Inter-Individual Differences in Pain And Analgesic Use in Oncology Patients Receiving Standard Care,” which uses hierarchical linear modeling. Because hierarchical linear modeling can predict trajectories of treatment response and evaluate inter-individual differences using predictors from baseline pain and analgesic scores, it can accommodate unbalanced trial designs, allow for data analyses when the number and spacing of the assessments vary across respondents, enable modeling of individual change in response to treatment, and allow for the identification of more complex patterns of changes in patient responses. Another example was a project called the “Effectiveness of the PRO-SELF Pain Control Program,” which looks at primary and secondary outcomes when a psycho-educational intervention is compared to standard care for oncology outpatients with pain from bone metastasis. The PRO-SELF Plus randomized clinical trial tested the effectiveness of two different doses of a psycho-educational intervention and evaluated sustainability and effects of pain management on other symptoms common in oncology patients (e.g., fatigue and sleep disturbance). The study utilized Growth Mixture Model Analysis to identify subgroups of participants with different symptom experiences for depressive symptoms to identify individuals who are at greatest risk for depressive symptoms, and to develop individualized interventions. The conclusions of the PRO-SELF Pain Control Program were that one-size psycho-educational intervention does NOT fit all oncology patients.

Another UCSF study, “Evaluation Of High Risk Patients Based On Their Experience With A Specific Symptom Cluster” used hierarchical cluster analysis to evaluate whether subgroups of patients with different experiences with a specific symptom cluster (pain, fatigue, sleep disturbance, and depression after radiotherapy) differed on important clinical outcomes. For example, patients scoring high on symptoms tended to be younger and less likely to be married or partnered, while patients scoring low had higher scores on quality of life.

Session 2: Translating Research into Tailored Clinical Practice

Moderator: David Thomas, Ph.D., National Institute on Drug Abuse

Identifying Risk Factors for Postsurgical Pain

Robert Edwards, Ph.D., Brigham and Women’s Hospital, Harvard University

Dr. Edwards stated that his aim is to improve postsurgical outcomes by designing, tailoring, and adapting to the factors shaping an individual’s risk for developing chronic post surgical pain. He discussed the prevalence and nature of persistent pain after various surgical procedures and the preoperative risk factors identified as correlates of postoperative pain. As the number of surgeries in the U.S. continues to expand at a fast pace, so does the amount of pain. Dr. Edwards showed data on persistent pain after a wide range of surgical procedures.

The most consistently observed risk factor for persistent postsurgical pain is severe acute postoperative pain. Other identified factors are preoperative pain in the area near the surgical target, pain problems elsewhere, and general stress and anxiety. Both animal and human studies suggest that smoking also can increase risk for postsurgical pain. Sleep onset insomnia symptoms during hospitalization for major burn injury are also predictors of chronic pain.

When looking at individual differences in pain sensitivity, researchers found substantial inter-individual variability for heat pain thresholds among 306 female college students. Another study showed that presurgical heat pain responses predicted postsurgical pain.

Diffuse noxious inhibitory control (DNIC), a term for how a second noxious stimulus can inhibit the response to an initial noxious stimulus, was applied to show that a presurgical DNIC can decrease postsurgical pain after thoracotomy or mastectomy.

When looking at catastrophizing (a set of negative cognitions, emotions, attitudes, and beliefs related to pain) both before and after surgery, researchers found that catastrophizing continued at the same level after several types of surgery, despite a decrease in pain. Higher levels of catastrophizing are associated with elevated interleukin-6 reactivity to pain. More IL-6 is also present in patients with failed disc surgery compared to individuals with successful disc surgery and with pain-free controls.

A multivariate analysis of various preoperative factors (e.g., of pain, distress, sleep, and education) can be effective in predicting long-term chronic pain up to seven years after surgery.

Trends and Risks of Chronic Opioid Therapy Among the Elderly
Michael R. Von Korff, Sc.D., Group Health Cooperative

Because NSAIDs and Cox-2 inhibitors are no longer drugs of choice for older patients, opioids are among a limited number of options. Dr. Von Korff focused on safety of chronic opioid therapy (COT) and tailored COT.

The American Geriatrics Society has recommended the choice of opiate therapy for chronic, severe pain, but Dr. Von Korff said the evidence for this recommendation is low quality. It is important therefore, to determine opiates' short- and long-term risks and level of pain control by considering both adequacy of pain control and patient safety along with the societal concerns about drug overdose, addiction, and abuse. Treatment guidelines for opiates are based on evidence from rather small, short-term trials in which partial pain relief was observed, along with some improvement in function

Dr. Von Korff and collaborators have used records and surveys to characterize plan participants at Group Health Cooperative and Kaiser-Permanente of northern California who take opioids. Between 1997 and 2005, the overall rate of opioid use increased from 2% to 4.5% among all adults, while opioid use in women over age 65 with severe pain increased from 8 to 9%. While many of the patients said that opiates were helpful, most indicated that they still had moderate to severe pain. Other research showed that death rates from opiate overdoses tripled during the study period, with 63% related to diverted drugs. From death certificate data, overdose deaths were more likely to occur among individuals under age 65 but did not drop off sharply with age

In community practice there was a nine-fold increase in overdose risk for those taking higher drug doses vs. lower ones. The health plan data also indicated that older people were more likely to overdose and were twice as likely to experience bone fractures than people under 65.

Dr. Von Korff reminded the audience that the effectiveness of opiates for pain control remains an open question. He noted a need for further understanding of complicating factors that can occur among patients on opiates, including overdose potential, serious fractures, hyperalgesia, aspiration pneumonia, exacerbation of depressive illness and sleep apnea, (fecal impaction, sexual dysfunction, dry mouth, opioid abuse and dependence, opioid diversion to family members, and motor vehicle accidents.

In addition, the following questions need to be addressed before health-care practitioners can tailor chronic opioid therapy to individuals: How does the COT risk-benefit ratio change with increasing opioid dose? Do risks differ for long-acting vs. short-acting opiates? (How are opiates actually being used in community practice? What are acute and chronic adverse effects of COT among patients with physical or psychological comorbid conditions? Does careful selection of patients for COT reduce risks? Does close monitoring of patients receiving COT reduce risks? To what extent do COT patients achieve sustained benefits in terms of participation in work and family life?

Psychopathology as a Predictor of the Efficacy of Pain Management Strategies
Ajay D. Wasan, M.D., M.Sc., Brigham and Women's Hospital, Harvard University

Dr. Wasan presented his work concerning how psychiatric symptoms impact pain treatment response at the level of the individual responder. He noted that negative affect can be a kind of central organizing principle when thinking about high levels of various psychiatric symptoms in patients with chronic, non-cancer pain, and that studying negative affect is a way to understand influences on treatment outcomes.

Affect refers to emotions, thoughts, and vital sense. Negative affect refers to a disrupted, poor, maladaptive state of affect involving sad emotions, an angry or anxious mood, and generally feeling helpless, hapless, and hopeless. The basis in the brain for negative affect appears to be related to heightened pain sensation.

Dr. Wasan grouped the types of psychiatric symptoms associated with chronic pain into two categories: core psychopathology and pain-related psychiatric symptoms. With some overlap, the first includes general anxiety, major depression, and character pathology, and the second includes pain, anxiety, catastrophizing, low self-efficacy, poor coping, and pain-related anger. 30% to 80% of patients presenting with pain have a psychiatric co-morbidity, and psychiatric problems repeatedly have been shown to be the strongest predictor of poor pain and disability outcomes.

Little research has been done on effectiveness of specific treatments and responders, based on the level of psychiatric symptoms. Dr. Wasan described relevant studies. The first study assessed response to opioid analgesia (IV morphine) for low-back pain in a double-blind, placebo-controlled, random crossover study of three groups with high, moderate, or low levels of psychiatric symptoms. The researchers found that patients with low psychopathology reported greater pain improvement (60%) than patients with severe psychopathology.

Dr. Wasan's group also looked at the level of facet pain before and after common nerve block procedures in a pain clinic. Again, patients with less severe psychopathology had a significantly higher improvement than those with severe psychiatric symptoms.

In a single-blinded study of acupuncture treatment (vs. needling at a sham point) for low-back pain, both the low and high psychopathology groups had 30% to 35% improvement, whereas the high psychopathology group had the lower response to the placebo treatment suggesting that psychiatric problems cannot explain everything.

Pain in Rheumatoid Arthritis: More Than Inflammation

Daniel H. Solomon, M.D., Ph.D., Brigham and Women's Hospital, Harvard University

Dr. Solomon recounted that two to three million Americans experience rheumatoid arthritis (RA), and that pain is an issue for them. Arthritis pain is linked with inflammation and occurs at multiple levels (e.g., affecting the synovial lining and cartilage).

He discussed several studies, the first of which looks at determining clinical predictors of pain in RA patients in disease activity score (DAS) remission. Despite this remission, many

of these patients still have pain. In a one-year longitudinal study of a cohort of 159 arthritis patients which had been treated aggressively, researchers found that one-third still had substantial pain. Correlating factors that predicted a high pain score at one year were a high pain score at baseline on the multidimensional health assessment questionnaire, being younger, being male, and having fatigue—with the baseline score as the strongest factor. Next researchers looked at quantitative pain and pain pressure thresholds and how these relate to disease activity, psychiatric distress, and overall pain sensitivity. In a cross-sectional study of 59 female RA patients, pressure pain thresholds were measured at three spots (wrist, thumb, trapezius), along with psychiatric distress and sleep problems. Conclusions of the study were that high C-reactive protein levels were associated with low pain thresholds at the wrist, but not at non-joint sites, and sleep problems were associated with low pain thresholds at joint and non-joint sites. Inflammation may heighten pain sensitivity at joints, and poor sleep may increase widespread pain sensitivity.

Dr. Solomon reported on a study of prescription opioid use among older adults with arthritis or low-back pain in a large Medicare population. Patients with RA had higher opioid use than patients with low back pain or osteoarthritis. Distinct predictors of chronic opioid use were found for the different groups of patients. For example, history of GI disease was a predictor of chronic opioid use in patients with low back pain, but not for those with RA. Use of psychiatric medications correlated with high chronic opioid use in all patient groups.

Rates of adverse effects of opiates were compared with those of COX-2 inhibitors or NSAIDs. For patients on opiates, the risk of cardiovascular events and fracture rates were higher. It is the short-acting opiates that are most often associated with fractures, usually early during their use.

Conclusions are that anatomic patterns of pain and pain pressure thresholds give clues to pain etiology and , chronic opioid use is common in RA, and is associated with significant toxicities. Better strategies for analgesia are needed—even in conditions like RA.

Announcement re RFAs

Story Landis, Ph.D., Director of the National Institute of Neurological Disorders and Stroke and Pain Consortium Co-Chair

Dr. Landis noted that there were only three applications for the recent request for applications (RFA) that offered competitive supplements (\$75,000) for research on the transition from acute to chronic pain. For a new RFA due out shortly, she hopes to see more applications.

Presentation of the Mitchell Max Award for Best Poster Presentation

Story Landis, Ph.D.,

After commenting on the breadth of pain topics covered by the posters at today's meeting, her appreciation of this opportunity to encourage young investigators, and the opportunity to honor the memory of a remarkable researcher, Dr. Landis announced that the judging committee has chosen Sarah Taque as the recipient of the Mitchell Max Award for Best Poster Presentation. Sarah is a predoctoral student at University of KansasHer poster is

entitled “Vitamin D Deficiency Causes Tissue Mechanical Hyperalgesia and Muscle Nociceptor Sprouting.”

Session 3: Emerging Therapies for Individualized Pain Management

Moderator: Wen Chen, Ph.D., National Institute on Aging

Emerging Therapies for Pain Management: Glial Targets

Linda R. Watkins, Ph.D., University of Colorado, Boulder

Dr. Watkins observed that work over the past 18 years shows that non-neuronal glial cells are key players in creating and maintaining pathological pain states. These cells are becoming potential targets for drug abuse, genomics (genetic polymorphisms for who to target for individualized therapies), and pain management. Glial cells can disregulate the actions of opiates and can potentiate drugs of abuse, such as alcohol.

Activated glial cells release a large variety of neuroexcitatory substances that tend to amplify pain. These increase the amount and expression of NMDA (N-methyl-D-glutamate) and AMPA (α -amino-3-hydroxyl-5-methyl-4-isoxazole-propionate) and down regulate GABA (γ -aminobutyric acid), outward potassium currents, glutamate transporters, and GRK2 (G-Protein-coupled Receptor Kinase 2). In all clinically-relevant animal studies, blocking the activation of glial cells or suppressing their pro-inflammatory cytokine products brings pain back to baseline.

Glial cells are activated by opiates. Blocking the glial cells could improve opiate analgesia and suppress tolerance, dependence, the rewards of drug-seeking, respiratory depression, and even opioid-induced constipation. Alcohol also activates glial cells—through toll-like receptor 4, which drives pro-inflammatory cytokines. (TLR-4 is also linked to neuropathic pain and to opiate activation of glial cells.) In a mouse model, blocking TLR-4 decreases alcohol-induced aphasia. Sleepiness in these drunk mice is also reduced by the blocking of TLR-4. A number of genetic polymorphisms for high glial pro-inflammatory products or low glial anti-inflammatory products (e.g., interleukin-10) can increase chronic pain states.

While opiates release dopamine in the drug reward center, inhibitors of glial activation can suppress it, leading to animals that have been on opiates having withdrawal symptoms. Similarly, alcohol activates glial cells, producing neuroinflammation as well as IL-1. An Australian researcher has shown that specific polymorphisms in a promoter area for IL-1 lead to an enhanced pro-inflammatory environment in an opiate-dependent population.

Emerging therapies that apply the new knowledge concerning glial cells are being tested in studies to treat neuropathic pain. AV411 was tested in a phase II trial. ATL313 [an is in preclinical development), IL-10, XT101 is in preclinical development, and CB2 agonists that suppress glial activation are in preclinical development and early trials.

The best known of these test drugs, AV411 has a safety record at lower doses as that of Ibudilast, a broad phosphodiesterase inhibitor and partial TL-4 antagonist. In animal models, AV411 suppresses neuropathic pain, opiate dependence and withdrawal, opiate reward, and relapse from methamphetamine.

ATL313, which is given intrathecally, is an adenosine-2A agonist. It inhibits pro-inflammatory cytokines and enhances IL-10 both peripherally and in the spinal cord. Just one dose has reversed neuropathic pain for 4 to 6 weeks; this appears to be attributable to a large increase in IL-10 production. Dr. Watkins also showed ATL313's effectiveness in two other models.

Xalud Therapeutics is working on gene therapy related to IL-10, delivering its XT101 to glial cells via microparticles. In several animal models of nerve injury, one intrathecal dose can be effective on neuropathic pain for three months. XT101 enhances analgesia, delays tolerance, and relieves tail paralysis in animal models of multiple sclerosis. Dr. Watkins anticipates exciting times as more of these test drugs move into human trials.

Resolvins: A Novel Therapy for Pain Management

Ru-Rong Ji, M.D., Ph.D., Brigham and Women's Hospital, Harvard University

Dr. Ji explained that resolvins are a new class of analgesics that are lipid mediated and derived from the omega-3 polyunsaturated fatty acids found in seafood. Basically, the concept is that resolvins can lead to the resolution of inflammation.

Dr. Ji showed the biosynthetic pathway for resolvins—worked out by the laboratory of Dr. Charles Serhan—along with inhibitors and potential receptors. Dr. Ji's group decided to test resolvins in a mouse model of inflammation. Aspects to be addressed today include peripheral actions associated with anti-inflammatory action, central actions involving modulation of synapse transmission, and pre-resolution action (which differs from anti-inflammatory action).

In the study of peripheral actions, researchers looked at whether an injection of resolvins could block the inflammatory action of carrageenan injected into a mouse paw. Carrageenan induces transient heat hyperalgesia. The resolvin RvE1 blocked not only the heat production but also the increased neutrophil infiltration and increased cytokine production that carrageenan causes. Thus, peripheral injection of resolvin can attenuate inflammatory pain.

Regarding central actions, intrathecal injection of resolvin was tested for the ability to reduce formalin-induced spontaneous pain. For formalin, there are two phases of action, with the second described as the result of central sensitization. The injected resolvin acted only on the second phase, not the first,--implying central activity. (The second phase can also be inhibited by morphine, Cox-2 inhibitors, and NS-398.)

When researchers compared the analgesia and efficacy of RvE1 with morphine and a Cox-2 inhibitor, they found the resolvin to be much more effective, even at a much lower dose.

Trying out various combinations of receptors (e.g., G-coupled protein receptors [such as ChemR23], inhibitors, siRNAs [small interfering RNAs]), and models to determine resolvins' molecular mechanism for central action, Dr. Li and colleagues determined that resolvins do not act in the same way as morphine, their effect is mediated by ChemR23, and ChemR23 is expressed in many parts of the nervous system, including presynaptic

and postsynaptic parts of the spinal cord.

Also, resolvins can act on persistent inflammatory pain as well as on the shorter-term pain of formalin models and can block the actions of TRPV1 (transient receptor protein V1) and TNF (tumor necrosis factor)- α (both of which cause an increase in glutamate release that the resolvins block). In addition, resolvins can block TNF-mediated activation of NMDA (N-methyl-D-glutamate) receptor via inhibition of the ERK signaling pathway.

Thus, resolvins can work on both presynaptic and postsynaptic mechanisms, probably via pERK signaling.

Concerning pro-resolution action, which is different from anti-inflammatory and anti-hyperalgesic actions and involves getting rid of immune cells through phagocytic action of macrophages, treating the macrophages with RvE1 increases their phagocytic activity.

The resolvins represent a novel class of analgesics that can act on prolonged inflammation. In addition, it may be possible to create a smaller, related molecule to act on signaling pathways.

Central Role of Protein Kinase-C Epsilon in Mediating Analgesic Synergy in Primary Afferent Terminals

George L. Wilcox, Ph.D., University of Minnesota

Dr. Wilcox focused on the first afferent synapse in the spinal cord, the release of neuropeptides from the primary afferent neuron onto secondary neurons, and on classes of analgesics that can synergistically attenuate that release. This synergism can result in needing 30-fold less drug to get the same analgesic effect in rodents as when the drugs are administered independently.

The two drug classes are opioids and alpha-2 adrenergics, which act through receptors to attenuate release of neuropeptides and glutamate from the primary afferent C fibers. As some of these drugs can have severe side effects (e.g., sedation and hypotension for clonidine), reducing the doses needed by synergistic actions could reduce these side effects.

The researchers looked more closely at drug synergistic effects of alpha-2 adrenergic antinociception and opioids on side effects of sedation and cardiovascular events. Only the antinociception effect was synergistic; sedation or cardiovascular effects were additive. Whereas the receptors for both drugs are known to couple through inhibitory G proteins, Dr. Wilcox's lab has found that an alternative type of coupling gives rise to the synergy: the alpha-2 adrenergic and delta opioid receptors co-localize in peptidergic primary afferent terminals (in spinal dorsal horn), and the agonists at these receptors produce analgesic synergy in vivo.

The co-localization can be demonstrated with immunocytochemistry that uses colors to distinguish the types of receptors. The lab has shown that endogenous analgesics, opioids and norepinephrine, as well as the test drugs, synergize at the same sites. Substance P also co-localizes to the site.

To look at how the receptors function to create the synergy, one has to consider whether they are in or on the same neuron or different cells. If on the same cell, would there be enough G proteins for them to interact? In an experiment measuring the release of CGRP, a neuropeptide, from C fibers in rat spinal cord the stimulation of this release by potassium was blocked synergistically by the two test drugs--as shown by various behavior-response curves. This synergy does not require synaptic activity by the neuronal circuitry:

There is a significant amount of evidence that the alpha-2 adrenergic and delta-opioid receptors are normally within a neuron, and not on its surface. However, a noxious stimulus (e.g., bradykinin) can bring them to the surface. When the researchers tested whether adding agonists could bring the receptors to the surface, clonidine did not bring out receptors, deltorphin brought out peptides, and the two together worked at a 100x lower concentration to bring out both the receptors and peptides.

Testing the removal of phospholipase C by an inhibitor showed that its presence was necessary for the agonists to work--whether separately or together. It also turns out that the enzyme protein kinase C, which is not generated in sufficient quantities by either clonidine or deltorphin alone, is generated when both are together,--and its presence is necessary for the synergy to occur. The ability of protein kinase C to stimulate the synergy has also been demonstrated by intrathecal injection of a PKC inhibitor into live mice, which prevents synergy. It appears that when both receptors are activated on the surface of a neuron, somehow that creates enough diacylglycerol to activate PKC. How the PKC works to cause synergy is not yet known.

Next, when looking at dorsal root ganglions in culture that were peptidurgic with PKC in them, Dr. Wilcox and colleagues looked for translocation of PKC--which is a sign of its activation. When a known activator is added, three isoforms of PKC are observed. No activation occurs with either clonidine or deltorphin, but when both are present, the epsilon isoform of PKC is activated. Use of epsilon knockout mice confirmed the importance of PKC epsilon as these mice showed none of the synergy of the wild-type mice when the drug combination was used. In future work, the lab plans to use the translocation assay to look for different receptor pairs that could also be creating synergistic effects and also to look for the targets for PKC near the cell membrane.

Emerging Therapies for Pain Management: Spinal Analgesics

James C. Eisenach, M.D., Wake Forest University

Addressing human uses of spinal analgesics, Dr. Eisenach noted that a small dose of opioid is used by 60% of U.S. women in labor--with dramatic pain relief. His objectives are to discuss pain genetics and biomarkers and give examples spinal mechanisms that can be targeted in oral drug therapy.

Pharmacogenetics of analgesics is an emerging field. For example, a common polymorphism in the opiate receptor can determine the dose necessary for a laboring woman's pain level to drop significantly from 0 within 3 minutes after opioid administration. The dose for a defined amount of pain relief was different for women with two different gene alleles—suggesting a pharmacodynamic difference in the allele function.

Dr. Eisenach's lab injected ketorolac, a cyclooxygenase inhibitor, by spinal application into human volunteers and human chronic pain patients who reported a non-significant reduction in pain scores. Two-thirds of the pain patients had normal prostaglandin levels (for PGE2) in their CSF after the injection, but one-third with high PGE2 levels showed a decrease after the ketorolac injection. In a secondary analysis, the patients with higher PGE2 levels were the ones with the greatest analgesic effect of ketorolac. In similar study using patients with cancer pain and injecting a corticosteroid, the group that had higher PGE2 levels also benefited from the corticosteroid while the group with lower levels did not.

Dr. Eisenach's lab is now doing a sampling study, by collecting CSF prior to the ketorolac injection—to look for a biomarker, possibly increased prostaglandins, that could identify patients who would benefit from analgesic effects of ketorolac.

Dr. Eisenach noted that clonidine given in the spinal space works on the alpha-2 adrenergic receptors that are activated by norepinephrine. An endogenous descending system releases the norepinephrine, which has an analgesic effect. Gabapentin's activation of this system is thought to be its route for analgesic effects because of the following observations: If gabapentin is administered directly into the locus coeruleus, from which the fibers that release norepinephrine descend, the anti-hypersensitivity effect of gabapentin can be blocked by spinal administration of noradrenergic antagonists.

Dr. Eisenach queried whether preventing the breakdown of acetylcholine could be a therapy for pain. One of the circuits engaged in the spine by alpha-2 receptors is a cholinergic one and acetylcholine release in the spinal cord participates in analgesia by spinal clonidine. Administration of a cholinesterase inhibitor neostigmine produced analgesia by a spinal mechanism. Unfortunately, neostigmine also produced extreme nausea and vomiting and was dropped from further study.

Closing Remarks and Adjournment

Josephine Briggs, M.D., Director, National Center for Complementary and Alternative Medicine and Pain Consortium Co-Chair

Dr. Briggs voiced enthusiasm presentations and discussions and for the hard-working program staff that made the meeting arrangements. She noted that last year's conference focused on the potential contributions of genetic polymorphisms to pain, and that this year's has proposed some practical implementations--along with offering both "splitting" (e.g., clusters and grouping by biomarkers) and "lumping" types of concepts (e.g., the role of emotional factors and psychological health in pain). Other talks today have also covered exciting work on resolvins, glial factors, and interactions between the delta opioids and the alpha-2 adrenergics that may lead to practical applications.

Dr. Briggs provided data from the National Health Interview Survey that illustrate the many types of alternative and complementary medicine that patients currently turn to as adjuncts for pain management. After inviting attendees to consider attending a webinar next week on low back pain, Dr. Briggs again thanked everyone present and said that NIH would welcome their further input and advice.