

**Highlights of**  
**The National Institutes of Health**  
**2<sup>nd</sup> Annual Research Symposium for Advances in Pain Research**  
**“Advances in Pain Research: Generalized Pain Conditions”**  
**May 1, 2007**

The 2<sup>nd</sup> Annual Research Symposium for Advances in Pain Research was held on May 1, 2007, in the Masur Auditorium, on the campus of the National Institutes of Health, Bethesda, Maryland. The symposium was sponsored by the NIH Pain Consortium and titled, “Advances in Pain Research: Generalized Pain Conditions.” The co-chairs of the event were Patricia A. Grady, Ph.D., R.N., Director of the National Institute of Nursing Research, Story Landis, Ph.D., Director of the National Institute of Neurological Disorders and Stroke, and Lawrence A. Tabak, D.D.S., Ph.D., Director of the National Institute of Dental and Craniofacial Research. The organizer and moderator was Linda L. Porter, Ph.D., of the Extramural Research Program of the National Institute of Neurological Disorders and Stroke.

The NIH Pain Consortium is a trans-NIH effort involving over 20 Institutes, Centers, and offices in the Office of the Director of the NIH. It was established to enhance research and promote collaboration. The goals of the NIH Pain Consortium are as follows:

- To develop a comprehensive and forward-thinking pain research agenda for the NIH
- To identify key opportunities in pain research, particularly those that provide for multidisciplinary and trans-NIH participation.
- To increase visibility for pain research, within the NIH intramural and extramural communities and also among pain advocacy and patient groups expressing their interest through scientific and legislative channels.
- To pursue the pain research agenda through public-private partnerships, wherever applicable. This underscores a key dynamic that has been reinforced and encouraged through the Roadmap process.

The daylong symposium was opened by **Dr. Patricia A. Grady**, who described the above goals of the NIH Pain Consortium. Dr. Grady also highlighted three important focus areas for the Consortium: pain management and treatment, emerging recognition of individual differences in response to pain and types of pain, and the emotional and biobehavioral aspects of pain.

The audience was reminded of the human and economic burden of pain in the US. It is often under-identified and under-treated. The economic cost is estimated at \$80 billion annually, more than twice the budget of the NIH. Pain is not the purview of one or two Institutes at the NIH; rather, it is an issue that is crosscutting.

Dr. Grady pointed to recent NIH Pain Consortium progress. One example comes from the Osteoarthritis Initiative (OAI), a public-private partnership between the National Institutes of Health (NIH) and private industry. The partnership seeks to improve diagnosis and monitoring of osteoarthritis (OA) and to foster the development of new treatments. OAI has released its first set of data, available to researchers worldwide to help expedite the pace of scientific research and the identification of biological and structural markers (biomarkers) for OA.

Another sign of progress is the discovery of a gene variant that affects acute pain sensitivity and the risk of chronic pain. Possible treatments are being investigated. In addition, said Dr. Grady, the National Institute on Drug Abuse recently launched the first large-scale national study to treat addiction to pain medications such as OxyContin and Vicodin.

**Dr. Linda Porter** introduced American Pain Society (APS) representative **Ronald Dubner, D.D.S., Ph.D., who** provided a brief summary of the APS mission and goals. APS is a multidisciplinary organization whose membership is composed of basic scientists, clinical scientists, and clinical practitioners who are interested in the study of pain. The members are united in their goal to improve the practice of pain management and transform public policy in order to enhance the understanding and treatment of pain. The vision of the APS is to improve the quality of life of all Americans and people throughout the world by making pain prevention and relief available.

Dr. Dubner cited three particularly important areas of NIH-APS collaboration: an ongoing dialogue between the APS and the NIH Pain Consortium leadership; a focus on translating basic research into the clinical arena; examining funding mechanisms that can best lead to advances in pain research and control.

### **PANEL SESSION: Mechanisms and Management of Neuropathic Pain**

*Session chair:* David Thomas, Ph.D. National Institute on Drug Abuse, National Institutes of Health

- **CRPS-I Reconsidered: A Unitary Hypothesis of Small-Fiber Axonal Injury Complex**

*Presenter:* Ann Louise Oaklander, M.D., Massachusetts General Hospital, Harvard Medical School

Dr. Oaklander is Assistant Professor of Neurology at Harvard Medical School and a member of the departments of Neurology and Pathology at Massachusetts General Hospital where she also directs the Nerve Injury Unit.

Dr. Oaklander described Complex Regional Pain Syndrome (CRPS). CRPS-I and II follow a trauma and are characterized by chronic pain, focal dysautonomia, and vascular dysregulation. In CRPS-I, there is no known explanatory nerve injury. In contrast, in CRPS-II, nerve injury is present but how that particular injury leads to the chronic pain is unclear.

Dr. Oaklander hypothesizes that CRPS-I patients do, in fact, have a nerve injury, and proposes that small-fiber axonopathy is the cause of CRPS-I and also of CRPS-II. Supporting data from her lab include finding that CRPS-I patients have a 30 percent reduction in the density of small nerve fibers at painful sites compared to ipsilateral control sites. Two other research groups have found similar small-fiber neurite losses as well as vascular and muscle abnormalities in CRPS-I patients. A third group has shown significant changes in cytokine levels in nerves from CRPS-I patients.

A new rat CRPS model has been developed by Dr. Oaklander and her colleagues in which a small injury to the tibial nerve below the knee results in mechanical and thermal hyperalgesia, dysautonomia, and a number of other CRPS-like symptoms. Using this model, they have reached a new understanding of CRPS. In CRPS, the trauma appears to damage the patients' small fibers. When the blood vessels associated with the nerves lose their enervation, endoneurial and extraneurial neurogenic inflammation sensitizes the nearby axons.

**Summary:** Drawing on this new understanding of CRPS, Dr. Oaklander suggests ending the dichotomy between type I and II CRPS and instead calling these types of injuries post-traumatic neuralgia (PTN), with a spectrum of severity from simple to complex. In addition, she suggests that the inflammatory mediators that are now shown to play a role in the disease would be good potential targets for the development of new therapies.

- **Neuropharmacology of Spinal Cord Injury Pain**

**Presenter:** Christine N. Sang, M.D., M.P.H., Brigham and Women's Hospital, Harvard Medical School

Dr. Christine Sang is an attending anesthesiologist at Brigham and Women's Hospital and at Children's Hospital in Boston. She is Director of Translational Pain Research at Brigham and Women's. She began the session with an overview of the complications of the clinical use of NMDA receptor antagonists in the context of spinal cord injury. She went on to explain that glutamate has a recognized role in peripheral and central neuropathic pain, and that NMDA receptor antagonist can reverse the allodynia in a variety of animal models of neuropathic pain.

The Sang lab focuses on the use in humans of high-dose dextromethorphan (about four times the levels approved for treatment of cough), whose primary active metabolite is a prototype NMDA receptor antagonist. The complicating factor in high dose dextromethorphan is its wide (nearly 10-fold) variability in dose required for therapeutic response due to genetic polymorphism in the 2D6 gene. Clinically, people of differing genotypes fall in to one of two categories: poor metabolizers, who have more side effects and less therapeutic effect; extensive metabolizers, who have a better therapeutic effect and fewer side effects.

**Summary:** Genetic polymorphism in the 2D6 gene, as well as some medications and other unknown factors, can lead to a large variability in the therapeutic response to high-

dose dextromethorphan. Doses, therefore, must be carefully titrated for maximum therapeutic benefit and minimum side effects.

- **Alternative Therapy for Painful Diabetic Neuropathies**

**Presenter:** Martin Stevens, M.D., University of Birmingham Medical School, Birmingham, U.K.

Dr. Martin Stevens is Professor of Medicine at the University of Birmingham and Birmingham Heartlands Hospital. He is Director of the Foot clinic at Heartlands Hospital.

Dr. Stevens pointed out that complications of diabetes—such as retinopathy, nephropathy, and neuropathy—can begin far in advance of a diagnosis. Diabetic neuropathy, characterized by persistent burning and sometimes shock-like pain, is quite common, and is particularly difficult to manage by conventional pharmacologic approaches. Surveys show that only approximately one-third of patients respond to conventional pharmacologic approaches. As a result, diabetic neuropathy patients tend to seek out a wide variety of alternative therapies.

Pharmacologic alternative therapies include the anti-oxidant alpha-lipoic acid, taurine, benfotiamine (a vitamin B1 derivative), thiamine, pyridoxine, and glycerol nitrate sprays or patches. Non-pharmacologic alternative therapies include acupuncture, massage, opsite spray or film, biofield therapies, electric or magnetic field therapies, near-infrared phototherapy, and low intensity laser therapy. Transcutaneous, percutaneous, and spinal electrical stimulation are non-pharmacologic alternative therapies that have been tested in clinical trials and found useful.

Dr. Stevens went on to describe a clinical trial from his laboratory, recently published in *Diabetes Care*, comparing Reiki (a type of biofield therapy) to “mimic-Reiki” care. Both study groups made equal improvements in pain perception and walking distance during the study periods. No benefit specific to Reiki was seen. They concluded that the reduction of pain symptoms and improved functional capacity observed in both groups was linked with the formation of a sustained partnership between the health care provider and the patient.

Another alternative therapy that Dr. Stevens’ lab has investigated is taurine, a ubiquitous beta-amino acid that is depleted in diabetes. Diabetic rat models have shown that treatment with taurine corrects neuropathy-related nerve blood flow deficits, partially corrects sciatic motor nerve conduction velocity decreases, has reversing effects on mechanical allodynia, and also has effects on calcium signaling in the dorsal root ganglia. Based on these animal results, Dr. Stevens and his colleagues are investigating the use of taurine in humans. They are recruiting 180 patients with peripheral diabetic neuropathy for a 12-week randomized clinical trial. Pain thresholds, small-fiber function, mood, and quality of life will be assessed.

**Summary:** For patients with painful diabetic neuropathies, there is a need for randomized clinical trials to assess the numerous available alternate therapy treatments. At the least, Dr. Stevens has found, a simple sustained partnership between health care provider and patient appears to lead to a degree of improvement in pain symptoms and functionality. Also, taurine replacement therapy, currently being tested in a randomized clinical trial by Dr. Stevens' group, may have value in the treatment of diabetic neuropathy.

**PANEL SESSION: Mechanisms and Inflammatory Pain**

**Session chair:** John W. Kusiak, Ph.D., National Institute of Dental and Craniofacial Research, National Institutes of Health

- **Mechanisms Underlying Chronic Inflammatory Pain**

**Presenter:** Jon Levine, M.D., Ph.D., University of California, San Francisco

Dr. Jon Levine is a professor in medicine, oral and maxillofacial surgery, anatomy, and neuroscience at the University of California, San Francisco. He began his presentation with an overview of the current understanding of pain, particularly acute inflammatory pain, explaining the sensitization of pain receptors by inflammatory mediators such as prostaglandin E2. The inflammatory mediators affect cell surface receptors and intracellular systems. Two major classes of drugs (aspirin and the non-specific NSAIDs; COX-2 specific inhibitors) have been developed to block the inflammatory mediators involved in the development of sensitization. New discoveries about biologic mechanisms within primary afferent pain receptors could lead to new classes of analgesics targeting these mechanisms.

Inflammatory pain also involves trophic factors (e.g., nerve growth factor, NGF), which are produced at the site of inflammation and can be taken up by cells to influence gene function and, hence, protein production. The proteins are involved in the sensitization process. Drugs are being tested to block the NGF at its receptor.

Dr. Levine believes that medical professionals are just beginning to distinguish between acute inflammatory pain and chronic inflammatory pain, although many still believe that chronic inflammatory pain is simply acute pain that persists. He suggests that clinicians should think of persistent inflammatory pain as a separate condition—as a disease rooted in the immune system as much as in the nervous system.

Evidence is also emerging, said Dr. Levine, of the role of gene regulation in chronic pain. He showed upregulation of mRNA in dorsal root ganglion neurons following electrical stimulation and discussed some of the mechanisms by which the increase in cell activity could potentially regulate genes in the primary afferent nociceptors through calcium, second messengers, and other ion channels. He also described work indicating that patients with back pain that persisted after surgery had a very specific genotype involving the cyclohydrolase pathway within pain receptors.

Dr. Levine described a rat model used in his lab. In this model, prostaglandin E2-induced hyperalgesia is followed by induction of an inflammatory response by carrageenan injection. They have shown that the inflammatory response to carrageenan can be altered by the administration of anti-sense to protein kinase C epsilon to include a different set of second messengers. This indicates that molecular changes in the primary afferent nociceptors could be involved in the development of chronic pain.

From a cell biology point of view, said Dr. Levine, inflammation changes the external milieu of a cell, and this change is registered by and effects integrins on the cell surface. Primary afferent nociceptors have been shown, by Dr. Levine's lab and others, to have a particular subset of integrins, alpha/beta heterodimers, on their surface. Cell signaling pathways appear to be altered by stimulation or blockage of various alpha or beta integrins.

**Summary:** The role of genetics in the development of chronic pain warrants further investigation. Additionally, many previously unconsidered factors in the cellular makeup or milieu of nociceptors, such as mitochondria, sex hormone receptors, integrins, and inflammatory mediators, are emerging as potentially important for understanding the development and mechanisms of chronic pain.

- **The Role of Glial Cells in Mediating Persistent Pain**

**Presenter:** Joyce DeLeo, Ph.D., Dartmouth Medical Center

Dr. Joyce DeLeo is the Irene Heinz Given Endowed Professor of Pharmacology and Anesthesiology, Vice Chair of the Department of Pharmacology, and Director of the Neuroscience Center at Dartmouth Medical Center. Dr. DeLeo introduced glial cells as central nervous system components whose role was once thought to be the "glue" for keeping other CNS cells of the place. It is now recognized that glial cells have a role in modulating long-term potentiation, depression, synaptic calcium concentrations, and a host of CNS activities. In addition, glial cells are involved in CNS homeostasis and protection. Research, including some from Dr. DeLeo's lab, is currently focused on how a glial cell-mediated critical balance in the nervous system can go awry.

In a peripheral nerve injury, explained Dr. DeLeo, within minutes to hours of injury, innate and adaptive immune reactions take place. Microglial surface antigens (including TNF, IL-1, IL-6, MHC class II and CD4) become enhanced, and astrocytes express various cytokines and chemokines, an innate immune response that can be described as "neuroimmune activation." Neuroinflammation, an adaptive immune response consisting of leukocyte recruitment into the CNS, follows.

A working hypothesis in Dr. DeLeo lab is that microglial cells that travel to injured neurons following proinflammatory mediator influx into the synaptic milieu may decrease neuronal sensitization and reduce persistent pain. Minocycline, one of several agents tested in Dr. DeLeo's lab appears to reduce microglial trafficking to injured neurons and may decrease the release of proinflammatory mediators. Also under investigation has been cannabionoid receptor 2 (CB2), present on neurons, glia, and

immune cells. Administration of CB2 agonist seems to inhibit microglial migration both *in vitro* and *in vivo* in acute and chronic pain models, so the lab has been moving to characterize this response molecularly and look into treatment possibilities. Finally, they have shown that propentofylline is able to increase glutamate uptake in astrocytes *in vitro*. It persistently reduces the level of mechanical allodynia in rat models, even after being washed out of the animals' system.

**Summary:** There are significant CNS glial-immune implications for chronic pain treatment, and modulating glia with a goal of reducing, not abrogating, glial travel appears to be a key treatment possibility. Minocycline, CB2 agonists, and propentofylline all exhibit modulating activity and warrant further investigation.

- **Biopsychosocial Mechanisms and Management of Rheumatoid Arthritis**  
**Presenter:** Francis J. Keefe, Ph.D., Duke University Medical Center

Dr. Frances Keefe is Professor of Psychiatry and Behavior Sciences and Associate Director for Research in Pain and Palliative Care Initiative at Duke University Medical Center. He is also Professor of Psychology, Social, and Health Sciences at Duke University. According to Dr. Keefe, the largest problem in arthritis pain treatment is that individual patient differences lead to vastly different outcomes following treatment. For instance, differences in measures such as pain control and rational thinking (belief in one's ability to control or decrease pain and avoid overly negative thinking) or in a patient's tendency to catastrophize (assume the worst outcome) have been shown to influence patient pain levels. Biological factors, psychological functioning, and social functioning are all interrelated, says Dr. Keefe, and researchers look at these factors in the context of a the biopsychosocial model that includes them all.

Coping skills and coping strategy appraisal, reports Dr. Keefe, are particularly important domains in patient assessment. A meta-analysis published in May 2007 by the Keefe lab concluded that coping skills training in rheumatoid arthritis patients produces significant improvements across multiple outcomes, not just pain, but also psychological distress and physical functioning.

Other research from Dr. Keefe's lab shows that spouse-assisted pain control coping skills trainings are very effective compared to training the patient and spouse separately. In another study by Dr. Keefe and colleagues, they show that coping skills training combined with telephone based intervention and refreshers, as well as periodic evaluation, show maximum benefits at follow-up rather at the end of the trial.

**Summary:** Converging evidence suggests that psychological and social variables, in addition to many biological variables, can influence the pain experience in people with inflammatory conditions like rheumatoid arthritis. Systematic training in pain coping skills for patients and spouses/caregivers combined with regular follow up and skills refreshers can provide improvements in pain and a number of other outcomes.

**PANEL SESSION: Mechanisms and Management of Treatment-induced Pain**  
**Session Chair:** Ann M. O'Mara, Ph.D., R.N., National Cancer Institute

- **“Mechanisms and Management of Opioid-induced Hyperalgesia”**

**Presenter:** Frank Porreca, Ph.D., University of Arizona

Dr. Porreca is Professor of Pharmacology and Anesthesiology at the University of Arizona. He is a recipient of the F.W. Kerr Award from the American Pain Society. Dr. Porreca described the typical cellular events that take place following opioid administration. First, opioid hyperpolarizes opioid receptors, inhibiting the influx of calcium into nerve terminals and preventing the release of excitatory transmitters, which inhibits the pain signal. This should increase sensory thresholds above baseline; however, under some circumstances, particularly after sustained or extended administration of opioids, Dr. Porreca’s lab and others have observed that opioids have an excitatory effect, lowering sensory thresholds.

This finding, combined with anecdotal reports of opioid-induced hyperalgesia in humans, led to the concept that opioids, in addition to their analgesic action, also have an hyperalgesic action. With the goal of further understanding and potentially finding an intervention to block this hyperalgesia, Dr. Porreca and his colleagues asked the following question: Is descending facilitation (mediated by putative pain facilitation cells, dubbed “on cells,” which may help pass on the flow of pain signals from the primary afferent fibers to the spinal cord) a mechanism of chronic pain, and does it mediate this opioid-induced hyperalgesia?

In rat models, Dr. Porreca and his colleagues worked to answer this question, finding that cholecystokinin (CCK2) receptors, which are found exclusively on neurons in the rostral ventromedial medulla, appear to play a role in this descending facilitation. Additionally, they found that CCK2 and mu opioid receptor-expressing neurons are similarly distributed. Further studies showed that blocking CCK2 receptors also blocked the hyperalgesic action of the opioids. These studies and others led Dr. Porreca and his colleagues to conceptualize the model of the hyperalgesic effect mechanisms, summarized in the paragraph below, following opioid treatment.

**Summary:** Evidence from the Porreca lab points to the following mechanism of opioid-induced hyperalgesic pain signaling. First, sustained opioid administration produces neuroplastic changes, which mimic inflammatory pain in the rostral ventromedial medulla, and initiates descending facilitation. Descending facilitation upregulates spinal dynorphin, a naturally occurring brain opiate, which then acts at bradykinin receptors to enhance transmitter release and enhance the pain signal.

- **“Chemotherapy-induced Pain”**

**Presenter:** Patrick M. Dougherty, Ph.D. University of Texas MD Anderson Cancer Center

Dr. Patrick Dougherty is a Professor of Anesthesiology and Pain Medicine. He is the recipient of the John Liebskind Young Investigator Award from the American Pain Society and the Patrick D. Weill Early Career Scholar Award from the International

Association for the Study of Pain. Dr. Dougherty started his presentation by stating that chemotherapy drugs are the single biggest component of treatment-related pain in cancer patients, and that approximately one in three people have a 50/50 chance of developing chemotherapy-related pain in their lifetime.

Dr. Dougherty noted that symptoms of chemotherapy-induced pain are remarkably similar across chemotherapy drugs (although Velcade and bortezomib induce the most severe reactions and Taxol the least severe). Symptoms include numbness, tingling, and cold or burning sensations, primarily in the glabrous skin on the palms of the hands and the soles of the feet.

Dr. Dougherty and colleagues are characterizing and determining the mechanisms of chronic chemoneuropathy. Their research in a variety of cancer patients indicates that chronic chemoneuropathy is characterized by an approximately 100-fold elevated stimulus threshold, impaired touch threshold in area of pain and beyond (possibly indicative of impaired A beta nerve fiber function), and impaired A delta nerve fiber function in the pain area.

**Summary:** Data from Dougherty's lab suggest that chronic chemoneuropathy is a spectrum of nerve compromise, a clinical syndrome, rather than separate pain mechanisms that are triggered by different chemotherapy drugs. Additionally, chemoneuropathy appears to be truly chronic, unchanged at one-year follow-up; therefore, developing interventions to prevent onset is a priority

- **“Burning Mouth Syndrome: Disinhibition of Oral Pain by Damage to Taste”**

**Presenter:** Linda M. Bartoshuk, Ph.D., University of Florida (Gainesville)

Dr. Linda Bartoshuk is the Bushnell Professor of Community Dentistry and Behavioral science at the University of Florida. She was elected to the American Academy of Arts and Sciences and the National Academy of Sciences. Concerning burning mouth syndrome, she explained that emerging evidence suggests a relationship to a possible secondary purpose of the taste system—inhibition of sensations, such as pain, that are incompatible with eating. There is currently great interest in the ability of taste to inhibit pain.

Her lab uses a “cross modality matching” method to compare burning mouth syndrome across patients. The patients are asked to rate their pain relative to an unrelated sensation (such as the brightest light they have ever seen), which is then applied as a standard. Using this method, variation in the standard will be the same, on average, between pain patients and controls.

In taste, explained Dr. Bartoshuk, there are “supertasters,” and “nontasters.” A supertaster carries an allele for a receptor, has high density fungiform papillae, and many times more nerve fibers mediating pain than the “nontaster.” Supertasters, therefore, perceive burns and tastes approximately three times more intensely than the nontasters.

Dr. Bartoshuk's working hypothesis is that burning mouth syndrome is an oral pain phantom, defined as a sensation such as a bitter taste in the mouth that never goes away. This is a serious problem similar to chronic pain syndrome. She further hypothesizes that in supertasters with taste damage (due to viral infection, antibiotic uses, childhood ear infections, or nerve damage during dental work), abrogation of the normal inhibition of the trigeminal system would result in phantom burning.

**Summary:** Experiments in Dr. Bartoshuk's lab confirm her hypothesis that burning mouth syndrome is an oral pain phantom. Administering oral anesthesia to nontasters produces numbness, but in supertasters with taste damage, anesthesia enhances their burning sensation.

### **E. Panel Session on Mechanism and Management of Visceral Pain**

**Session Chair:** John W. Kusiak, Ph.D., National Institute of Dental and Craniofacial Research

- “Hormonal Modulation of Colorectal Pain”  
**Presenter:** Richard J. Traub, Ph.D., University of Maryland Dental School

Dr. Traub is a founding member of the University of Maryland Research Center for Neuroendocrine Influences on Pain and chair of a special interest group on sex, gender, and pain of the International association for the Study of Pain. Women, he reported, have been shown to have lower pain thresholds, higher pain ratings, and less tolerance for pain than men. In addition, visceral pain syndromes such as irritable bowel syndrome and interstitial cystitis are more prevalent in women whose symptoms may fluctuate with the menstrual cycle.

In order to elucidate the role of the gonadal hormones in visceral pain processing and determine the mechanisms that underlie sex differences in visceral pain, Dr. Traub's lab used a colorectal distention model of visceral pain in rats in which distension of a balloon in the descending colon of the rats produces a natural visceral stimulus like an obstruction that would stretch the colon wall and produce pain. Female rats were more sensitive to colorectal distension and the sensitivity was partially estrogen-mediated.

The researchers drew several conclusions from the work: first, given their additional finding that estrogen receptor alpha is co-localized with the NMDA receptors in the spinal cord, they suggest a possible anatomical framework by which estrogen directly modulates NMDA receptor activity in dorsal horn neurons. Secondly, preliminary data shows that females may have more NMDA receptor localized in the plasma membrane than males. Males tend to have a similar amount of NMDA but more cytosolic localization. Intact females also have a higher level of phosphorylated NR1 than males, which may be driving the NMDA receptor into the plasma membrane.

**Summary:** The differential distribution of the total pool of NMDA receptors (i.e. more receptors with cytosolic localization in males versus plasma membrane localization in females) may contribute to the sex differences in pain, and warrants further investigation.

- **“Cross-organ Interactions and their Clinical Implications: Lessons from Research on Endometriosis”**

**Presenter:** Karen J. Berkley, Ph.D., Florida State University, Tallahassee

Dr. Berkley is the Mackenzie Professor and Distinguished Professor of Neuroscience at Florida State University. Her current research focuses on the neuromechanism of pelvic pain. She explained, first, the differences in the human and rodent ovarian cycles including that rodent cycles are only four days long and do not contain a luteal phase. Therefore, rodent studies are not always directly applicable to human biology, and caution must be used in their translation.

Dr. Berkley went on to say that research in her lab—including data on changing magnitude of response to tactile stimulation of different parts of the hindquarters across the estrous cycle, and data showing the same nerve turning off or on in response to different internal—has led to a revision in the way the researchers think about pain. The nervous system, they suspect, is responding to many types of information (not just pain or touch), and that all the nervous system is responding to the stimuli. Their research on endometriosis, says Dr. Berkley, is done in this context.

The lab used an autotransplant lab model to study endometriosis, vaginal hyperalgesia, and pelvic pain. Using this rat model, Dr. Berkley’s lab determined that endometriosis (but not sham endometriosis) increases vaginal hyperalgesia, and that the severity of the hyperalgesia correlates with estradiol levels during the cycle. Additionally, visceromotor responses, pressor responses, and blood pressure responses to vaginal distention in the rats were greater in proestrus (high estradiol) than metestrus (low estradiol). The lab also showed that the severity of muscle and blood pressure symptoms does not correlate with the amount of cystic material.

They also investigated how endometriosis affects pain associated with kidney stones. Using another rat model, they determined that pain behavior is associated with kidney stones, and endometriosis increases the pain as expected. What was not expected, says Dr. Berkley, was that kidney stone pain was silenced in sham-endometriosis animals. One explanation is that transplanted endometrial cysts vascularize and sprout nerves that are involved in excitatory and inhibitory interactions in the central nervous system. Experiments support this explanation, and the lab is currently working to further elucidate the silencing mechanism.

**Summary:** Mechanisms underlying the symptoms of endometriosis are complex and include sensory fibers and sympathetic fibers in abnormal tissue, vascularization, growth factors, endocannabinoids, and CNS interactions, as well as more straightforward influences of estradiol. Further investigation is warranted to clarify these mechanisms and explore the silencing mechanisms.

The meeting adjourned following closing remarks by Dr. Linda Porter.