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The logo features the letters 'TmJ' in a large, stylized serif font. The 'T' and 'J' are dark red, while the 'm' is a lighter red. A horizontal purple bar passes behind the letters, with a thin red vertical line intersecting it. Below the 'J' and the bar, the word 'Science' is written in a dark red, italicized serif font.

Science

the journal of The TMJ Association, Ltd.

TMJ Science

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The Sixth Scientific Meeting of The TMJ Association, Ltd.

Comorbid Chronic Pain Conditions— Mechanisms, Diagnosis and Treatments

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Preface

Patients with TMJ disorders are frequently debilitated with conditions of persistent generalized pain that extends far beyond the region of the head and neck. The same may be said of millions of affected patients that exhibit shared comorbid conditions with TMJ disorders such as irritable bowel syndrome, endometriosis, interstitial cystitis, vulvodynia, fibromyalgia, chronic fatigue syndrome, and chronic headache. Given the poor understanding of the initiating stimuli and the underlying mechanisms of chronic generalized pain, the Sixth Scientific Meeting of The TMJ Association, Ltd., was convened to review what is currently known about persistent generalized pain and explore ways to advance research in this field. The meeting was attended by scientists with unusually diverse research expertise in chronic pain disorders and other research areas. The significance of the meeting was underscored by the participation of seven NIH Institute, Office, and Center Directors; the leaders of four patient advocacy groups comprising the Chronic Pain Research Alliance; and numerous NIH Program Staff. The meeting provided an opportunity for participants to present their recent research findings, exchange ideas on the most important areas of focus in coexisting pain conditions, and develop transformative research approaches for these conditions. In addition, high-risk research areas and training opportunities were discussed.

There was a remarkably high level of engagement and commitment by the participants of this meeting who recognized that there is a need to change the way science views chronic pain conditions and especially those chronic pain conditions that commonly coexist in individual patients. If the recommendations from this meeting can gain traction in the research community, a major paradigm shift will be underway as the study of chronic pain conditions will likely be transformed from isolated, disease silo- and symptom-based research into a broader, mechanism-based multiple-disease, or “new disease”-based research endeavor. It is our hope that this meeting and the resulting recommendations will provide the initial traction to move the entire pain field forward in new directions for the ultimate benefit of the millions of patients with these chronic, overlapping pain conditions.

Allen W. Cowley, Jr. Ph.D.
Chairman, Scientific Meeting Program Committee

John W. Kusiak, Ph.D.
Director, Molecular and Cellular Neuroscience Program
National Institute of Dental and Craniofacial Research
National Institutes of Health, Bethesda, MD

The theme of the sixth scientific meeting builds upon evidence from the five previous meetings demonstrating that Temporomandibular Disorders (TMD) are a complex family of conditions influenced by genetics, sex, environmental and behavioral triggers. These mediate the vulnerability of patients to TMD and typically manifest as more than jaw and muscle pain and jaw dysfunction. The sixth meeting focuses on the pathophysiological processes underlying the chronic pain conditions which coexist with TMD and constitute Comorbid Chronic Pain Conditions (CCPC). They include chronic fatigue syndrome, chronic headache, endometriosis, fibromyalgia, irritable bowel syndrome, interstitial cystitis and vulvodynia.

Scientific Meeting Program Committee

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The Sixth Scientific Meeting of The TMJ Association
Comorbid Chronic Pain Conditions - Mechanisms, Diagnosis and Treatments
Federation of American Societies for Experimental Biology
Bethesda, Maryland
June 5-7, 2011

Sunday, June 5, 2011

3:00 – 3:30 p.m.

Welcome

Terrie Cowley, President and Co-Founder, The TMJ Association, Ltd.,
Milwaukee, WI

Martin Frank, Ph.D. Executive Director,
American Physiological Society, Bethesda, MD

National Institutes of Health Welcome

Story C. Landis, Ph.D., Director, National Institute of Neurological Disorders
and Stroke, National Institutes of Health, Bethesda, MD

Vivian W. Pinn, M.D., Director, Office of Research on Women's Health,
National Institutes of Health, Bethesda, MD

Lawrence A. Tabak, D.D.S., Ph.D., Principal Deputy Director,
Office of the Director, National Institutes of Health, Bethesda, MD

Remarks

Allen W. Cowley, Jr., Ph.D., Program Committee Chairman,
Medical College of Wisconsin, Milwaukee, WI

3:30 – 4:05 p.m.

**Association of Central Sensitivity Syndromes with Chronic Diseases Having
Structural Pathology**

Muhammad B. Yunus, M.D., University of Illinois College of Medicine at Peoria,
Peoria, IL

4:05 – 4:40 p.m.

**Fundamentals of What We Know and Do Not Know about Comorbid Chronic
Pain Conditions, Including the Role of the Somatomotor and Autonomic
Nervous Systems**

Wilfrid Jänig, Dr. Med., Christian-Albrechts-Universität zu Kiel, Kiel, Germany

4:40 – 5:15 p.m.

Capturing 3D Tissue Complexity In Vitro

Linda Griffith, Ph.D., Massachusetts Institute of Technology, Cambridge, MA

5:15 – 6:15 p.m.

Food, Drink and Posters

6:15 – 6:45 p.m.

Chronic Pain Research Alliance Round Table

*Chair: K. Kimberly McCleary, President and CEO,
The CFIDS Association of America, Charlotte, NC*

Chronic Fatigue Syndrome

K. Kimberly McCleary, President and CEO,
The CFIDS Association of America, Charlotte, NC

Endometriosis

Mary Lou Ballweg, President and Executive Director,
Endometriosis Association, Milwaukee, WI

Temporomandibular Disorders

Terrie Cowley, President, The TMJ Association, Ltd., Milwaukee, WI

Vulvodynia

Christin L. Veasley, Executive Director,
National Vulvodynia Association, Silver Spring, MD

Session 1:

Epidemiology and Clinical Definition of Comorbid Chronic Pain Conditions

*Session Co-Chairs: Emily L. Harris, Ph.D., M.P.H., Translational Genetics and Genomics Program, National Institute of Dental and Craniofacial Research, National Institutes of Health, Bethesda, MD
Gary J. Macfarlane, Ph.D., University of Aberdeen, Scotland, United Kingdom*

6:45 – 7:10 p.m.

The Epidemiology of Comorbid Chronic Pain Conditions

Gary J. Macfarlane, Ph.D., University of Aberdeen, Scotland, United Kingdom

7:10 – 7:35 p.m.

Human Genetic Association Studies of Comorbid Chronic Pain Conditions

Shad B. Smith, Ph.D., University of North Carolina at Chapel Hill, Chapel Hill, NC

7:35 – 8:00 p.m.

Patterns and Impact of Comorbidity of Headache and Other Chronic Pain Conditions in the U.S. General Population

Tarannum Lateef, M.D., M.Sc., Genetic Epidemiology Research Branch, National Institute of Mental Health, National Institutes of Health, Bethesda, MD

Monday, June 6, 2011

8:00 – 8:30 a.m.

National Institutes of Health Welcome

Isabel Garcia, D.D.S., M.P.H., Acting Director, National Institute of Dental and Craniofacial Research, National Institutes of Health, Bethesda, MD

Barbara M. Alving, M.D., Director, National Center for Research Resources, National Institutes of Health, Bethesda, MD

Josephine P. Briggs, M.D., Director, National Center for Complementary and Alternative Medicine, National Institutes of Health, Bethesda, MD

Robert H. Carter, M.D., Deputy Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD

Session 2:

Translational Comorbid Chronic Pain Conditions Research and Therapeutic Developments - Human and Animal Model Systems

Session Co-Chairs: Andrea Sawczuk, D.D.S., Ph.D., Division of Clinical Research Resources, National Center for Research Resources, National Institutes of Health, Bethesda, MD

Michael W. Salter, M.D., Ph.D., Hospital for Sick Children and University of Toronto Toronto, Ontario, Canada

- 8:30 – 8:35 a.m. **Clinical and Translational Science Awards Pain Researchers Interest Group**
Andrea Sawczuk, D.D.S., Ph.D., Division of Clinical Research Resources,
National Center for Research Resources, National Institutes of Health,
Bethesda, MD
- 8:35 – 8:55 a.m. **Chronic Widespread Pain: Models to Mechanisms**
Jon D. Levine, M.D., Ph.D., University of California, San Francisco,
San Francisco, CA
- 8:55 – 9:15 a.m. **Neuronal-Glial Interactions in Pathological Pain**
Michael W. Salter, M.D., Ph.D., Hospital for Sick Children and
University of Toronto, Toronto, Ontario, Canada
- 9:15 – 9:35 a.m. **Molecular and Genetic Analysis of Pain-Sensing Neurons in Dorsal Root Ganglia**
Xinzhong Dong, Ph.D., Johns Hopkins University of Medicine, Baltimore, MD
- 9:35 – 9:55 a.m. **Neural Mechanisms of Pelvic Visceral Pain, Endometriosis, Cannabinoids and
Pelvic Pain Organ Function**
Karen J. Berkley, Ph.D., Florida State University, Tallahassee, FL
- 9:55 – 10:15 a.m. **Discussion led by Dr. Andrea Sawczuk**
- 10:15 – 10:35 a.m. **Break**
- 10:35 – 10:40 a.m. **National Institutes of Health Pain Consortium**
John W. Kusiak, Ph.D., Director, Molecular and Cellular Neuroscience Program,
National Institute of Dental and Craniofacial Research, National Institutes of
Health, Bethesda, MD
- 10:40 – 11:00 a.m. **Epigenetics in Pain and Analgesia – Pharmacogenetics – Implications for
Therapeutics**
Jörn Lötsch, Dr. Med., Goethe-University, Frankfurt am Main, Germany
- 11:00 – 11:20 a.m. **Epigenetic Regulation of Visceral Pain Due to Neonatal Inflammatory Insult**
Sushil K. Sarna, Ph.D., University of Texas Medical Branch, Galveston, TX
- 11:20 – 11:40 a.m. **Vulvodynia and Comorbid Chronic Pain Conditions – A Population-Based Study**
Barbara D. Reed, M.D., M.S.P.H., University of Michigan, Ann Arbor, MI
- 11:40 – 12:00 p.m. **Discussion led by Dr. Michael Salter**
- 12:00 – 1:15 p.m. **Lunch and Posters**
- Session 3:** **Experimental Models and Systems Approaches to Address Mechanisms of
Chronic Pain and Related Comorbid Conditions**
*Session Co-chairs: Andrew Greene, Ph.D., Medical College of Wisconsin,
Milwaukee, WI*
*Douglas A. Lauffenburger, Ph.D., Massachusetts Institute of Technology,
Cambridge, MA*
- 1:15 – 1:30 p.m. **Chronic Pain – The Human Dimension**
Donald M. Birk, Chairman of the Board of Directors, The TMJ Association, Ltd.,
Milwaukee, WI
Kevin D. Clark, Vice President, The TMJ Association, Ltd., Milwaukee, WI

- 1:30 – 1:50 p.m. **Chronic Clinical Pain Conditions are Distinct and Specifically Interact with the Brain**
A. Vania Apkarian, Ph.D., Northwestern University, Chicago, IL
- 1:50 – 2:10 p.m. **Primary Afferent Nociceptors and the Circuits That They Engage to Produce Chronic Pain**
Allan I. Basbaum, Ph.D., University of California, San Francisco, San Francisco, CA
- 2:10 – 2:30 p.m. **Cognitive Ontologies for Neuropsychiatric Phenomics Research**
Robert M. Bilder, Ph.D., University of California, Los Angeles, Los Angeles, CA
- 2:30 – 2:50 p.m. **Understanding Cell Signaling Dysregulation in Inflammation Contexts: From Qualitative Pathway Maps to Quantitative Network Operations**
Douglas A. Lauffenburger, Ph.D., Massachusetts Institute of Technology, Cambridge, MA
- 2:50 – 3:10 p.m. **Discussion led by Drs. Andrew Greene and Douglas Lauffenburger**
- 3:10 – 3:30 p.m. **Break**
- Session 4:** **Approaches and Emerging Findings from Large Cohort Studies - Risk Domains and Determinates of Comorbid Chronic Pain Conditions**
Session Chair: Suzanne D. Vernon, Ph.D. Scientific Director, The CFIDS Association of America, Charlotte, NC
- 3:30 – 4:00 p.m. **Unraveling Complex Persistent Pain Conditions**
William Maixner, D.D.S., Ph.D., University of North Carolina at Chapel Hill, Chapel Hill, NC
- 4:00 – 4:30 p.m. **The Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network**
Emeran A. Mayer, M.D., University of California Los Angeles, Los Angeles, CA
- 4:30 – 5:00 p.m. **Migraine and TMJ Disorders**
Richard B. Lipton, M.D., Albert Einstein College of Medicine, Bronx, NY
- 5:00 – 5:30 p.m. **Discussion led by Dr. Suzanne Vernon**
- 6:30 p.m. **Dinner at Bethesda Marriott Hotel, 5151 Pooks Hill Road, Bethesda, MD**

Tuesday, June 7, 2011

- 8:30 – 11:30 a.m. **Breakout Working Groups**
- Group 1. Epidemiology and Sex Differences in Comorbid Chronic Pain Conditions**
Co-Chairs: Gary J. Macfarlane, Ph.D., University of Aberdeen, Scotland, United Kingdom
Emily Harris, Ph.D., Translational Genetics and Genomics Program, National Institute of Dental and Craniofacial Research, National Institutes of Health, Bethesda, MD

**Group 2. Diagnosis of Comorbid Chronic Pain Conditions:
Phenotypes, Genotypes and Biopsychosocial Factors**

*Co-Chairs: Emeran A. Mayer, M.D., University of California Los Angeles, Los Angeles CA
Michael W. Salter, M.D., Ph.D., Hospital for Sick Children and University of Toronto,
Toronto, Ontario, Canada*

Group 3. Basic and Translational Studies and Animal Models

*Co-Chairs: Karen J. Berkley, Ph.D., Florida State University, Tallahassee, FL
Andrew S. Greene, Ph.D., Medical College of Wisconsin, Milwaukee, WI*

Group 4. Next Generation Therapies for Comorbid Chronic Pain Conditions

*Co-Chairs: Suzanne D. Vernon, Ph.D., Scientific Director, The CFIDS Association of
America, Charlotte, NC
Linda Griffith, Ph.D., Massachusetts Institute of Technology, Cambridge, MA*

Groups to Develop Consensus on:

1. What studies should be conducted to distinguish Comorbid Chronic Pain Conditions (CCPC) from other pain syndromes?
 - a. Criteria needed to establish case definition of CCPC
 - b. The tools to assess and diagnose CCPC
2. What research areas are most important for the research community to pursue?
 - a. Best approaches
 - b. Necessary resources
3. What are the best approaches to develop treatment modalities for CCPC?
4. What approaches are necessary to train, foster, and sustain a CCPC research community?
5. What are the high-risk research areas that have the potential to substantially advance our understanding of CCPC?

11:30 – 12:30 p.m.

Lunch and Poster Session

12:30 – 2:30 p.m.

Groups' Presentations and Recommendations – Discussion and Modifications

2:30 – 3:00 p.m.

Overall Summary of Meeting Recommendations and Action Items

3:00 p.m.

Closing Remarks

Drs. Allen W. Cowley, Jr. and John W. Kusiak

Chronic Pain—The Human Dimension

By Beryl Lieff Benderly

Discussions and presentations at the Sixth Scientific Meeting of The TMJ Association, an advocacy organization based in Milwaukee, Wisconsin, focused mainly on findings and issues from recent research on comorbid chronic pain conditions (CCPC), including temporomandibular joint disorders (TMD), headache, endometriosis, interstitial cystitis, vulvodynia, irritable bowel syndrome, fibromyalgia, and chronic fatigue syndrome. Underlying and motivating this research, however, is the lived experience of patients with chronic pain, who must daily cope with disabling disorders that as yet lack effective treatments. A shared drive to find relief for the surprisingly common, yet inadequately understood, affliction of chronic pain binds together a coalition of patient advocacy organizations representing people who suffer from these apparently different—yet in some ways tantalizingly similar—conditions.

As the scientific presentations at the meeting repeatedly indicated, the comorbid chronic pain conditions share a number of biological features that suggest the possibility of common neurophysiological roots. But as representatives of various patient groups made clear, the burdens that these disorders impose on patients share other features as well, including limitations on daily activities, sleep disturbances, fatigue, depression, anxiety, difficulty in diagnosis, and the frustration of lacking either a clear explanation of why the conditions occur or of what can be done to alleviate them.

Among those bringing the viewpoint of patients and their relatives to the meeting, Donald M. Birk, Chairman of the Board of Directors of The TMJ Association, Ltd., and Kevin D. Clark, TMJA's Vice President, each recounted his wife's struggle with chronic TMJ pain and



Elizabeth & Don Birk

its effect on both her and the family. In both cases, a dearth of accurate information made diagnosis and treatment extremely challenging. Having such information could have drastically shortened Mrs. Birk's distressing "odyssey" among numerous care providers, her husband said. In its absence, Birk noted, far too many practitioners offer patients unproven, largely ineffective, and even harmful treatments.

Indeed, said Clark, whose wife has TMD as well as symptoms of endometriosis and fibromyalgia, she would be far better off today had practitioners "done nothing" to treat her condition, because a number of the treatments she tried did harm without providing relief. The Clarks' lengthy, but as yet unsuccessful, search for answers has however, inspired their dream of bringing patients together, challenging medical professionals, supporting research, and spreading accurate information—all goals of The TMJ Association and the other patient advocacy groups. Clark and Birk both expressed hopes that the 2011 meeting would advance those goals



Kevin Clark

and hasten the day when effective treatments will reduce the suffering of their wives and all others with chronic pain.

The Chronic Pain Research Alliance, a coalition of The TMJ Association, Ltd., the CFIDS (Chronic Fatigue Syndrome and Immune Dysfunction Syndrome) Association of America, the Endometriosis Association, and the National Vulvodynia Association, also strongly supports those goals. Speaking for the coalition, Kim McCleary, President and CEO of the CFIDS Association, described the Campaign to End Chronic Pain in Women. This national effort, launched with a May, 2010 event on Capitol Hill in Washington, DC, aims to increase research funding and scientific attention to an issue that receives far less money and interest than its importance merits.



Chronic Pain Research Alliance members on Capitol Hill

“Up to 50 million American women suffer from poorly understood and neglected chronic pain conditions,” she said. Six conditions alone: chronic fatigue, endometriosis, fibromyalgia, interstitial cystitis, temporomandibular disorders and vulvodynia “add as much as \$80 billion to our annual health care bill,” she said. The amount per patient that the federal government spends on chronic pain research is a small fraction of spending on many other diseases, she added. Furthermore, the training available to clinicians about chronic pain is shockingly inadequate. As a result, McCleary said, women “are routinely misdiagnosed, shuffled from office to office, inappropriately treated and left without answers or hope” by clinicians who lack knowledge and understanding of chronic pain.

She cited the example of Laura Hillenbrand, the author whose best-selling book, *Seabiscuit*, became a popular movie. Despite Hillenbrand’s notable accomplishments, for years severe chronic fatigue syndrome kept her from most normal activities, including even leaving her house. McCleary expressed the coalition’s hope that the current meeting would both advance research and increase understanding of the conditions in the clinical and scientific communities.

Comorbid Chronic Pain Conditions— Mechanisms, Diagnosis and Treatments

Report on the Sixth Scientific Meeting of The TMJ Association, Ltd.

By Beryl Lieff Benderly

Temporomandibular joint disorder (TMD), a pain condition that occurs in one or both jaws that can become chronic and severely limit jaw movements, is one of a cluster of chronic conditions that often occur in the same individuals, usually women, causing unremitting and disabling pain. Besides TMD, the conditions include endometriosis, vulvodynia, fibromyalgia, chronic fatigue syndrome (CFS), migraine and other chronic headaches, interstitial cystitis (IC), irritable bowel syndrome (IBS), and chronic pelvic pain. They are considered comorbid because they occur together more often than chance can explain. In addition, the conditions share other features. Together they affect upwards of 50 million people in the United States.

Until recently, clinicians and medical scientists considered each comorbid chronic pain condition (CCPC) separately, as a wholly distinct entity. They defined each on the basis of its symptoms, although these are often inexact and can overlap. Because of this separate focus, each CCPC has generally been diagnosed and treated by its own array of medical or, in the case of TMD, dental professionals. Each has developed its own advocacy organizations and patient networks. Each has attracted its own cadre of researchers.

A Paradigm Shift

In the past several years, however—in large measure through the work reported at or inspired by the five previous

TMJA scientific meetings held since 2000—knowledge of the sometimes striking commonalities among the CCPC has grown and spread. TMD and the other CCPC, for example, all either exclusively or predominantly affect women of reproductive age. All of them have unknown causes, lack clear diagnostic criteria, and involve pain whose intensity does not reflect bodily anomalies or pathologies, even if, as in the case of endometriosis, tissue abnormalities may be present. Advocates, researchers and clinicians now suspect that these commonalities may indicate more than intriguing demographic or epidemiological coincidences, but reflect common underlying pathological processes. This new orientation amounts to a paradigm shift away from focusing on the particular body organ and symptoms and toward some shared root causes.

The TMJ Association's sixth scientific meeting was designed to build on these developments. The intent was to move the scientific community and the knowledge base towards a systematic examination of underlying physiological mechanisms and away from the longstanding "silo" approach that sees each condition as a unique entity to be resolved by concentrating on particular end organs or organ systems. To accomplish this, the meeting brought together experts from a wide range of disciplines, fields and approaches, researchers who in the past may not have often collaborated or, in many cases, even communicated with one another. Each invited investigator

represented a body of knowledge and research that appears at least potentially promising in understanding features or mechanisms underlying one or more of the CCPC.

In addition, the program included talks by representatives of patient organizations and prominent figures from components of the National Institutes of Health (NIH) active in research on chronic pain. The scientific meeting thus afforded an unusual opportunity for a diverse gathering of knowledgeable and informed people to share expertise and insights and to spark new ideas and collaborations.

The Nervous System as Key

Indeed, among the meeting's most impressive outcomes was the finding that a number of researchers from very different approaches to clinical, translational and basic science have independently developed similar ideas about how best to advance understanding of the CCPC. Prominent among these ideas is the aforementioned paradigm shift away from symptom-defined conditions to the mechanisms and pathways of chronic pain. Some speakers even suggested that the symptom clusters that currently define CCPC based on the end organ affected may actually be obscuring what is happening in patients' nervous systems.

Chronic pain, several speakers emphasized, is a disease of the nervous system and not merely of the organs or body parts where people appear to experience it. Decades of trying to find and correct anomalies in the jaw in TMD, or in the prostate or vulva in chronic pelvic pain, or in endometrial tissue in endometriosis, for example, have not produced effective treatments for pain. Establishing criteria based not on clusters

of symptoms but on neurophysiological patterns may thus constitute a crucial step in understanding why patients suffer and how to help them. The new criteria, speakers noted, may or may not correspond to the way the various pain conditions are currently characterized, but may help to organize a growing body of data, including genetic influences and other risk factors, and could ultimately lead to more effective therapies.

In opening the meeting, The TMJ Association's President and Co-Founder, Terrie Cowley, underscored the need for innovative research to produce treatments that can better patients' lives. Citing the 1996 finding of an NIH conference on TMD that the knowledge, treatments and research then in existence were totally inadequate, she noted that patients' situations have not markedly changed in the intervening years. "Our hope is in science," she said.

Martin Frank, Ph.D., Executive Director of the American Physiological Society, The TMJ Association's sponsor on the campus of the Federation of American Societies for Experimental Biology in Bethesda, Maryland, which hosted the meeting, also welcomed participants with a reminder of the 50 million people who are "in desperate need of treatments that work and don't cause harm".

The current meeting's emphasis on the comorbid disorders is an extension of the most recent TMJA scientific meeting, held in 2008, noted Allen W. Cowley, Jr., Ph.D., of the Medical College of Wisconsin, chair of The TMJ Association's program committee. The 2008 meeting had emphasized the search for common features among pain disorders rather than looking at TMD in isolation. The goal of the current

meeting, he added, was to seek the links that tie the common features together, further challenging existing dogmas and exploring new ideas.

Following is a summary of the meeting's scientific presentations, aligned according to subject matter and approach rather than to their order in the meeting agenda.

The NIH Commitment to Pain Research

Evident at the meeting was the strong and growing commitment of the National Institutes of Health to research on chronic pain—a commitment shown both by NIH financial support for the meeting and by the active participation of NIH leadership. Vivian W. Pinn, M.D., Director of the Office of Research on Women's Health, commended TMJA “on developing a collaborative effort” to explore issues “of great interest” to her office. Lawrence Tabak, D.D.S., Ph.D., Principal Deputy Director of the Office of the NIH Director, observed that in the past an anatomical focus had obscured possible interrelations among pain syndromes. Story Landis, Ph.D., Director of the National Institute of Neurological Disorders and Stroke, praised the meeting's current focus on underlying mechanisms as an extraordinary advance for the field in investigating the “very interesting puzzle” of how acute pain is transformed in chronic pain.

The need to investigate the features of each condition as well as the mechanisms underlying them are primary goals, emphasized Isabel Garcia, D.D.S., M.P.H., Acting Director of the National Institute of Dental and Craniofacial Research (NIDCR). Barbara Alving, M.D., director of the National Center for Research Resources, commented on the depth, breadth and “reaching out” of the

meeting and its interest in exploring the mind-body connection in pain. Essential to understanding that connection, said Josephine Briggs, M.D., Director of the National Center for Complementary and Alternative Medicine, will be developing clear definitions of processes and phenomena. Robert Carter, M.D., Deputy Director of the National Institute of Arthritis, Musculoskeletal and Skin Diseases, discussed efforts to improve future patient care by improving the education of medical students about pain management. John Kusiak, Ph.D., Director of the Molecular and Cellular Neuroscience research portfolio at NIDCR emphasized the growth of NIH's commitment to pain research by noting that the NIH Pain Consortium started 20 years ago with 2 institutes, but today some 16 NIH institutes and centers participate.

The Broader Context

The Basic Science Perspective

The initial presentations established the overall scientific context for the meeting. Speaking from the perspective of basic science, Wilfrid Jänig, Dr. Med., of Christian-Albrechts University in Kiel, Germany, examined the “fundamentals of what we know and don't know about CCPC, including the role of the somatomotor and autonomic nervous systems”. He explained that two of the three major categories of chronic pain, chronic inflammatory pain and neuropathy pain, are well defined as to symptoms and diagnosis. In addition, research has related each of these either to biochemical, physiological or morphological changes in the afferent nerves that carry impulses from the limbs and organs (the peripheral nervous system) to the spinal cord and brain (which together constitute the central

nervous system or CNS), or to related changes in the CNS.

Origins of the pain involved in the CCPC, on the other hand, are not understood but involve alterations related to the autonomic nervous, somatomotor nervous and neuroendocrine systems. Some kind of dysregulation within the central nervous system that also involves certain key hormones is implicated, Jänig said. The cause and nature of this dysregulation are also not known, although they may involve a “mismatch in communication” between incoming and outgoing brain signals.

Jänig suggested that a condition known as chronic regional pain syndrome, which also involves extensive dysregulation of the pathways carrying signals to and from the central nervous system, may provide insight into the CCPC. He gave a detailed description of the elements of the nervous system involved in signaling loops relevant to this condition and ways that they may relate to certain CCPC.

Unraveling the mystery of the CCPC and improving diagnosis and treatment will, he said, take the combined efforts of basic scientists, clinical researchers and clinicians and will require a more focused research approach. Fortunately, Jänig believes that the experimental tools needed to affect this study already exist.

The Clinical View

Muhammad B. Yunus, M.D., Professor of Medicine in the Section of Rheumatology at the University of Illinois College of Medicine at Peoria, viewed the CCPC from a clinical perspective. He saw very important clinical implications for the various syndromes in that they all involve

central sensitization. Central sensitization is defined as increased responsiveness to stimuli associated with changes in pain pathways in the central nervous system. Yunus focused on fibromyalgia, which, like conditions such as TMD, irritable bowel, vulvodynia, and headaches, does not correlate with any observable structural pathologies within the bodies of patients. He acknowledged that people with fibromyalgia often also have one or more of the other CCPC, and vice versa.

Less well known, Yunus said, is the fact that fibromyalgia also often occurs in people who have diseases with well-established structural origins, such as rheumatic diseases, including rheumatoid arthritis and systemic lupus erythematosus, infectious diseases such as HIV, hepatitis C, and Lyme disease, and other disorders such as diabetes and Crohn’s disease. Very few studies have examined possible associations between organic diseases and other CCPC, Yunus noted.

But associations between conditions do not imply a causal relationship, he emphasized. Which of a patient’s conditions comes first and whether each is implicated in the onset of others varies from person to person. Diseases with structural pathologies, however, often appear to precede fibromyalgia. The mechanisms underlying the associations between diseases involving structural pathology and fibromyalgia are therefore quite various and require considerably more research, he continued. Possible links appear to include genetic, endocrine and immune factors, and central sensitization caused by neurological mechanisms or by pain from a peripheral source such as arthritis. Sleep deprivation and dysfunction of the hypothalamus

and pituitary gland related to anxiety and stress can also play a role in triggering central sensitization.

Regardless of why and how a given patient develops fibromyalgia and another disease or condition, the presence of fibromyalgia “has enormous clinical implications,” Yunus said. The overlap in symptoms between fibromyalgia and other conditions may cause physicians to fail to diagnose one or both of them correctly. Doctors may erroneously conclude that, for example, a patient’s lupus or rheumatoid arthritis is more active than is actually the case. This error, Yunus said, “may result in improper use of medications with serious side effects” as well as failure to take advantage of methods useful in managing pain, such as central nervous system drugs and cognitive behavioral therapy.

“Physicians need to be aware that fibromyalgia has huge implications for management,” and to look for its presence along with “every chronic disease”.

Following these context-setting opening talks, presenters explored a wide range of more specific issues relating to the CCPC and their interactions.

The Definitional Dilemma

As the initial presentations indicated, a major unresolved issue in research on the CCPC is the lack of clear and agreed-upon parameters and definitions of the pain phenomena that patients experience and of the symptom clusters currently used to denote the conditions.

The Need for Detailed Epidemiologic Studies

The relative lack of high-quality population studies that look at the overlap of diagnosed pain conditions provided the focus for the presentation by Gary J. Macfarlane, Ph.D., professor of epidemiology at the University of Aberdeen, Scotland. Studies show that every one of the CCPC occurs more often among women, he said, but added that the conditions also reveal several different patterns across the lifespan. For example, the pattern observed in such conditions as low back pain and fibromyalgia, shows high numbers of sufferers starting early in life, increasing with age into the sixties, and then falling off at older ages. This may indicate, Macfarlane suggested, that people with widespread pain are likelier to die at earlier ages than the population at large. In a second pattern, typical of hip, knee and foot pain, the number of sufferers continues to increase throughout the lifespan. In a third pattern, often present in abdominal and orofacial pain, numbers rise from adulthood but fall off with advancing age.

Overlap among the conditions is striking, Macfarlane continued, so that patients may meet criteria for several syndromes apart from their main diagnosis. Even more striking, however, are features common among the conditions including anxiety, depression, sleep disturbance and interference with daily life. Still, he warned, it is far too simple to think that the CCPC have one common etiology or set of associated features. It will be essential to delineate and then study more homogeneous groups within the larger patient population to establish a basis for understanding the conditions.

Examples of Overlaps

Tarannum Lateef, M.D., M.Sc., of the National Institute of Mental Health at the NIH, added information about overlap among conditions. Migraine headache, for example, is often comorbid with other pain conditions, as well as with allergies, stroke, and anxiety. According to the National Health and Nutrition Examination Survey, a nationally representative study conducted periodically, migraine or severe headache sufferers are almost 3 times more likely to have other pain conditions than persons without migraine, she said. In another survey, headache sufferers were 3.3 times likelier to have other chronic pain and almost 4 times likelier to have irritable bowel syndrome. Children with migraine are more than twice as likely as others to have chronic pain and nearly 3 times as likely to have back and neck problems. She also emphasized the important implications that comorbidity of these conditions can have for treatment.

Genetic Factors

As in many areas of modern medical research, genetics can offer important insights in the study of pain, Shad Smith, Ph.D., of the University of North Carolina, reported. Several lines of evidence from human and animal research point to a hereditary element in how individuals respond to pain and a number of genes have been implicated. A study in twins, for example, found that chronic fatigue, migraine and irritable bowel syndrome, appear to have genetic components. Identifying the genes associated with a particular pain condition can potentially help predict who is at risk for becoming ill, contribute to understanding the underlying

biological processes, and aid clinicians in individualizing treatment.

It is highly likely, Smith continued, that there are genes common to a number of chronic pain conditions, but also genes unique to particular conditions. He went on to describe studies that are seeking genes associated with TMD by following populations through time (prospective studies) and other studies comparing people with and without conditions (case-control studies). The studies are testing for 350 genes known to be involved in transmission of pain signals within the nervous system and pathways that regulate how people perceive pain, as well as genes activated in relation to inflammation, mood and emotion.

While genetic studies have identified genes relevant to CCPC, Smith cautioned that “all these disorders are highly complex” and probably result from the interactions of many genes as well as multiple environmental factors.

The Search for Solutions

Translational Research

CCPC investigators are pursuing a wide variety of approaches in hopes of finding better treatments. This work may use human patients or animal models mimicking various aspects of human diseases. Animals used for these studies generally come from genetic strains developed specifically for research. While animals can never completely replicate human disease and many differences exist between humans and the species chosen, such as rats, animal models can very usefully illuminate physiological processes and suggest connections that may prove relevant to humans.

Karen Berkley, Ph.D., of Florida State University, for example, described research on endometriosis, an estrogen-dependent condition in which a type of tissue that normally lines the uterus, the endometrium, grows abnormally at sites outside the uterus. Symptoms can include severe and disabling menstrual pain (dysmenorrhea), painful intercourse, chronic pelvic pain, and muscle pain. Very significantly, however, the symptoms a woman experiences do not necessarily reflect either the location or the extent of the abnormal growths. Women with endometriosis often also experience other pain conditions including TMD, irritable bowel syndrome and interstitial cystitis. While the mechanisms underlying endometrial pain are not well understood, she said, research using a rat model as well as human studies indicate that the extrauterine tissue recruits a nerve supply. Both sensory and sympathetic nerve fibers develop at the abnormal tissue sites and form estrogen-sensitive two-way connections to the central nervous system. Such a process might well give rise to pain sensitization either at the local or CNS levels, Berkley said.

Berkley also addressed the issue of dysmenorrhea, noting that it is very common among menstruating women and especially so among adolescent girls. Nevertheless, menstrual pain is very poorly understood and gets minimal attention from researchers. Brain imaging studies, however, reveal differences between women who do and do not suffer from it, she said, adding that this indicates that much more research is needed. Dysmenorrhea should therefore be considered a chronic pain condition that probably contributes to the observed comorbidities, she said, although such a link has not been definitely established.

The Role of Non-Neuron Nerve Cells

Studies show that several types of nervous system cells, specifically, neurons, microglia and astrocytes, are implicated in pathological pain, stated Michael Salter, M.D. Ph.D., of the University of Toronto Centre for the Study of Pain. This alters the traditional conception in which neurons were considered the only cells transmitting signals to, from, and within the brain. Microglia and astrocytes, which belong to a category of cells known as glia, from the Greek for “glue,” were long believed to provide only structural frameworks and support for neurons. It is now clear, however, that glial cells play an active role in pathological pain, Salter said.

Ten to 20 percent of glial cells are of the type called microglia, which function as immune cells within the nervous system, in that they perform surveillance and scavenge for damaged cells and other unneeded materials. Microglia acting within the spinal cord and the brain stem (the lower portion of the brain) respond, for example, when nerves in the peripheral system are injured (peripheral neuropathy). They suppress inhibitory mechanisms that would dampen the responses of pain-sensitive neurons (nociceptors) and in other ways contribute to enhanced responses to pain. Salter noted that although this observation has been known in the literature for a long time, it has only recently gotten the attention it deserves. Understanding the signaling that occurs among glial cells and between glial cells and neurons is therefore an important area of research that can provide information not available from the previous, neuron-centric view of pain, he said. It may also suggest new approaches to treating and managing chronic pain.

Moving from Models to Mechanisms

Jon D. Levine, M.D., Ph.D., of the University of California, San Francisco, discussed advances in the study of fibromyalgia. His laboratory uses animal models that exhibit some of the condition's features, especially elevated pain sensitivity and anxiety. These make it possible to study the relationship between stress and the widespread pain characteristic of fibromyalgia. This work, in Levine's words, is helping to move the research from "models to mechanisms" that underlie the condition. Various situations known to be stressful to rats, including unpredictable sounds, being placed in an environment where they are forced to swim, and the need to use an unfamiliar form of bedding, have been shown to increase their sensitivity to pain.

In the condition known as allodynia, for example, a normally painless stimulus such as a touch feels painful, as when sunburned skin is touched. Evidence shows that nerve fibers that carry pain signals to the brain contribute to this effect, Levine said. These findings suggest that the widespread pain of fibromyalgia does not result from central sensitization alone, but that changes in pain receptors outside the central nervous system also contribute and, specifically, that pathological changes in the peripheral nociceptors may be involved.

Risk Factors

Research on the risk factors for two pain syndromes related to the bowel—irritable bowel syndrome and functional dyspepsia—has been moving ahead, reported Sushil Sarna, Ph.D., of the University of Texas Medical Branch in

Galveston. Studies in animal models indicate that these conditions can relate to adverse events that happen early in an individual's life, such as inflammation of the gut, severe diarrhea or emotional stress. A likely explanation for this connection, Sarna said, is that changes within the gut resulting from these events cause changes at the level of epigenetics.

Epigenetic changes affect the expression of genes in cells rather than the underlying structure of the DNA, which constitutes the individual's genome. Epigenetic changes occur throughout the life course and some of them can be permanent. Such changes permit organisms to adapt to changing conditions and are very sensitive to chemical changes within the body, especially very early in life. For this reason, events that occur soon after birth can have very long-lasting effects, Sarna said.

He described experiments with rats showing that epigenetic changes triggered by inflammation and other insults to the animal's colon shortly after birth resulted in the animals as adults experiencing stomach hypersensitivity that includes abdominal pain after eating. The evidence suggests that severe inflammation at that very young age altered the expression of genes involved in regulating sensitivity, with the effects lasting into adulthood. Specifically, he said, severe inflammatory insult during the neonatal period affects expressions of genes involved in nociception. He went on to relate this animal research to humans by noting that each year in the United States, 22,000 children under age 5 suffer diarrhea serious enough to cause hospitalization. As in the animals, he suggested, this may cause epigenetic changes that later result in irritable bowel and other pain syndromes.

Seeking New Drug Targets

The search for new drugs has long been a significant issue in pain research. The pain drugs currently available provide disappointing results for many people, said Jörn Lötsch, Dr. Med., of Goethe University in Frankfurt, Germany. Individuals vary considerably in how they respond to particular drugs and side effects can be very serious. Genetics strongly influences an individual's experiences of pain. As an extreme example, he noted that the syndrome known as congenital insensitivity to pain with anhidrosis (lack of sweating) relates to a mutation in the NTRK1 gene. Current genetic research is allowing scientists to identify a number of molecules and nociceptive processes that may be useful as targets for new drugs, as well as the genes related to them. Drugs can be designed with an aim of countering, suppressing or enhancing the actions or effects of the molecules produced by particular genes.

The importance of epigenetic processes regulating gene expression in pain pathways and responses, he added, makes epigenetics the next frontier of pharmacological research. This research can yield drugs designed to turn on or off the expression of particular genes. Such an approach has, for example, already proven effective against pain in a mouse model of endometriosis, although no such drug is currently available for humans. He predicted that genetic and epigenetic approaches in pharmacology will some day allow pain treatments to be tailor-made for each patient.

The serious and harmful side effects of today's pain drugs occur because the drugs target molecules that are widely present in the tissues of the body, noted

Xinzhong Dong, Ph.D., of Johns Hopkins University, as he introduced a discussion of research aimed at finding new ways to achieve pain relief. Because they affect many cell types, today's pain medications give rise to collateral damage in one form or another. Dong described efforts to overcome this problem by finding genes uniquely expressed in the nociceptor cells that sense pain and targeting the molecules generated by these pain-specific genes, thus sparing unrelated tissues and obviating harmful side effects. Genes of the Mrg group look promising and are currently under study, he said. Both behavioral and physiological studies on animals suggest that these genes are involved in suppressing or inhibiting chronic pain. Comparable genes exist in humans and thus appear to be candidates for new drugs against pathological pain.

New Approaches to Pain Research

In addition to the longstanding methods discussed at the meeting, researchers are exploring innovative and potentially useful approaches to the study of pain, some of which come from fields not previously associated with pain research.

Allan Basbaum, Ph.D., of the University of California, San Francisco, described work in animal models that investigates a variety of molecules expressed in the peripheral nervous system by nociceptors, the sensory cells that initially respond to a pain stimulus. These receptor molecules appear to be only minimally expressed in the central nervous system but may determine subpopulations of nociceptors according to whether the cells respond strictly to heat pain, say, or only to mechanical pain. In turn these subpopulations appear to be

differently regulated. As an example of such specificity, Basbaum's group has established that some subpopulations of nociceptors selectively express the mu opioid receptor while others express the delta opioid receptors. Experiments in which cells that produce different receptor molecules were transplanted to sites of nerve injury showed that the molecules can reverse the chronic pain induced by the injury. Further detailed studies of the functioning of specific molecules within the nervous system could, he suggested, contribute to much greater understanding of, and potentially much greater control over, chronic pain in humans.

Applying engineering principles to the signaling networks of cells has helped to clarify the dysregulation that occurs in cancer and also to predict whether new drugs will produce severe liver toxicity in some individuals, stated Douglas Lauffenburger, Ph.D., of the Massachusetts Institute of Technology. Such an approach could, he continued, possibly contribute to understanding the dysregulation of the cell signaling that occurs in chronic pain and also to development of new pain drugs.

Strategies from informatics, which involves the design of computer-based information systems, could also be useful for understanding pain, suggested Robert Bilder, Ph.D., of University of California, Los Angeles. They could, he said, help advance research on chronic pain by defining and clarifying relationships, concepts, categories and connections within the large mass of often unclearly defined and categorized data on pain available now and in the future. The approach, he said, has already been used in neuropsychiatry to develop "ontologies," or systems that

formally specify the concepts and objects within a domain of knowledge and the relationships among them, for example, in schizophrenia. As in neuropsychiatry, he noted, researchers working on CCPC need to deal with extremely complex sets of symptoms and syndromes and to identify very complicated pathways involving cellular and molecular features and the sensations, experiences and behaviors of patients.

Linda Griffith, Ph.D., of Massachusetts Institute of Technology, who discussed recent advances in tissue engineering, suggested that similar bioengineering approaches can be helpful in understanding and developing treatments for conditions like endometriosis.

Research-based Dissent

"A dissenting voice" to the approaches advanced by many of the presenters came, however, from A. Vania Apkarian, Ph.D., of Northwestern University. Studies using non-invasive functional MRI brain imaging methods that Apkarian has done on a form of chronic pain have made him "cautious" about the "idea that comorbidity implies common mechanisms," he said. "Different chronic pain conditions have different activity signatures and different anatomical signatures," and brain activity also strongly relates to the individual's perception of the intensity of pain, he stated. He noted, however, that his studies focus on patients with chronic back pain and exclude people with additional pain conditions.

Apkarian believes that to study the CCPC, researchers must first understand each of the components separately at the level of brain activity and then understand

the specific interactions among each pair at that same level. Distinguishing the degree of overlap among the CCPC must therefore depend on studies that have not yet occurred, he said.

Insights from Current Population Studies

While the need for more detailed epidemiology studies to better define the CCPC and characterize patient populations was a theme echoed throughout the meeting, several investigators reported on a number of large-scale studies that are underway on people who either have or may develop selected chronic pain conditions.

The OPPERA Study

William Maixner, D.D.S., Ph.D., of the University of North Carolina spoke about the Orofacial Pain Prospective Evaluation and Risk Assessment (OPPERA) study, which also involves collaborators at the Universities of Buffalo, Maryland and Florida. The five-year project follows 3,276 adults who did not have TMD when the study began and is intended to document new TMD cases as they occur and track the condition's evolution and relationship to other pain conditions. Already, 258 new TMD cases have been noted in the study population. In addition, OPPERA is following 200 persons already diagnosed with TMD at the study's outset.

Initial findings are currently under review and will be published soon, Maixner said. OPPERA data already available confirm, however, that TMD and the other CCPC are complex conditions related both to amplification of pain and to psychological features such as anxiety

and depression, he noted. Fewer than 30% of the TMD patients in the study have only that single pain condition. Headaches, for example, are much more common in TMD patients than in other individuals, as are other forms of chronic pain. Individual characteristics such as pain thresholds and the person's degree of body awareness strongly predict whether an individual develops a pain condition, he added.

Maixner referred to results reported earlier by Shad Smith, a member of the OPPERA team, showing that a number of genes have been related to the presence of pain conditions, even though many of them probably account for only a small portion of the risk for pain conditions. These results also suggest that TMD patients, and patients with the CCPC generally vary greatly, Maixner said. A key to gaining greater understanding of the conditions must be identifying subgroups among the larger diagnostic categories that are homogeneous in terms of physiology or experience of pain, he said. Doing so will mean a better chance of isolating relevant factors, and data from OPPERA should contribute to that effort, Maixner noted.

Mapping Pelvic Pain

Another large project, the newly launched Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network, combines the efforts of clinicians, translational researchers and basic scientists at a dozen universities. The study's director, Emeran A. Mayer, M.D., of the University of California, Los Angeles, described two syndromes defined by symptoms that both involve chronic pain in the pelvic area, interstitial cystitis and chronic pelvic pain, and

which are also accompanied by other symptoms. At present, the causes, course and other features of these conditions, as well as any patterns of association with other chronic pain conditions, are unclear and research has not yet produced effective treatments. The main focus of research has largely been on the possibility of inflammation or infection in the bladder or prostate, he said.

MAPP, however, takes a far more comprehensive view of the conditions, Mayer explained. It has undertaken a study of 300 individuals with conditions of chronic pelvic pain with the aim of clarifying the condition's epidemiology, symptoms, physiological markers, predictive and risk factors, and other features. The study uses a variety of methods, including brain imaging, genetic studies, and pain testing. Now, in the second year of this multiyear project, the MAPP Research Network will ultimately generate and make available to other researchers a wide range of previously unavailable data and information about these conditions, Mayer said.

Tracking Migraine

Migraine, a chronic and often disabling disorder whose main symptom is severe headaches, affects 30 million Americans, representing 18% of women and 6% of men. The condition is genetically heterogeneous, explained Richard B. Lipton, M.D., of Albert Einstein College of Medicine. Autosomal dominant forms of the disorder that relate to genetic variants FHM and CADASIL have been identified, but they are rare. The genetics of the more common forms are complex and highly varied. Lipton went on to discuss the American Migraine Prevalence and Prevention (AMPP) study, which has tracked 10,000 persons with migraine

over a period of 5 years, examining the relationship of the two variants of migraine, episodic and chronic, and also their relationship with other chronic pain conditions.

Migraine involves hypersensitivity in regions of the nervous system and is associated with other pain disorders, Lipton said. Patients may exhibit topical allodynia, experience other pain conditions such as TMD, and suffer from depression and anxiety. Reciprocally, the larger the number of TMD symptoms a person has, the greater is his or her risk of migraine. Both migraine and TMD increase the risk of allodynia.

Identifying Vulvodynia

A population study aimed at clarifying some aspects of the relationship between vulvodynia and other chronic pain conditions will track 2,500 women for the years between 2008 and 2013, said Barbara Reed, M.D., M.S.P.H., of the University of Michigan. The study will identify individuals in this population who have vulvodynia, clarify the course of the condition, and evaluate genetic elements affecting risk. Because women with vulvodynia also are known to have a higher risk of TMD, fibromyalgia, interstitial cystitis and irritable bowel, the study will screen for these conditions as well.

Reed said that preliminary data show TMD in about 5% of the study population overall, 7.5% with IC, about 10% with each of IC and vulvodynia, and about 12% with fibromyalgia. Overall, 68.9% of the study population have none of the conditions, 21% have one of them, 7% have 2 and 2.5% have 3 or more. Of the women who have any of the conditions,

however, only about half have only one, while 30% to 40% have 2 and about 20% have 3 or more. Additionally, women with one pain syndrome often have symptoms associated with others, even if they are not diagnosed with other conditions. Women with any pain conditions also appear to have had symptoms of heightened sensitivity in childhood. These findings may represent a general predisposition to heightened pain sensitivity, Reed said, or they may indicate overlap among the symptoms. Research that shifts the focus from condition diagnoses to the existence of pain and that identifies specific subgroups among patients will be key to clarifying these issues, she said.

* * *

Toward the Future

The 2011 conference was the first TMJ Association scientific meeting explicitly embodying the new research paradigm based on seeking underlying processes and mechanisms involved in chronic pain rather than studying particular conditions defined by symptoms and traditional diagnoses. As such, it produced widespread agreement among participants that this innovative approach may produce important advances in both understanding and, ultimately, treatment of chronic pain conditions. Participants also agreed that realizing the new paradigm's potential will require a wide range of further epidemiological, clinical and basic science studies. These could, if successful, significantly increase not only the scientific understanding of pain, but—even more importantly—the wellbeing of tens of millions of patients who now suffer its effects.

Research Recommendations from
THE SIXTH SCIENTIFIC MEETING
OF THE TMJ ASSOCIATION, LTD.

*Comorbid Chronic Pain Conditions (CCPC)—
Mechanisms, Diagnosis and Treatments*

A Paradigm Shift

The major conclusion of this meeting was that there is a need to shift the focus from the isolated study of a number of chronic pain conditions each with its own set of involved organs, symptoms, clinical specialists and treatments, towards study of the mechanisms underlying nervous system dysregulation and dysfunction that may be the common basis for these conditions.

Participants concluded that there was insufficient data to distinguish CCPC from other widespread chronic pain conditions. There was consensus, however, that the common characteristic of CCPC patients was “*multi-organ system hypersensitivity*” and the Working Group made the following recommendations:

1. Conduct prospective population-based epidemiological studies to determine the natural history of CCPC. These studies could be of case-control design with a longitudinal dimension; they should include subjects from adolescence and of both sexes, and use a standardized set of phenotypes (described below). Twin and family cohorts and if possible unique populations exposed to environmental stressors are encouraged. To achieve cost-savings, planners should consider leveraging existing patient cohorts and CTSA programs as well as national (OPPERA, MAPP) and international studies (e.g., Scandinavian cohorts) as appropriate. CTSA programs in academic medical centers should be included when possible to provide the integrated resources associated with these programs for data analysis, translational research, pilot studies, and training.

2. Develop a case definition and diagnosis for CCPC and redefine the case definition and diagnostics for individual chronic pain conditions. In accordance with the paradigm shift that emerged, developers should look to establish novel diagnostic criteria for CCPC and for the individual chronic pain conditions. These diagnostic criteria should be guided by results derived from biomathematical modeling of large phenotypic data sets, and should transcend the current symptom-based classifications. Diagnostic approaches to identify new criteria relying on existing and novel phenotypes (see #4 on page 22) would be transformative of the chronic pain research field. Participants strongly believed that these changes are necessary if we are going to succeed in eliminating current categories/descriptors used to describe the various individual comorbid conditions (such as fibromyalgia, chronic fatigue, TMD, IBS, etc.).

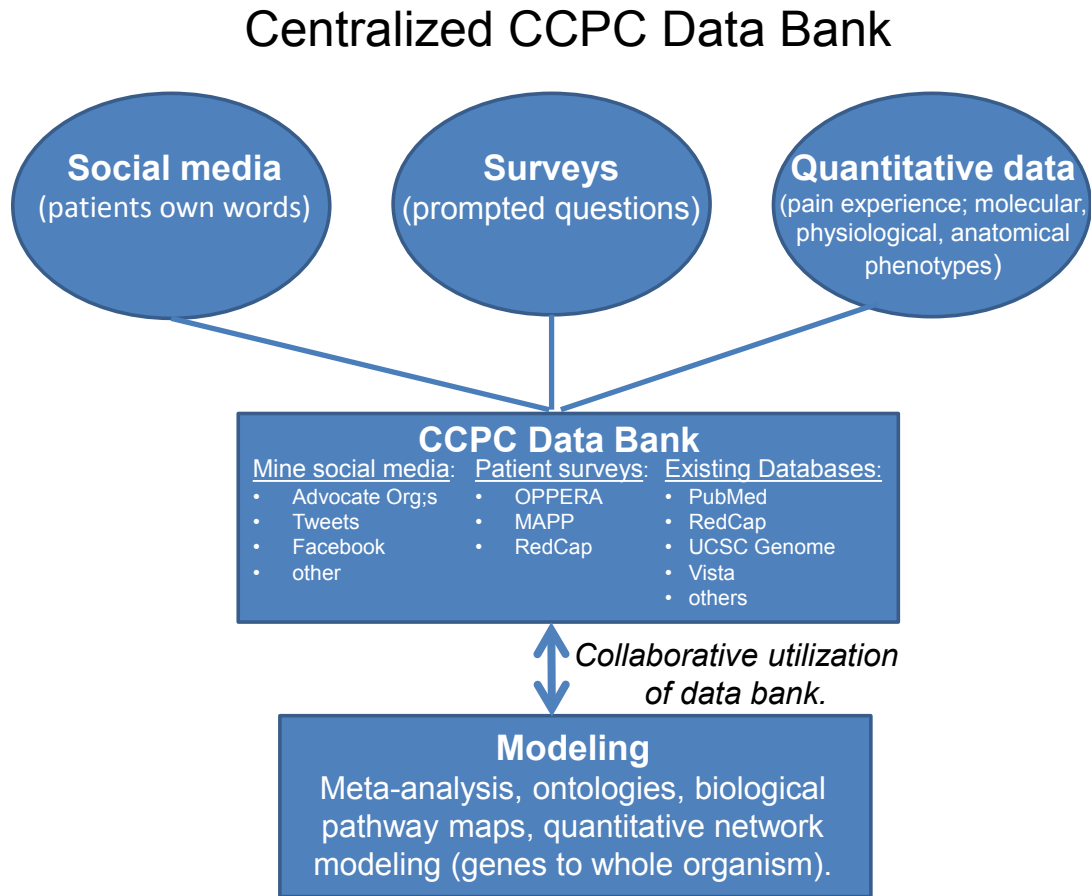
3. Develop neurobiological profiles. Biologically based quantitative data are needed to distinguish different pain types among CCPC patient groups and to inform hypothesis-driven research. Since routine laboratory tests may look normal in CCPC subjects, a broader and deeper battery of tests must be pursued along with patient symptoms. These should generally include (a) neurobiological profiles for quantifying pain, specifically deep somatic and visceral pain domains (not just cutaneous pain); (b) quantitative data for autonomic, somatomotor, endocrine, and microbial systems; and (c) quantitative data for blood cytokine/chemokine profiles characterizing immune/inflammatory responses. Efforts should be made to obtain early indicators of CCPC. Standardization of these testing procedures, nomenclature, and methods for quantitative analysis of these data would be essential.

4. Create an online centralized CCPC data bank to serve as a curated repository and shared reference source. Such a resource would serve basic and clinical scientists and enable formulation of testable hypotheses for systematic experimental studies on animals and human subjects. This knowledge base should include:

- a. Information obtained directly from patients describing their own symptoms by mining social media sources (Twitter, Facebook, etc.) to enrich physician-based histories and surveys.
- b. Data from patient surveys and existing studies (e.g., OPPERA, MAPP) and databases that will incorporate time, natural history, longitudinal data.
- c. Quantitative and qualitative data mined from existing medical literature such as PubMed.

5. Support collaborative research using the CCPC data bank. Conventional and novel biometric analytical tools should be designed to aid in the search and meta-analysis of the data bank. Ontologies and biological pathways should be built with an atlas to link concepts to the literature and define CCPC diseases (see <http://www.pubbrain.org>). Qualitative molecular and biological pathway maps and quantitative network modeling should be applied to move from a 'metaphorical' description of CCPC to a formal model. This would include models containing DNA sequence and gene/mRNA/protein expression, dynamic protein operations, cell signaling pathways, structural and functional brain networks, and scaling of model systems to the level of complex tissue and organ biology. The validation of the hypotheses generated by these models will require testing in basic animal and other model systems.

Figure 1. Data Bank to obtain “signatures” of comorbid chronic widespread pain conditions.



Breakout Group Notes

Group 1. Epidemiology and Sex/Gender Differences in Comorbid Chronic Pain Conditions (CCPC)

►Overlap of CCPC:

- Current clinical studies have shown overlap of CCPC.
- There is a need for prospective population-based studies to determine the natural history of CCPC.
- Rationale is to help understand and inform about potential mechanisms.
- Note that “comorbid” does not imply common mechanisms.

►Prospective study:

- Population should be recruited from a defined sampling frame.
- Recruit persons with and without established CCPC, and follow them prospectively.
- Include persons from adolescence and both sexes
- Risk factors should be evaluated including:
 - Demographic factors
 - Psychological factors/trauma
 - Mechanical trauma (obesity)
 - Inflammatory markers and immune function
 - Lifestyle
 - Experimental pain measures
 - Early adverse life events
 - Genetic factors

►Definition of CCPC:

- Many of the conditions have validated criteria, but these criteria are limited and do not include somatic and psychological comorbidities. It was not clear how to delineate CCPC from other pain syndromes. This was identified as a clear need. (Use of pain diaries was suggested.)

►Methodological issues and recommendations:

- Data collection (big issue of all Groups – see recommendations).
- To achieve cost-effectiveness use existing national or international studies to collect additional outcome data, e.g., Orofacial Pain Prospective Evaluation and Risk Assessment (OPPERA); Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP).
- Unsuitability of standard medical records (e.g., HMO) for these conditions was emphasized.

►Other studies recommended:

- Twin studies/ family studies to address the question of “if I have a twin/ relative with e.g., fibromyalgia, am I at increased risk of developing comorbidities?”

- Consider study of cohorts of persons exposed to environmental factors (e.g., Katrina) – long-term effects?
- Efficacy of treatment across CCPC – behavioral/complementary. If one of the CCPC conditions is ameliorated, what is the likelihood of amelioration of the comorbid condition?
- Studies to determine what happens to the CCPC in an individual who subsequently develops another pathology associated with pain (e.g., cancer) and what happens to the CCPC when you treat the new pain?
- Studies to determine if abolishing the peripheral input (e.g., local anaesthetic) from site thought to be the initial irritant (e.g., jaw in TMD) abolishes CCPC, or just the particular condition that is targeted?

Group 2. Diagnosis of Comorbid Chronic Pain Conditions: Phenotypes, Genotypes, Biopsychosocial Factors

- ▶The group concluded that there is currently insufficient information to distinguish CCPC from other widespread chronic pain conditions, since inflammatory and neuropathic pain conditions can be accompanied by CCPC characteristics. The Group recommended research directed toward this end:
 - Large scale, multicenter (potentially international) case-control study (about 2000-3000 patients) aimed at extensive phenotyping.
 - Case-control design with a longitudinal dimension.
 - Reduce age of inclusion and study child to adult (CTSAs of the NIH have a child health component).
 - Include as controls a non-pain population and some comparator pain condition thought not to be comorbid (potentially sickle cell disease).
 - Have enrollment initially based on the most prevalent syndromes as currently defined by syndrome-specific symptom criteria.
 - Utilize an agnostic analysis approach where all enrolled patients are analyzed without consideration of symptom criteria.
 - Don't need to start from scratch since OPPERA and MAPP infrastructures and repositories can be used.
 - Funnel all data into a National Data Repository for general use and analysis.

A major goal of the proposed study is to develop new diagnostic criteria, based on emerging phenotypic and genomic data clusters from advanced biomathematical modeling of extensive databases of biological/clinical phenotypes, regardless of initial symptom-based diagnosis. The goal is to replace the current categories/descriptors (such as FM, CFS, TMJ, IBS, etc.) with new diagnostic categories, which share biological mechanisms and respond to specific therapies (e.g., CCPC type 1, type 2, etc.). This is a low-risk paradigm shift.

▶Approach:

Tier 1 phenotypes: high throughput standardized phenotypes (biological samples from easily accessible body fluids (e.g., blood, saliva, urine); biomarkers of these fluids (“omics”); genotyping; QST; biopsychosocial data; neural autonomic data;

brain imaging (structural/resting state)→then use advanced mathematical modeling approaches (machine learning, random forest, etc.) →identify clusters and endophenotypes.

Tier 2 phenotypes: based on “pattern” clusters→carry out molecular brain imaging (glial cells); genomics/proteomics/omics on CSF. Characterize and understand mechanisms of already existing therapies, including the reason why most therapies only work in subsets of individual syndromes (evaluate antidepressants, anticonvulsants, anxiolytics, cognitive behavioral drugs, etc.). Use information from drug testing to validate new diagnostic patterns.

►The group recommended that:

- Studies take advantage of OPPERA and MAPP cohorts, methodologies, instruments and repositories for the CCPC study.
- A National Data Repository be established for general use; that support be provided for development of methods for integration of multiple, large, complex data sets.
- Computational analysis needs to be at the center of a national program and integrated from the beginning with all CCPC studies.
- Phenotyping: Base the initial enrollment on standardized case definitions. This would be followed by re-categorization/classification based on phenotypic patterns emerging from advanced modeling approaches that evolve from the variety of data in the Data Repository.
- NIH should bring program leaders together and agree to an operationalized set of common diagnostic criteria to start the study.
- To the extent possible, use should be made of the existing CTSA infrastructure and ancillary institutional resources (bioinformatics, training program/mentoring structure, etc.).

►Potential payoff:

- This approach should give a definitive answer to the broad issue of whether CCPC actually exist, or whether a particular pain condition is part of the CCPC rubric, and whether there are subgroups within each CCPC that share biological features.
- It is likely that this approach will lead to whole new diagnostic classifications for all the disorders.
- From this large data registry, future ancillary studies (RO1-based hypothesis-driven research grants) will evolve for detailed investigation.
- Development of new tools: new approaches are needed to assess neural inputs to the brain based upon multimodal imaging, molecular brain imaging, non-neuron imaging, and regional microflora characterization.
- From the biological pathway analyses, investigators should be able to move rapidly back and forth from human data to mechanistic-based experimental animal data.

- ▶ Treatment modalities:
 - As the CCPC studies obtain the needed quantitative data, the Tier 1 analysis (see above) can be used to determine diagnostic, surrogate end points, and treatment targets.
 - Potential therapeutic targets can be developed and tested in animal models and moved to humans.

- ▶ Training:
 - Recruitment and training of faculty, residents, technical staff, post-doctoral and clinical research fellows, graduate students, in addition to training of technical staff, post-doc and student level are needed to study CCPC.
 - Training programs should be multi-institutional (via CTSA Programs, etc.).
 - Training needs to focus on multi-disciplinary approaches (basic and clinical specialties related to the neurosciences, brain imaging), genomics/ proteomics/epigenetics, statistics, computational biology, etc.).
 - Information about CCPC needs to be developed and distributed to each institution.
 - Specific K awards in comorbid persistent pain conditions or sabbatical K18 awards are needed so there is training at junior and senior levels specifically for CCPC. Clinical and basic scientists outside the traditional pain area should be specifically targeted.

- ▶ Development of new methodologies for modeling CCPC are recommended.

- ▶ High-risk new research areas:
 - Funding of ancillary RO1 type grants for existing consortia (OPPERA, MAPP) to explore new directions in research.

Group 3. Basic and Translational Studies, Animal Models, and

Group 4. Next Generation Therapies for Comorbid Chronic Pain Conditions

- ▶ Establish firm diagnostic criteria for each disorder, allowing a better definition of “*multi-organ system hypersensitivity*.” This term was derived from discussion by this combined group at this meeting and appears to capture an important common feature of CCPC.
 - Convene a team of scientific and clinical experts to agree upon common metrics for multi-organ system hypersensitivity when diagnosing any individual disorder.
 - Best practices and standardized methods must be used.
 - Recognize that symptom severity does not correlate with amount of the disease (examples include: TMJ anatomical injury with and without pain; ectopic growth with endometriosis).
 - Determine early indicators of each disorder:
 - Establish screening criteria for each.
 - Determine what characteristics of acute pain might be early indicators

- Quantitative data are needed for different pain types from different CCPC patient groups:

- Need to address specifically deep somatic and visceral pain domains, not just cutaneous pain.

- Recognize that routine lab tests generally look normal; differences may appear on deep phenotyping approaches, such as cytokine differences, etc.

- Quantitative changes in autonomic parameters are needed.

- Quantitative data on endocrine and cytokine parameters are needed.

- Data on the somatomotor systems are needed.

- In acute pain, each subject weights pain; need to map perception as well as stimulus characteristics.

- ▶Generate neurobiological profiles for the different CCPC clinical syndromes (such as FMS, CFS, CPP, vulvodynia, endometriosis, IBS, etc.) based on quantitative studies of the following parameters:

- Pain:** ongoing, evoked by mechanical and/or thermal stimulation from different parts of the body (body surface, deep somatic tissues including skeletal muscle, joints, fascia and viscera) as carried out in the QST analysis of the German Pain Network (see W. Magerl et al. Pain 2010: 151:598-605).

- Non-painful somatosensory and visceral sensations** evoked by mechanical and/or thermal stimulation from different parts of the body (body surface, deep somatic tissues [skeletal muscle, joints, fascia] and viscera).

- Changes related to the autonomic nervous system** (blood pressure, heart rate variability, sweat gland activity, parameters related to the visceral organs, other).

- Changes of the somatomotor system** (determined by somatosensory evoked potential (SEP) recordings and continuous EEG monitoring)

- Neuroendocrine data** related to the HPA axis, the sympatho-adrenal system; cytokines in the blood and CSF.

- Brain data** (resting state, cortical morphometry, white matter connectivity, molecular) obtained with multimodal imaging methods

- ▶Compare the quantitative data obtained from patient groups with those obtained from healthy controls (age-matched, gender-matched, etc). As summarized in the Recommendations, a quantitative National Data Bank should be established:

- The patient data must be normalized with respect to data obtained from healthy controls so the data on the control group subjects must be obtained in the same way as those from the patients. Thus, the patient data will undergo a z-transformation to provide characteristic quantitative profiles for each patient CCPC group.

- These data will then be used to establish a quantitative data bank for the different patient groups. This data bank will progressively grow and be a curated online living database, adding data forthcoming from each of the patients and controls. The bank will serve as an open reference source for the research groups working in this field.

- This quantitative data bank will serve clinicians to describe and more effectively characterize – across medical disciplines – the different groups of patients within the rubric of CCPC.
 - The data will serve clinicians and basic scientists (including clinician-scientists) to formulate testable hypotheses for systematic experimental investigations on animals (behavioral models, reduced in vivo experiments, reduced in vitro, etc.) and on human subjects (healthy and patients) as experimental models.
 - The data bank will enable one to determine the quantitative overlap in the characteristics between the different groups of patients and serve as the basis for discussion of potential changes of classification/reclassification of syndromes ranging under CCPC.
 - The data bank will serve clinicians in the discussion and design of new treatment strategies that are more mechanistically based.
- ▶ Standardization of testing procedures, nomenclature and quantitative documentation of the data.
- It is imperative that testing procedures be carefully standardized between different centers and across different medical disciplines.
 - Persons who conduct the quantitative testing procedures on the patient groups must be systematically trained so that the data obtained in the different centers are collected, to the extent possible, under the same conditions. The testers must be blinded if possible (see Maier et al 2009).
 - It is recommended that a working group be established to develop standards for all clinical testing procedures, technical procedures, actual measurements, documentation and analysis of data.
- ▶ Develop animal models that describe multi-organ system hypersensitivity.
- Animal models and research need to incorporate common features of multi-organ system hypersensitivities rather than representing separate/individual diseases.
 - Brain, autonomic, neuroendocrine, neuro-immune and somatomotor mechanisms should be studied.
 - A partial list of the disorders/diseases that fall into this category include:
 - Temporomandibular Disorders
 - Endometriosis
 - Chronic fatigue syndrome
 - Fibromyalgia
 - Functional dyspepsia
 - Interstitial cystitis
 - Vulvodynia
 - Irritable bowel syndrome
 - GERD
 - Multiple chemical sensitivities

- ▶ It is critical to collect data that will inform hypothesis-driven research.
 - An important hypothesis to test is whether early life events contribute to multi-organ system hypersensitivities as reflected through measurable biochemical and anatomical metrics.
 - It is recommended that predictive indicators be identified (such as cytokines, chemokines, genetic, epigenetic, brain imaging, patient symptoms, etc.)
 - Capturing patient populations early in the development of their disease through use of social media was recommended.
 - Utilize next generation data mining and pattern recognition tools to develop a word/cue
 - Incorporate cue lists to direct people in need to appropriate information (e.g., websites) or help (e.g., primary care)
 - Creation of a knowledge base from:
 - New trends – social media, mining tweets
 - Patient-based mining
 - Old trends – standardized tools
 - Mine what we know
 - Existing data: survey data from patients, EMR, existing studies. e.g., MAPP, American Migraine Prevalence and Prevention (AMPP) and databases (REDCap). Need to incorporate time, natural history, and longitudinal data.
 - Mine existing medical literature (PubMed).

- ▶ Query this knowledge base using conventional and novel approaches.
 - Utilize qualitative pathway maps and quantitative network analyses.
 - Apply these analyses to inform research and patient care.
 - Utilize this knowledge base and develop ways to move this information into the medical mainstream.

- ▶ High-risk new research areas for multi-organ system hypersensitivities found in CCPC patients.
 - Determine how changes in autonomic, neuroendocrine and immune networks contribute to multi-organ system hypersensitivities.
 - Involvement of visceral and somatic body tissues?
 - What is the spectrum of these changes in multi-organ system hypersensitivities?
 - Determine how undifferentiated cells and stem cells can be used to modify (reprogram) multi-organ system hypersensitivities.
 - Develop ontologies and therapies (e.g., drug repurposing and next gen) for multi-organ system hypersensitivities.
 - Identify key knowledge base inputs such as inclusion of patient-described symptoms, and diagnostic, clinical and biomedical data that can be identified and retrieved.
 - Develop new approaches to clinical trials based on learning from existing trials to take advantage of unintended possible benefits for multi-organ system hypersensitivities.

- Develop human and animal epigenetic research to capture consequences of early life experiences and the environment.
- It is recommended that studies be developed to determine why some patients with diagnosed disease have pain and others have no pain.
Examples: TMJ (patients with no apparent joint destruction WITH PAIN vs. patients with severe joint destruction and NO PAIN); endometriosis (patients with few lesions and extreme pain vs. patients with Stage IV lesions but minimal/no pain)
- Define the spectrum (from none to max) and subtypes (implants vs. neuropathic) of multi-organ system hypersensitivities.
- Utilize knowledge gained from studies in the cancer field of inflammation and other signaling changes that occur with chronic pain.

Comments at the Final Plenary Session

Dr. Jon Levine: Major features of widespread pain: intersecting experience; views these many conditions as “neuropathies” since they respond to the same drugs as neuropathic pain conditions; routine lab tests look normal; but when looking deeper you see differences such as cytokine differences; has model of CNS/neuropathic pain (issue of peripheral sensitization vs. central sensitization).

Dr. Michael Salter: Importance of neural-glia interactions. Microglia are considered immune cells (macrophage lineage). After nerve injury, glial cells increase in number, change from surveillance to activated state. Glial-derived protein interaction in spinal cord and brain stem occurs. Purinoreceptor (P2X4 receptor) stimulation reverses hypersensitivity; P2X4 KO mice fail to develop hypersensitivity after nerve injury.

General comments related to need to distinguish between acute and chronic pain:

- a. Acute – can be intermittent or sustained pain but goes away when the stimulus is removed.
- b. Chronic – is unrelenting and is not removed if the stimulus is removed.
- c. Mechanisms of plastic changes in nervous system poorly understood; whether and how can these changes be reversed is major issue.
- d. Why does it develop only in some people? (genetic background; epigenetic?) (Löttsch; Sarna; Reed – all emphasize the need to study children to adult).

Dr. Robert Bilder: Tools are needed to build collaborative knowledge bases. These are generally descriptive and not mechanistic while his own tools can yield hypotheses related to mechanistic pathways and allow one to mine the literature for things such as pain (as he does with schizophrenia using “PubBrain”) and builds cognitive ontologies and an atlas to link concepts to the literature and define “task specification”.

Dr. Douglas Lauffenberger: Uses cell signaling circuitry to move from a “metaphorical” description to a formal model (i.e., from general concept of extracellular cues to cell signaling – to model with DNA sequence → mRNA → protein → dynamic protein operations). By doing multipathway analysis and 3D tissue studies in IBD mouse he is able to examine what cytokines are made by macrophage cells under different conditions.

Dr. Suzanne Vernon: Emphasizes that one must be careful trying to lump too many things into a single category, a danger faced as we explore comorbid conditions. “Comorbid does not imply common mechanisms”. Lumping is problematic since as Dr. Alan Light has shown there are different patterns of gene expression at the molecular level with exercise in patients with CFS and FM, even though both experience the same pain and physical symptoms.

Dr. William Maixner: Indicated that “pressure pain threshold” is the best predictor of “pain sensitivity” to be used in case/control studies since pressure points reflect to a greater extent muscle-like pain. He also emphasized the importance of evaluating autonomics (orthostatic challenges HR/BP) in TMD since he has shown greater HR at rest and that baroreceptor gain and set point changed leading to more variability of HR and blood pressure.

Dr. Emeran Mayer: Emphasized that in contrast to OPPERA, all patients are symptomatic (not case/control). It seems uncertain if the pain phenotype of the MAPP study is the same as that of the OPPERA study (pressure pain). Both he and Dr. Maixner emphasized the importance of gathering intermediate phenotypes/endophenotypes and the need to use meta-data from phenotyping to describe the disorder rather than using traditional nomenclature.

Dr. Richard Lipton: Emphasized that migraine differs from other chronic pain in that it is “episodic”. It is a disorder of brain hyper-excitability; a heterogeneous genetic disorder with heritability of 40-60%. Some forms are autosomal dominant; and genes all involve ionic pumps. There is no single brain locus. He notes that based on AMPP (American Migraine Prevalence and Prevention) criteria for migraine, TMDs are clearly in the region of pain. Risk factors for migraine include obesity, stress, depression and TMD. It is unknown if depression is a marker itself for migraine, a risk factor, or a consequence.

Dr. Wilfred Jänig: Emphasized the importance of the following references related to Chronic Pain:

- Baron, R., Fields, H., Jänig, W., Kitt, C., Levine, J.D. Reflex Sympathetic Dystrophy/Complex Regional Pain Syndromes (CRPS): State-of-the-Science. *Anaesthesia and Analgesia* 95, 1812-1816 (2002). “This is a report about a data bank of patients with neuropathic pain obtained with sensory testing in Germany”.
- Baron R, Tölle TR, Binder A, Birbaumer N, Birklein F, Gierthmühlen J, Flor H, Geber C, Hüge V, Krumova EK, Landwehrmeyer GB, Magerl W, Maihöfner C, Richter H, Rolke R, Scherens A, Schwarz A, Sommer C, Tronnier V, Uçeyler N, Valet M, Wasner G, Treede RD. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): somatosensory abnormalities in 1236 patients with different neuropathic pain syndromes. *Pain* 150:439-50 (2010).
- Stanton-Hicks, M., Jänig, W., Hassenbusch, S., Haddox, J.D., Boas, R., Wilson, P. Reflex sympathetic dystrophy: changing concepts and taxonomy. *Pain* 63, 127-133 (1995). “ A highly influential paper on CRPS”.

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