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TMJ Science

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Fifth Scientific Meeting of The TMJ Association, Ltd.

Can Studies of Comorbidities with TMJDs Reveal Common Mechanisms of Disease?

In This Issue

The Fifth Scientific Meeting of The TMJ Association focused on conditions often found to be comorbid with temporomandibular joint and muscle disorders (TMJDs). These include chronic headache, generalized pain conditions, irritable bowel syndrome, endometriosis, interstitial cystitis, vulvodynia, fibromyalgia, chronic fatigue syndrome, and rheumatoid arthritis.

The goal of the meeting was to discover if there are common roots and physiological pathways among these conditions, in this way furthering our understanding of all of them and perhaps providing novel targets for diagnosis and therapy. Because the meeting had been designed to bring together scientists and clinicians knowledgeable about each of the complex conditions named above, we hoped to stimulate cross-collaborative studies as a means to accelerate research progress and ultimately benefit patients. Toward that end we had also invited young investigators to stimulate their career commitments to engage in TMJD and related research. As in past TMJ Association scientific meetings, patients themselves participated in panel presentations and discussions, providing opportunities for experts and patients to learn from each other in formal and informal exchanges.

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One War, Many Fronts

Patients and patient advocates have always been welcome at The TMJ Association's scientific meetings, but at the 2008 meeting they were also featured on the program with a roundtable discussion of their own. Although each of the speakers made a presentation on behalf of the condition and constituents they represented, one was left with the impression that—sociologically certainly, and probably biologically, too—all these conditions have a kinship.

Even a dispassionate listener couldn't help but notice how often the same issues arose about two or more of these multi-systems illnesses. A case in point was the frequency with which patients whose primary diagnosis was irritable bowel syndrome or TMJDs had unnecessary and often harmful surgery. So, too, was the admonition patients repeatedly heard from doctors telling them to "learn to live with it." Said Mary Lou Ballweg of the Endometriosis Association of this situation, "I don't know what it's going to take to get gynecologists to deal with women's pain." Other speakers noted that this was not unique to gynecologists.

As if all of this wasn't sufficiently disturbing, there was the impact on quality of life, not to mention the damage done to career prospects, such as interstitial cystitis patients having to urinate as many as 60 times a day, or fibromyalgia patients having to dress so slowly that they cannot keep a job because they can't get to work on time.

Similarly, what can be expected of a marriage in which the wife's chronically stinging genital pain due to vulvodynia discourages intercourse? The symptoms of burning and rawness alone can rule out her use of menstrual tampons or even wearing close-fitting slacks, while making riding a horse, bicycle or motorcycle miserably uncomfortable. Moreover, many women with vulvodynia suffer other chronic pain conditions, most notably, TMJDs, fibromyalgia and/or interstitial cystitis, though the full extent of comorbid conditions has yet to be determined.

Not every sufferer from these or the other disorders represented at the roundtable is severely incapacitated by them. Still, the point was clear that chronic pain conditions and their complexities are, in themselves, diseases that the medical and scientific communities need to take much more seriously.

Meanwhile, there is this: the choice of subject for the scientific meeting and the opportunity for a roundtable, allowing attendees to hear from the patients themselves what it is like to experience the conditions under discussion, was inspirational. It is already bringing the patient groups together to cooperate, collaborate, and advocate for the very research that can benefit them one and all.

The Fifth Scientific Meeting of The TMJ Association, Ltd.

Can Studies of Comorbidities with TMJDs Reveal Common Mechanisms of Disease?

Federation of American Societies for Experimental Biology
Bethesda, Maryland
June 1-3, 2008

Sunday, June 1, 2008

7:00 – 7:15 p.m. **Welcome**
Terrie Cowley, President, The TMJ Association, Milwaukee, WI

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

National Institutes of Health Welcome and Directives
Lawrence A. Tabak, D.D.S., Ph.D., Director, National Institute of Dental and Craniofacial Research, National Institutes of Health, Bethesda, MD

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

7:15 – 8:00 p.m. **Clinical Symptoms and Comorbidities of TMJD Patients**

TMJDs: Overcoming the Scientific Challenges of a Complex Phenotype
Christian S. Stohler, D.M.D., Dr. Med. Dent.
University of Maryland Dental School, Baltimore, MD

Overlaps Between Tension-Type Headaches and TMJDs
Peter Svensson, D.D.S., Ph.D., Dr. Odont.
School of Dentistry, University of Aarhus, Denmark

TMJDs: A Mosaic of Clinical Phenotypes and Systemic Disorders
William Maixner, D.D.S., Ph.D.
University of North Carolina at Chapel Hill, Chapel Hill, NC

8:00 – 9:00 p.m. **Patient Roundtable**
Chaired by Drs. Christian S. Stohler, Peter Svensson, and William Maixner

Chronic Headache
Teri Robert, Help for Headaches & Migraine, Parkersburg, WV

Generalized Pain Conditions
Claire W. Patterson, Board Director
American Chronic Pain Association, Rocklin, CA

Irritable Bowel Syndrome
Nancy J. Norton, President, International Foundation for Functional Gastrointestinal Disorders, Milwaukee, WI

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

Interstitial Cystitis
Barbara J. Gordon, R.D., M.B.A., Executive Director
Interstitial Cystitis Association, Rockville, MD

Vulvodynia
Christin Veasley, Associate Executive Director
National Vulvodynia Association, Silver Spring, MD

Fibromyalgia
Lynne Matallana, President, National Fibromyalgia Association, Anaheim, CA

Chronic Fatigue Syndrome
Suzanne D. Vernon, Ph.D., Scientific Director
The CFIDS Association of America, Charlotte, NC

Rheumatoid Arthritis
Calaneet Balas, President & CEO
Arthritis Foundation Metro DC Chapter, Washington, DC
Sandy Canfield, Patient Advocate, Burke, VA

Temporomandibular Joint and Muscle Disorders
Terrie Cowley, President, The TMJ Association, Milwaukee, WI

Monday, June 2, 2008

8:15 – 8:35 a.m. **Welcome**
Martin Frank, Ph.D., Executive Director, American Physiological Society Bethesda, MD

Opening Remarks
Barbara M. Alving, M.D., M.A.C.P., Director, National Center for Research Resources, National Institutes of Health, Bethesda, MD

Opening Remarks
William J. Heetderks, M.D., Ph.D., Director, Extramural Science Programs
National Institute of Biomedical Imaging and Bioengineering
National Institutes of Health, Bethesda, MD

Session 1: ***Chronic Headache***

8:35 – 8:50 a.m. **Chronic Headache and TMJDs**
Richard B. Lipton, M.D., Albert Einstein College of Medicine, Bronx, NY

8:50 – 9:05 a.m. **Role of Neuronal-Satellite Glial Cell Interactions in the Underlying Pathology of Migraine and TMJ Disorders**
Paul L. Durham, Ph.D., Missouri State University, Springfield, MO

9:05 – 9:15 a.m. **Discussion**
Peter Svensson, D.D.S., Ph.D., Dr. Odont.
School of Dentistry, University of Aarhus, Denmark

Session 2: ***Generalized Pain Conditions***

9:15 – 9:30 a.m. **The Challenges of Targeting Mechanisms of Pain Following Nerve Injury**
Christine N. Sang, M.D., M.P.H., Brigham and Women's Hospital
Harvard Medical School, Boston, MA

9:30 – 9:45 a.m. **Glia as the "Bad Guys" in Dysregulating Pain and Opioid Actions: Implications for Improving Clinical Pain Control**
Linda R. Watkins, Ph.D., University of Colorado at Boulder, Boulder, CO

9:45 – 9:55 a.m. **Discussion**
Ronald Dubner, D.D.S., Ph.D., University of Maryland Dental School, Baltimore, MD

9:55 – 10:10 a.m. **Break**

10:10 – 11:10 a.m. ***Selected Summary Poster Presentations***
(Posters are listed in the abstract booklet on pages 32-45)

Poster A: Catechol O-Methyltransferase (COMT) Met/Met Genotype Influences Cortisol Response and Pain Symptoms after Minor Motor Vehicle Collision (MVC)
Samuel McLean, M.D., M.P.H.
University of North Carolina at Chapel Hill, Chapel Hill, NC

Poster B: Effect of Intranasal Delivery of Carbon Dioxide on Trigeminal Ganglion Neurons: Inhibition of Neuron-Glia Gap Junction Communication and SNAP-25 Expression
Filip Garrett, Missouri State University, Springfield, MO

Poster C: Contribution of Primary Afferent Input to Trigeminal Glial Activation, Cytokine Induction and NMDA Receptor Phosphorylation
Hu Wang, Ph.D., M.D., University of Maryland Dental School, Baltimore, MD

Poster D: Sex Differences in Peripheral Delta Opioid Receptor (Dor) Function and Involvement of G Protein-Coupled Inward Rectifying Potassium Channels (Girk) in Dor-Mediated Attenuation of Masseter Hypersensitivity
Jongseok Lee, Ph.D., University of Maryland Dental School, Baltimore, MD

11:10 – 1:00 p.m. **Lunch and Poster Session**

Session 3: ***Irritable Bowel Syndrome / Endometriosis / Interstitial Cystitis / Vulvodynia***

1:00 – 1:15 p.m. **Clinical and Neurobiological Aspects of Brain-Gut Interactions in IBS Patients**
Emeran A. Mayer, M.D., University of California, Los Angeles, Los Angeles, CA

1:15 – 1:30 p.m. **Neural Mechanisms of the Pains of Endometriosis and Comorbid Disorders**
Karen J. Berkley, Ph.D., Florida State University, Tallahassee, FL

1:30 – 1:45 p.m. **Clinical Features and Neurobiological Aspect of Interstitial Cystitis**
Larissa V. Rodriguez, M.D., University of California, Los Angeles, Los Angeles, CA

1:45 – 2:00 p.m. **Neural-Epithelial Interactions in Interstitial Cystitis**
Lori A. Birder, Ph.D., University of Pittsburgh School of Medicine, Pittsburgh, PA

2:00 – 2:15 p.m. **Discussion**
Allen W. Cowley, Jr., Ph.D., Medical College of Wisconsin, Milwaukee, WI

Session 4: ***Fibromyalgia***

2:15 – 2:30 p.m. **Mechanisms in "Central" Pain Syndromes: Lessons Learned from Fibromyalgia**
Daniel J. Clauw, M.D., University of Michigan, Ann Arbor, MI

2:30 – 2:45 p.m.	**Comorbidity of TMJDs and Fibromyalgia** Lesley M. Arnold, M.D., University of Cincinnati College of Medicine, Cincinnati, OH
2:45 – 2:55 p.m.	**Discussion** William Maixner, D.D.S., Ph.D. University of North Carolina at Chapel Hill, Chapel Hill, NC
2:55 – 3:10 p.m.	**Break**
3:10 – 3:25 p.m.	**Generalized Pain Syndromes: Mechanisms** Jon D. Levine, M.D., Ph.D., University of California-San Francisco, San Francisco, CA
3:25 – 3:40 p.m.	**Imaging the Cognitive Modulation of Pain in Fibromyalgia** Dane B. Cook, Ph.D., University of Wisconsin-Madison, Madison, WI
3:40 – 3:50 p.m.	**Discussion** John W. Kusiak, Ph.D., National Institute of Dental and Craniofacial Research, National Institutes of Health, Bethesda, MD
Session 5:	***Chronic Fatigue Syndrome***
3:50 – 4:05 p.m.	**Understanding the Biology of Chronic Fatigue Syndrome to Improve Objective Diagnosis and Intervention** Suzanne D. Vernon, Ph.D., The CFIDS Association of America, Charlotte, NC
4:05 – 4:20 p.m.	**Research Advances in Chronic Fatigue Syndrome** Nancy G. Klimas, M.D., University of Miami Miller School of Medicine, Miami, FL and Miami Veterans Healthcare System, Miami, FL
4:20 – 4:30 p.m.	**Discussion** Christian S. Stohler, D.M.D., Dr. Med. Dent. University of Maryland Dental School, Baltimore, MD
Session 6:	***Rheumatoid Arthritis***
4:30 – 4:45 p.m.	**Rheumatoid Arthritis and Cardiovascular Risk** Joan M. Bathon, M.D., Johns Hopkins University, Baltimore, MD
4:45 – 5:00 p.m.	**Rheumatoid Arthritis Immunopathogenesis** Alisa E. Koch, M.D., University of Michigan Medical School, Ann Arbor, MI and Veterans Administration Ann Arbor Healthcare System, Ann Arbor, MI

5:00 – 5:10 p.m. **Discussion**
Stephen L. Gordon., Ph.D., Gordon BioMedical Consulting, LLC, Carey, NC

6:30 p.m. **Dinner at Bethesda Marriott Hotel, 5151 Pooks Hill Road, Bethesda, MD**

Tuesday, June 3, 2008

Session 7: ***Temporomandibular Joint and Muscle Disorders***

8:30 – 8:45 a.m. **Mechanisms of Deep Tissue Pain in the Orofacial Region: Role of Glial-Cytokine-Neuronal Interactions in the Trigeminal Transition Zone**
Ke Ren, Ph.D., University of Maryland Dental School, Baltimore, MD

8:45 – 9:00 a.m. **Human Brain Neurotransmitter Responses to Temporomandibular Pain and Psychophysical Correlates**
Jon-Kar Zubieta, M.D., Ph.D., University of Michigan, Ann Arbor, MI

9:00 – 9:15 a.m. **Animal Models of Depression and TMJ Pain Processing**
David A. Bereiter, Ph.D., University of Minnesota School of Dentistry, Minneapolis, MN

9:15 – 9:25 a.m. **Discussion**
Ronald Dubner, D.D.S., Ph.D., University of Maryland Dental School, Baltimore, MD

Workshop Summary Report
9:25 – 9:45 a.m. **A Systems Approach to Understanding TMJDs**
John T. Watson, Ph.D., University of California, San Diego, La Jolla, CA

9:45 – 10:15 a.m. **Selected Summary Oral Poster Presentations**
(Posters are listed in the abstract booklet on pages 32-45)

Poster E: Prevalence of Comorbid Conditions in Individuals with TMJD Compared to Matched Controls
Raymond G. Hoffmann, Ph.D., Medical College of Wisconsin, Milwaukee, WI

Poster F: Modulation of Tactile Responsiveness in Somatosensory Cortex by Noxious Heat: Implications for Female TMD Patients
Mary Beth Nebel, University of North Carolina at Chapel Hill, Chapel Hill, NC

10:15 – 10:30 a.m. **Break**

10:30 – 12:00 p.m. **Break-out group discussions to assess and summarize commonalities among these complex conditions and develop recommendations for future research directions**

Group 1. **Basic Mechanisms Underlying Comorbidities of the Complex Diseases Presented**
Discussion led by Dr. Christian Stohler

Group 2. **Clinical Comorbid Features Shared by the Complex Diseases Presented**
Discussion led by Dr. Peter Svensson

Group 3. **Diagnostic Approaches and Development of Biomarkers Predictive of these Complex Disorders and their Shared Features**
Discussion led by Dr. William Maixner

Recommendations to be developed addressing the following issues:

1. What research areas would mutually benefit TMJDs and these other complex diseases which share comorbidities?
2. Are there ways in which genomic screening and imaging modalities can be utilized to define the vulnerability of individuals to the commonly defined comorbidities and lead to individualized therapeutic and preventive approaches?
3. How can academic and clinical programs be implemented that would coalesce the scientific expertise needed to study and implement these approaches?

12:00 – 1:30 p.m. **Lunch and Poster Session**

1:30 – 2:30 p.m. **Discussion Leaders' Presentations of Recommendations**

2:30 p.m. **Closing Remarks/Evaluation**
Lawrence A. Tabak, D.D.S., Ph.D.,
Director, National Institute of Dental and Craniofacial Research, National Institutes of Health, Bethesda, MD

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National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institute of Biomedical Imaging and Bioengineering
National Institute of Diabetes and Digestive and Kidney Diseases
National Institute on Deafness and other Communication Disorders
National Institute on Drug Abuse
Office of Rare Diseases
Office of Research on Women's Health

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This meeting would not have been possible without our dedicated volunteers.

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Can Studies of Comorbidities with TMJDs Reveal Common Mechanisms of Disease?

Report on the Fifth Scientific Meeting of The TMJ Association, Ltd.
By Judith Randal

Pain in one or both jaws, which restricts movement and spreads into surrounding tissues, is the key feature of temporomandibular joint and muscle disorders (TMJDs), a set of complex and poorly understood conditions, popularly called TMJ, that affects more than 10 million Americans at any given time.

Though nothing is wrong with that description, it misses two important points. One is that TMJDs can be seriously disabling, particularly if they become chronic. The other is something that The TMJ Association, a patient advocacy organization based in Milwaukee, WI, has been hearing from sufferers for years—that many are persistently troubled by one or more painful conditions in addition to their TMJD.

According to Terrie Cowley, the Association's co-founder and President, these conditions include (among others) allergies, chronic fatigue syndrome, chronic headache, endometriosis, fibromyalgia, interstitial cystitis, irritable bowel syndrome, rheumatoid arthritis and vulvodynia. All of them and TMJDs, too, have a predilection for women in their childbearing years. Some think this is only a coincidence, but the pattern has been so consistent over the years that The TMJ Association has reason to suspect that there is more to it than mere coincidence.

More specifically, an online survey was conducted by The TMJ Association in 2006 that asked people in the Association's registry what other persistently painful conditions (if any) they had in addition to their TMJDs. For the purpose of comparison, the survey also recruited some of the respondents' friends who did not have TMJDs, but were of the same age, gender and educational level, and asked if any persistently painful conditions troubled them. Survey respondents with TMJDs reported a significantly higher rate of the comorbid conditions on the Association's list than the respondents' friends.

It is not just that TMJD patients seem to have an increased risk of having a comorbid condition, but the reverse may also be true. This has made some scientists suspect that TMJDs and the other medical conditions on the Association's list may more accurately be described as disorders that are associated with each other than as unrelated illnesses.

The need to probe the interrelationship of these various conditions guided the planning for The TMJ Association's Fifth Scientific Meeting. The meeting, *Can Studies of Comorbidities with TMJDs Reveal Common Mechanisms of Disease?,* held June 1-3, 2008, on the Bethesda, MD campus of the Federation of American Societies for Experimental Biology, may well have been the first of its kind.

Ms. Cowley opened the meeting by welcoming attendees and thanking the various meeting co-sponsors—eight agencies of the National Institutes of Health (NIH), corporate and individual sponsors, volunteers and staff. She

reminded her audience, "This meeting is about comorbidities of TMJDs, in particular conditions of chronic pain. Chronic pain is all-encompassing," she noted. "It causes profound changes in the individual and transforms social and family relationships. Jobs are lost and career dreams abandoned. Women forego having children. Chronic pain can lead to bankruptcy, divorce and suicide. One TMJ patient told me that pain is the reason she misses passionately kissing her husband. Moreover, we have learned over the years that if patients have TMJ pain, they probably have other pain conditions as well and vice-versa. Pain is seldom limited to one body part or one named condition, and certainly not to just one part of the brain."

Next to speak was Allen W. Cowley, Jr., Ph.D., Chairman of the Department of Physiology at the Medical College of Wisconsin, who chaired this meeting's program committee. "TMJDs and their comorbidities often share other similarities in addition to their common symptoms," he said. "As already noted, the most obvious of these is their collective affinity for women of reproductive age. They also share such features as being of unknown cause, lacking clear diagnostic criteria and being plagued by the paucity of information about how well, or poorly, various treatments for them work. The cumulative effect of all of this is that the sufferers are stigmatized."

Dr. Lawrence A. Tabak, Director of the National Institutes of Health's National Institute of Dental and Craniofacial Research (NIDCR), next addressed the audience. In order to familiarize physicians with TMJDs, Dr. Tabak reported that a short article had been published in the March 12, 2008 issue of *The Journal of the American Medical Association* (JAMA). Noting JAMA's wide readership and the respect it enjoys among health professionals, Dr. Tabak called the Journal's acknowledgement "that TMJDs are real is a remarkable step forward in itself." The article also noted that, "Tens of thousands of dollars a year are spent for unnecessary treatments of thousands of patients." Unfortunately, TMJD sufferers often do not know that many treatments they may be offered are of unproven value and so risk making decisions—for surgery, for example—that they may later regret. As an indication of the seriousness of this issue, Dr. Tabak showed the audience an NIDCR public awareness campaign slide of a subway and bus billboard display, which appeared throughout Washington, D.C.'s Metro System. Featuring three attractive young women, it is captioned simply, "Less is often best in treating TMJ." The billboard provides the NIDCR website where viewers can access more information.

Three additional speakers from the National Institutes of Health followed Dr. Tabak. Vivian Pinn, M.D., Director of the Office of Research on Women's Health, commented, "There is not one of these topics that will be discussed here that has not been of concern to my office. That so many disparate diseases and disorders should be focused on together is extraordinary, especially the idea that there may be a final, common pathway for all of them."

Story Landis, Ph.D., Director of the National Institute of Neurological Disorders and Stroke, also spoke of it being "extraordinary" to have a single meeting focus on so many disparate disorders, but noted that all of them involved the nervous system—in itself a kind of unifying principle.

Stephen Katz, M.D., Ph.D., Director of the National Institute of Arthritis and Musculoskeletal and Skin Diseases, cautioned that pain mediated by the nervous system may be only the most obvious of the clinical features that TMJDs and comorbidities have in common. He urged researchers to always be aware of the potential that other clinical features could be shared among these other conditions. As an example, he said that his institute has a "strong interest" in learning whether there is some connection "between generalized arthritis and the behavior of the jaw joints in patients with TMJDs."

Genome Tools

In his talk, Dr. Tabak also alluded to what was likely the most difficult issue facing the meeting: whether it will be possible to pin down the relationships, if any, between TMJDs and the various comorbidities with sufficient precision and clarity to make biological sense of their togetherness. Despite the fact that each of these conditions is in itself very complex, Dr. Tabak seemed to think that the tools of modern genomics (the comprehensive study of genes and their function) can be used to identify commonalities and singled out one such tool to illustrate what he had in mind.

The tool is "gene expression profiling" or microarray analysis. It relies on tiny devices, called gene chips, that can identify the DNA present at as many as 500,000 specific spots along the genome at a time. These chips, also called arrays, have taken scientists an important step beyond gene sequencing. Gene sequencing can indicate the genes present in a cell and their location, but cannot tell what the genes are doing or to what extent they are doing it. In contrast, microarray analysis detects which genes in a given study sample are turned on and which are not. And more: by varying the conditions of experiments using the technique, scientists can get detailed information about the behavior of the cells and how the cells' molecules are functioning, both individually and as a whole. Methods that make it possible to color-code the molecules facilitate the task, as do computerized equipment and sophisticated software. These new research tools make it possible to analyze the enormous amounts of data generated by scientific studies.

Dr. Tabak provided an example of how powerful genomic techniques can be. He cited a recently published paper in which scientists are using the techniques to identify the mechanisms and pathways that determine whether or not breast cancers become metastatic.

Changing the Mindset

Christian S. Stohler, D.M.D., Dr. Med. Dent., Dean of the University of Maryland Dental School, then focused the meeting's attention on current TMJD community concerns. "It troubles me," he said, "that many people are preoccupied with the taxonomy of TMJDs—the way they are classified by health professionals as predominantly *oral* disorders—because such a mindset can get in the way of creative thinking." He blamed the taxonomy mindset, too, for how it defines a comorbid condition in relation to TMJDs. People tend to think of a comorbid condition as more than one disease existing in the same patient at the same time, the suggestion being that the two develop along separate biological paths. Rather, it seems to him that it is at least as logical to think that some elements of the disease process contribute to both disorders and so work hand in hand.

In any case, Dr. Stohler stressed that there may be many ways to frame questions about TMJDs which could help scientists gain insights on how to better understand them. "For example," he said, "little is known about differences in jaw development and function in boys age 11-17 compared to girls of those ages. Yet, given the predilection of TMJDs for young women, there might be much to be learned from looking into that."

Headache

Like Dr. Stohler, Peter Svensson, D.D.S., Ph.D., Dr. Odont. of Denmark's University of Aarhus, has long been interested in TMJDs, though his particular interest is in the possible relationship between tension type headaches (TTH) and TMJDs. He spoke of the now "reasonably good evidence" (largely based on his own studies) that myofascial TMJD patients, patients having muscle pain in their heads, "are more likely to have a TTH problem and vice versa." He warned, however, that although two respected classification systems have documented similarities between TMJDs and TTH, the systems have also documented some distinct differences between the two sorts of complaints. In his view, therefore, it would be "premature… to consider them as identical entities."

The Role of Glia

Paul L. Durham, Ph.D., of Missouri State University in Springfield, was another of the meeting's presenters. His interest is in the interactions between the nerve cells (neurons) of the trigeminal nerves and the so-called satellite glial cells associated with them.* Interactions between the two sorts of cells are thought to play a role in several painful diseases, including migraine headaches and TMJDs.

Dr. Durham suspects that the glial cells themselves can become excited to the point where they release chemicals that sensitize the trigeminal neurons, making them more reactive to stimuli to which they might otherwise respond only slightly or even ignore. The effect on the patient, so this thinking goes, is to lower the pain threshold thus increasing susceptibility to migraine and tension type headaches, TMJD problems, or any combination of these.

Dr. Durham hopes to elucidate exactly how this process is set in motion and how it is maintained. Based on his studies, increased signaling between satellite glial cells and trigeminal nerves can lead to an inflammatory cycle that is likely to play an important role in the underlying pathology of both migraine headaches and TMJDs. Indeed, Dr. Durham believes this cycle may help to explain why it is not unusual for the same patient to have both complaints. His further hope is that his work will lead to the identification of molecular markers that can be measured with a simple saliva test so that health professionals can definitively diagnose migraines and TMJDs.

Linda R. Watkins, Ph.D., of the University of Colorado in Boulder, is another investigator committed to glia research and one of the pioneers in the field. She noted that it used to be thought that perception of pain was exclusively due to neurons, that when people were hurt, a series of neurons relayed the information from the injury site to neurons in the spinal cord and from there to sites of consciousness in the brain. Like Dr. Durham, Dr. Watkins has shown that central nervous system glia can participate in the process by releasing

* The trigeminal nerves are a pair of three branched nerves which transmit sensation from the face and parts of the head to the brain. The satellite glial cells associated with these nerves regulate the response of the nerves to changes in their physical or chemical environment. Thus, glial cells can modulate the degree to which nerve cells react to stressful stimuli in response to injury to the trigeminals or to inflammation of the chewing muscles, as can occur in TMJDs.

chemicals that act on the neurons and that when they do, pain tends to intensify.

Dr. Watkins told the meeting attendees that this phenomenon largely explains why some chronic pain patients need ever larger doses of opioid drugs (morphine, for example) to obtain relief as time goes on. Calling glia, the "bad guys here," she said that they also contribute to such characteristics of opioid addiction as the craving for drugs and withdrawal symptoms.

On the other hand, she and her colleague, Mark Hutchinson, Ph.D., recently discovered a kind of silver lining to the glial cloud. They have discovered that the surfaces of neurons and the surfaces of glia have different receptors for opioids. This observation immediately suggested to the pair that it should be possible to find drugs that would act on neurons to provide pain relief, but block the relief-neutralizing effects of glial activity. Dr. Watkins said that candidate drugs for this purpose are already under development.

In Search of Risk Factors

Meanwhile, it is thought that a study called OPPERA (Orofacial Pain: Prospective Evaluation and Risk Assessment), funded by NIDCR, will help scientists determine if there are risk factors for TMJDs, much as there are for heart disease, in the hope that this information can be put to work for patients. This $19.2 million study was launched in December 2005, and the investigators are in the process of recruiting 3,200 healthy volunteers aged 18-44, which is the age range typical for the onset of TMJDs.

William Maixner, D.D.S., Ph.D., of the University of North Carolina (UNC), Chapel Hill, is the project's chief scientist and also headed an earlier, smaller three-year study of 240 initially TMJD-free women which laid the groundwork for the larger one. The earlier study followed the women to see which of them would develop a TMJD and the OPPERA study will do the same with its participants, which also includes men. Depending on when they enter the study, participants in OPPERA will be followed for 3-5 years. Some volunteers will be seen at Maixner's own institution; others are being recruited for studies at the dental schools of the University of Maryland, Baltimore, the State University of New York at Buffalo, and the University of Florida, Gainesville.

"Insofar as is known," said Maixner, "OPPERA is the first large prospective risk factor study in the field of chronic pain." *Prospective* is the key word here because it means that people enrolling in OPPERA have no way of knowing, when they enter the study, whether they will develop a TMJD before it is over—nor do the scientists conducting the study. This means that there is little chance that bias will creep in to distort study results. By contrast, there is a considerable likelihood that bias can affect studies done "retrospectively"—i.e., on people who already have a disorder—which is why such studies are less credible to the scientific community.

Volunteers taking part in OPPERA receive a baseline examination of their jaws and measures of jaw function, and are tested for pain sensitivity, have blood samples collected for genetic analysis, and provide sociodemographic information and responses to a variety of psychological tests. Everyone in the study agrees to answer questionnaires

from home from time to time. These are carefully designed to ferret out any signs of incipient TMJDs.

Participants having such signs may be asked to revisit the clinic where they were enrolled to be thoroughly examined to determine whether they now truly qualify for a diagnosis of a TMJD. Those whose symptoms fit the diagnosis will then be tested so that new findings about them can be compared with their baseline data.

The investigators hope that this process will yield leads that will eventually make it possible for scientists to detail the biological, psychological and genetic factors that, as Dr. Maixner has put it, "contribute to the onset and maintenance of a TMJD." Nor will any hint of other chronic pain conditions—fibromyalgia, irritable bowel syndrome, chronic fatigue syndrome, etc.,—that appears in the course of the OPPERA study be ignored. In fact, it is Dr. Maixner's educated guess that lessons learned about TMJDs from his study will have "substantial relevance to these other conditions."

Finding the Right Drug for a Patient's Pain

Christine N. Sang, M.D., M.P.H., is Director of the Translational Pain Research program at the Brigham and Women's Hospital and the Harvard Medical School, both in Boston. An anesthesiologist and pain specialist by training, her research consists almost entirely of studies aimed at identifying the underlying mechanisms of pain and targeting specific pain mechanisms with selective drugs with the goal of improving patient care. (In scientific circles, "translational" research is research that focuses on readily moving discoveries from the laboratory into medical practice. Traditionally, a lot of laboratory research, often called basic research, has instead been focused on testing hypotheses.)

Dr. Sang told The TMJ Association meeting attendees that better ways to prevent, diagnose and treat chronic pain are "a great unmet need. The field has been hampered," she said, "by the tendency of physicians to treat chronic pain solely on the basis of the patient's diagnosis—like diabetes, when the pain is due to diabetic neuropathy, for example—or what nerves were injured by trauma." In her view, pain is made up of heterogeneous mechanisms and the mix of sensations that chronic pain patients experience varies from one to another, regardless of the source or location of their pain.

Sophisticated batteries of tests and meticulous attention to her patients' histories are, therefore, among Sang's research tools. "Our challenge is to identify within individual patients which specific mechanisms are operating to produce which signs and symptoms," she said, "so that we may improve the diagnoses and initiate novel treatment strategies for pain."

Still, she pointed out, these goals can be hard to achieve. As an example, she noted that dosing issues can limit the ability of clinical trials to detect treatment effects of candidate drugs for pain management. Thus, a drug may be judged a failure in a trial simply because the dose used was too low to measurably benefit most of the participants. Moreover, since chronic pain and its biological underpinnings significantly differ from one person to the next, the variability among patients can also make it hard to reliably detect treatment effects.

On the other hand, the drug's side effects might well limit how much the dose could be increased. Also to be taken into account, for the sake of patient safety, are differences in the rates by which individuals clear drugs from their systems. Further obstacles can arise, even late in a drug's development. For instance, a new drug that appeared safe during clinical trials may lead to adverse events or illness once it is on the market because far more people are using it. Adverse events may also occur because of the way the new drug interacts with another drug a patient may be taking.

Functional Disorders and Stress: Irritable Bowel Syndrome

Emeran Mayer, M.D., of the University of California, Los Angeles, is a gastroenterologist who has studied irritable bowel syndrome (IBS) and considers the "functional" nature of this disorder to be key. "Functional" is one of several terms physicians use when speaking of illnesses without a detectable structural or biochemical cause and which are described primarily by their symptoms. As Mayer noted, IBS is one of the more common of such complaints but, with the possible exception of rheumatoid arthritis, virtually all of those discussed at the comorbidity meeting qualify as "functional." It is noteworthy that pain is a feature of them all.

Dr. Mayer emphasized that enhanced sensitivity to stress seems to drive both the abdominal symptoms of IBS (notably, recurrent abdominal pain and discomfort and altered bowel habits) and the predominant symptoms of other functional disorders. All of them diminish the quality of life and result in excessive health care utilization, he noted. Beyond that, functional disorder patients tend to experience an amplification of pain and the dysregulation of nervous system activity that is thought to account for it. In healthy persons, for example, cascades of signals conveyed from the gut to the brain and in the reverse direction do not routinely elicit sensations of pain or other discomfort in the absence of a discernible cause. Not so in persons with functional disorders. Their sensitivity to pain is enhanced and their pain thus intensified because of distortions of the information flow. Fortunately, cognitive behavior therapy often enables patients to learn to correct, or at least modify those distortions, and thus helps many of them manage the pain of IBS or other functional disorders.

However, there is more to the picture of these disorders than amplified pain perception. Dr. Mayer mentioned several other sorts of inquiry that may be relevant to IBS, including one strongly suggesting that at least some cases may be due to large populations of bacteria in the lower intestines, where their number is ordinarily low. Mayer cautioned that although the list of abnormalities linked to IBS is growing, it is far from clear which of them is fundamental to an understanding of the disorder and which are secondary effects.

Endometriosis

Karen J. Berkley, Ph.D., of Florida State University in Tallahassee, has pursued a career-long interest in chronic pain conditions in women and reported on her research on endometriosis. In this disease, deposits of endometrial tissue, the tissue lining the uterus which builds up and then is shed during the menstrual cycle, somehow attach themselves to places outside the reproductive organs or elsewhere in the abdomen.

Often called "transplants" or "implants," these deposits then form cysts that can impair fertility and make life miserable in other ways. For instance, patients may be subject to severe menstrual cramps or chronic pelvic pain, or the disease can make defecating, urinating or having sex a painful ordeal.

While the pain often responds to drugs or surgery that can suppress the production of estrogen, there is, as of yet, no entirely successful therapy for the disorder. Moreover, Dr. Berkley told attendees that "endo" sufferers also experience other chronic pain conditions, including irritable bowel syndrome, interstitial cystitis, fibromyalgia, and TMJDs.

Interestingly, there is an animal model of endometriosis. Female rats can be made to develop a condition which closely resembles its human counterpart. Using the model, Berkley and her colleagues discovered that endometrial tissue that grows where it is not meant to be can acquire its own nerve supply, a finding that helps explain much about endometriosis, including why it is often, though not always, accompanied by pain. And Berkley and her collaborators have replicated the discovery in humans by, among other things, studying tissue from "endo" patients who were treated surgically.

Dr. Berkley believes this finding also explains why women with endometriosis are at risk for other chronic pain conditions. As evidence, she noted that, "endo rats appear to develop pain symptoms similar to those associated with conditions that co-occur in women with endometriosis, specifically interstitial cystitis, uterine pain and kidney stones."

Interstitial Cystitis

Two presentations were devoted to interstitial cystitis (IC), a painful bladder disorder that further plagues sufferers with sensations of urgency necessitating frequent trips to the bathroom. These symptoms also occur in "garden variety" cystitis, an acute inflammatory condition of the bladder associated with infection. Infection is *not* a factor in chronic interstitial cystitis and its cause is unknown.

In her presentation, Larissa V. Rodriguez, M.D., a clinician at the University of Los Angeles in California, reported that in the case of IC, "most medications that have been studied in well-designed placebo-controlled studies have failed to show efficacy over placebo." She also used the term "functional disorder" to describe IC, and suggested that stress plays a role in triggering the central nervous system to over-react to stimuli and even to react in the absence of stimuli. She further suggested that some stress factors seem to apply specifically to IC, but that others may operate in functional disorders more generally.

The second speaker on interstitial cystitis was Lori A. Birder, Ph.D., of the University of Pittsburgh School of Medicine. Cats, particularly neutered cats, often develop a disorder called feline urological syndrome or feline interstitial cystitis (FIC). She told the meeting that FIC "exhibits nearly all of the characteristics and symptoms of human IC" and that alterations in the urothelium, the membrane lining the bladder, is one of the things seen in both affected cats and affected humans.

Dr. Birder went on to explain that the urothelium had long been viewed as only a protective and passive barrier. Now,

however, molecules have been identified in its cells which can send chemical messages to nearby nerves, and the nerves in turn can communicate with them. Much remains to be learned about these signals and their nervous system pathways. Dr. Birder and her colleagues are hopeful that continued studies of human patients and the cat model will eventually lead to improved treatment for both species.

Dr. Birder also contributed further information on the role of glial cells in intensifying pain. She noted that, in the course of their studies of glial activity in FIC cats, the shape of the cells can change, as can the behavior of their surface membranes and proteins in their interiors. Whether such structural and functional changes occur in glia in other chronic pain conditions is an interesting question for research.

Fibromyalgia

Fibromyalgia (FM) can be briefly described as a disorder featuring chronic and widespread musculoskeletal pain (affecting the muscles, ligaments, tendons and joints), fatigue and multiple tender points. Whether it is biologically related to the other conditions that were discussed at the meeting is unknown. However, Lesley M. Arnold, M.D., of the University of Cincinnati College of Medicine in Ohio, suspects that at the very least, there is some connection between FM and TMJDs.

Arnold reported that it is far more common for patients whose primary diagnosis is FM to also have a TMJD condition than for patients whose major complaint is a TMJD to also have FM. Despite that, she told the meeting there is both genetic and other evidence that is strongly suggestive of links between the two. On the genetic front is an enzyme called COMT (catechol-O-methyltransferase) which, Dr. Arnold noted, "substantially influences" how sensitive people are to pain. The gene coding for this enzyme is polymorphic, meaning that it comes in several versions, each slightly different in its sequence of DNA. Accordingly, there are several slightly different versions of the enzyme molecule for which the gene codes. What researchers have found is that people's sensitivity to pain largely depends on the version of the COMT gene they have inherited, and those with the high sensitivity version are at greater risk of developing FM and/or TMJDs.

In further reviewing how fibromyalgia and TMJDs may be related, Arnold noted that studies showing patients with one or the other disorder tend to score high on psychological tests for depression and somatization (experiencing emotional stress as bodily symptoms). She also reported that both disorders respond to treatment with antidepressants.

Brain Imaging

Functional magnetic resonance imaging (fMRI) is a technique that records differential blood flow in the brain, thus allowing scientists to see which parts of the brain are most active in a variety of situations, including while pain is occurring. Dane B. Cook, Ph.D., of the University of Wisconsin–Madison, explained that fMRI studies had enabled him to show that heat stimuli, some painful, some not, produce greater responses in the regions of the brain that deal with pain when the subjects being tested have FM than when they are healthy controls.

This, he stated, is one of several indications that there is something about the central

nervous system in FM patients that leads to intensified responses to pain that then tend to be maintained and become chronic. That "something" operates unconsciously. However, whether it is in play only with FM, or applies to chronic pain conditions more generally, is unknown. Unknown, too, is whether that "something" has qualitative as well as quantitative effects. To get at these issues, Dr. Cook and his group are conducting an fMRI study that focuses on the cognitive behavior of patients subjected to a painful stimulus. FM patients are being compared to two other groups: patients with rheumatoid arthritis and normal controls. All the participants will be women. Analysis of the data the study has generated so far has already produced some preliminary results.

One of the study's components, for instance, is to confront study participants exposed to painful stimuli with an intellectually challenging task, e.g., the Stroop Color-Word Test, to see whether the mental effort required to performing the test acts as a distraction and thus dulls the pain. Thus far, it seems that the test is less able to distract the study's FM participants than the others. This suggests both that pain is somehow amplified in patients with FM and that a malfunction of their central nervous systems is to blame.

Daniel J. Clauw, M.D., a researcher at the University of Michigan, Ann Arbor, told the meeting attendees that he and his colleagues have recently made a discovery that may help to identify that disturbance. It involves glutamate, a neurotransmitter conveying signals between neurons, and a paired structure deep in the brain, called the insula.

In brief, the Michigan scientists learned from fMRI brain scans of FM patients that their insulas were unusually active when they were in pain. The researchers suspected that glutamate may be responsible because it is an abundant neurotransmitter in the brain and known to excite neurons in response to stress. Using a method called proton magnetic spectroscopy, researchers were able to show that, indeed, glutamate levels in the patients' insulas fell when their pain was eased. Acupuncture was used for this purpose.

More research is needed to elucidate the role glutamate may play in fibromyalgia and in other chronic pain conditions, as well. Still, it is surely of interest that clinical trials of drugs that dampen glutamate activity have already shown promise for the treatment of fibromyalgia.

The Role of Estrogen

The presence of another University of Michigan, Ann Arbor scientist on the meeting's speaker roster had a special resonance. Jon-Kar Zubieta, M.D., Ph.D., led a study famous for its discovery that people's tolerance to pain is heavily influenced by which version of the COMT gene they carry, but—though it is now largely forgotten—the study was part of an effort to understand why conditions like TMJDs, FM and depression are predominantly female complaints. A key component of the study, in fact, was to simulate TMJD in the 15 young healthy men and 14 young healthy women who served as test subjects by injecting controlled amounts of salt water into their jaw muscles.

In 2003, when news about the pain tolerance gene broke, Dr. Zubieta was

quoted as saying "…this work is helping tell us how important individual differences are in the experience of pain and other significant stressors." His presentation at the 2008 TMJ Association scientific meeting expanded on that theme, using as examples further discoveries that have been made with the assistance of sophisticated brain imaging techniques.

Research done by Dr. Zubieta and his colleagues has further suggested that, just as individual differences can shape the pain experience, so too, can conditions that may vary in the same individual. In this case, the subjects were young women who underwent brain scans after twice being subjected to a controlled dose of a painful stimulus—once when their estrogen levels were high and once when they were low.

Endogenous opioids are the brain's natural system of chemicals that come into play and provide some protection against being overwhelmed by pain. The scans showed that the activity of these chemicals was significantly greater when the women's estrogen levels were high than when they were low. Moreover, this finding tallied with how the women themselves rated their pain, both physically and emotionally, making it unsurprising that low estrogen levels were consistently associated with greater suffering.

Chronic Fatigue Syndrome

Many chronic pain disorders have historically been dismissed as mere hypochondria and thus not to be taken seriously—perhaps none more so than chronic fatigue syndrome (CFS), which is also known as chronic fatigue immune dysfunction syndrome (CFIDS) and myalgic encephalopathy (ME). However, listening to the presentations at The TMJ Association's meeting was to underscore that this is not an imaginary illness—the pain, profound fatigue, sleep disturbances and disruptions in memory and concentration that are prominent features of CFS have a biological basis.

Suzanne D. Vernon, Ph.D., a molecular biologist, has been the scientific director of the CFIDS Association of America since late 2007. She assumed this position, having come from the Centers for Disease Control and Prevention (CDC), where, near the end of her 17-year tenure, she was responsible for planning and overseeing a large and groundbreaking study of CFS. This multidisciplinary effort produced a solid phalanx of reports, greatly enhancing the legitimacy of CFS in the eyes of the scientific community.

The reports were published in the April 2006 issue of *Pharmacogenomics.* As the "genomics" in that journal's name implies, one of the study's most important findings was that, even though CFS is not inherited in the relatively simple way of eye color, for example, it does have a genetic component, one due to variations in multiple genes rather than in just one (as in the eye color example). The pattern of inheritance makes people vulnerable to the disease, but does not guarantee that they will develop it.

The study found that whether people develop CFS or not appears to hinge on complex interactions of their vulnerability genes, both with one another and with environmental factors and what the consequences of those interactions are over time. Vernon said the study had defined environmental factors broadly to include such things as infections, trauma, emotional stress, and personal habits and

attitudes. A noteworthy feature of the study was that its 277 participants were methodically explored for these factors, often in ingenious ways.

Still another of the study's intriguing findings was that instead of being a single disease, CFS is seemingly at least five conditions, some more severe than others and each likely due to a different mix of genetic and environmental factors. Dr. Vernon was confident that genomics research is capable of identifying these subtypes and that the biomarkers that will then be needed to differentiate them will follow.

The availability of biomarkers (generally proteins found in blood) can also be expected to lead to improvements in diagnosis and provide leads for developing drugs and other treatments that will be tailor-made for patients having one or another form of CFS. "There are already examples of how genomic information, including biomarkers, has been used to customize therapeutic interventions in a variety of diseases," Dr. Vernon told the meeting. "If it can happen for other diseases, it can happen for CFS and what she called 'other complex chronic conditions,' too."

Dr. Vernon has a strong ally in fellow CFS researcher Nancy G. Klimas, M.D., of the University of Miami, Florida and the Miami Veterans Healthcare System. Knowledgeable about every aspect of CFS, she is excited by the prospect of diagnostic markers in various stages of development and confident that the subgrouping of patients will prove to be "key to effective therapy."

Dr. Klimas noted that it used to be that the best that could be expected from clinical trials of CFS treatments was improved symptom relief. "No longer." said Dr. Klimas. Instead, discoveries about the biological underpinnings of the disorder are giving rise to trials with the more ambitious objective of fundamentally changing the course of the disease.

Rheumatoid Arthritis

There were two presentations at the meeting on rheumatoid arthritis (RA). While RA is similar to the other conditions discussed, insofar as the disease disproportionately affects women of reproductive age, it is also different from them. RA is an autoimmune disorder in which the body's immune system attacks joints and cartilage, creating painful and deformed joints. Patients also are at high risk of developing life-shortening cardiovascular disease, presumably because atherogenesis, the process whereby fatty plaques are laid down in the inner linings of the arteries, progresses at a faster rate in RA patients than in the general population. Why this should be so was the question addressed by Joan M. Bathon, M.D., of Johns Hopkins University in Baltimore, Maryland. She reported what she called "strong circumstantial evidence" that specific chemical pathways that develop in the body as a consequence of RA are to blame.

Alisa E. Koch, M.D., of the University of Michigan, Ann Arbor and the Veterans Administration Healthcare System, spoke of evidence that smoking increases the risk of developing RA and worsens the disease in those who already have it. However, most of her presentation dealt with discoveries in molecular biology that have elucidated how RA is set in motion and how the ensuing immune system malfunctions continue to eat away at the sufferers' joints.

Among those discoveries was that cytokines, proteins produced by immune system cells as cellular messengers, play a pivotal role in initiating and sustaining the inflammatory process that is at the heart of RA. Some 20 cytokines have been identified to date. One of these "bad actors" is tumor necrosis factor alpha (TNF-alpha). There are now four drugs on the market that dampen its activity and have been widely prescribed for several inflammatory diseases, including RA. Dr. Koch predicted that more drugs will be produced, targeting one or another cytokine. Other researchers are more cautious, citing reasons of safety and cost—upwards of $12,000 a year. Most likely successor drugs would cost at least as much. Since September 2008, the Food and Drug Administration has required tougher warning labels on TNF-alpha blockers, which would probably apply to other cytokine drugs, as well. Even so, TNF-alpha blockers have been hailed as the most important recent advance in the treatment of RA.

Basic Research

Animal studies figure importantly in pain research and four interesting experiments using laboratory rats were presented at the meeting. In one, Ke Ren, Ph.D., and his colleagues at the University of Maryland, Baltimore, described progress in detailing how glia, cytokines and neurons interact to set the stage for orofacial pain to become chronic.

In another study, David A. Bereiter, Ph.D., and his fellow researchers at the University of Minnesota, Minneapolis, were inspired by the observation of female gender and depression as risk factors for TMJDs. The study entailed inducing depression-like behavior in male and female rats by subjecting them to forced swims, a method the scientists thought suitable because it has been used to predict the effectiveness of candidate drugs for the treatment of depression. This study led to insights about the role of estrogen on nervous system events that are not consciously experienced but nonetheless have consequences that affect the perception of pain. Indeed, their findings lead them to believe that men tend to be spared chronic pain disorders like TMJDs because they have far less estrogen circulating in their blood than women.

A third research group, at the University of California, San Francisco, Jon D. Levine M.D., Ph.D., and his colleagues are exploring the most prominent feature that chronic illnesses like TMJDs, FM, CFS and IBS share, generalized pain. That is defined as pain that is widespread, persistent, and of unknown cause. To understand the underlying mechanisms for generalized pain, Dr. Levine and his team have turned to rats for their experiments. A surgical procedure is performed to disrupt vagus nerve activity in the abdomen, producing a generalized heightened sensitivity to pain (hyperalgesia) and, under some circumstances, to other kinds of stress. In subsequent experiments, Dr. Levine and his colleagues have shown that the increased pain sensitivity depends on activity of the adrenal medulla, suggesting that chronic activity of nervous system pathways in response to stress, which leads to the release of adrenal hormones, can contribute to generalized pain. Other experiments confirmed a role for cytokines in triggering a marked increase in hyperalgesia in response to a sound stressor.

In planning the 2008 meeting, Dr. Allen Cowley and his colleagues sought to eliminate the barriers that have set TMJDs apart from comorbid disorders that frequently accompany them and those disorders from TMJDs. The ideas that were suggested and the views exchanged went a long way to accomplish that goal. As the meeting drew to a close, it was clear that a better understanding of the conditions discussed can reasonably be expected to flow from the realization that some, and perhaps all of them, have common biological underpinnings. Ultimately, and most importantly, it will be the millions of patients who suffer from these disorders who will benefit from the research studies emerging from the recommendations generated by the meeting.

Research Recommendations from

THE FIFTH SCIENTIFIC MEETING OF THE TMJ ASSOCIATION, LTD.

Can Studies of Comorbidities with TMJDs Reveal Common Mechanisms of Disease?

The meeting was organized and supported by The TMJ Association with co-sponsorship by eight agencies of the National Institutes of Health[1] (NIH). Earlier studies have indicated that many patients with TMJDs suffer a range of comorbid conditions including chronic headache, generalized pain conditions, irritable bowel syndrome, endometriosis, interstitial cystitis, vulvodynia, fibromyalgia, chronic fatigue syndrome, and rheumatoid arthritis. The meeting sought to determine if there are common genetic factors and mechanistic pathways that link these comorbidities, accounting for their co-occurrence in patients. Following presentations and discussions by experts in the selected conditions as well as patient testimony, attendees met in planning sessions to develop research recommendations to advance understanding of the etiology and pathogenesis of these disorders and guide the development of diagnostics and therapy for all of these conditions. The following recommendations were further refined by the Program Committee.

PAIN: THE COMMON ELEMENT

Based upon 39 oral presentations and subsequent discussions, attendees concluded that chronic debilitating pain was the feature most shared among the comorbid conditions discussed. Chronic pain is a condition that transcends the boundaries of biomedical research and clinical specialties as well as the mandates of the categorical institutes and centers of the NIH. As such, a focus on chronic pain research will provide a major opportunity to fill a gap in biomedical research, one which no single component of NIH should or could tackle alone. The opportunities for discoveries in this field have never been greater, but the complexity of the biology remains a daunting challenge. The NIH, with its current emphasis on interdisciplinary and multidisciplinary research teams, is uniquely positioned to catalyze the research needed to advance understanding of the mechanisms of chronic pain and transform this scientific knowledge into tangible benefits for people in pain and society as a whole.

SEARCHING THE GENOME

The primary recommendation that emerged from the meeting was to launch a genome-wide association study (GWAS) to identify genes associated with chronic pain across a wide spectrum of persistent pain conditions. It was recommended that this research would be conducted in two phases.

Phase I. This would entail conducting a large-scale case-control genome-wide SNP analysis on patient populations suffering from common persistent pain conditions. Biological samples, case status, and intermediate[2] and endophenotypes[3] would be obtained from discipline-specific programs (e.g., subjects with chronic pain conditions from TMJDs, chronic

headache, generalized pain conditions, irritable bowel syndrome, endometriosis, interstitial cystitis, vulvodynia, fibromyalgia, chronic fatigue syndrome, and rheumatoid arthritis). Subjects would be obtained from community populations, as maintained and provided by patient advocacy organizations, academic center populations, and pharmaceutical studies. The goal of the Phase I GWAS screen is to identify putative risk factors (i.e., intermediate and endophenotypes) and to identify genetic variants (e.g., haplotypes and genes) related to chronic pain and the intermediate and endophenotypes that are measured in common across the different patient populations. Added value would be gained by including additional phenotypes common to many, but not all, of the other comorbid conditions. This research would benefit individuals with chronic pain conditions as well as all of the associated scientific and clinical specialties, NIH institutes and centers.

Critical to any such project is access to large cohorts of patients. The extensive patient advocacy organization registries, university programs, and the pharmaceutical industry would probably provide sufficient numbers of well-phenotyped chronic pain populations and DNA samples to permit a well-powered GWAS. In addition, we propose that these studies be designed and conducted in collaboration with expert extramural NIH and the National Center of Biotechnology Information investigators.

The analysis would be unique in that to date, other GWAS studies have focused on gene associations with a specific disorder, such as fibromyalgia or chronic fatigue. Interestingly, recent GWAS-based studies to identify genes of complex diseases have been remarkably successful in spite of the fact that such success would not have been predicted even a year ago. Associated genetic variations can serve as powerful indicators of regions of the human genome where the disease-causing problem resides, although the associated variants themselves may not directly cause the disease.

Genetic associations, once identified, can provide researchers with information to guide the development of strategies to detect, treat, and prevent common diseases. Such studies have been useful in finding genetic variations that contribute to common, complex diseases such as asthma, prostate cancer, diabetes, heart disease, psychiatric illness, Parkinson's disease, obesity, and Crohn's disease, as well as genetic variants that influence responses to anti-depressant medications. Upon identification of candidate gene regions within the genome associated with chronic pain, follow-up DNA sequencing studies of gene loci of interest can be conducted to identify the functional polymorphisms that contribute to the expression of persistent pain phenotypes.

Phase II. Given genes that have been identified as common to pain in TMJDs and comorbid pain conditions, Phase II recommendations call for studies to determine if there are sets of genetic polymorphisms and functional pathways related to each of the disease-specific syndromes previously referred to in the preamble. Phase II studies would be hypothesis-driven with prospective and longitudinally designed studies that would include research related to mechanisms of transitioning from acute to chronic pain, identification of genetic markers and risk factors, strategies for building interdisciplinary and multidisciplinary research teams, and novel tools required for such research.

A. **From Acute to Chronic Pain**

An important question to be explored would be how acute pain conditions evolve into sustained chronic pain conditions even in the absence of the initial stimulus. These prospective studies would require a multidisciplinary team of investigators in genetics, bioinformatics, and a range of basic, clinical and behavioral disciplines.

B. **Genetic Markers and Risk Factors**

Another important component of Phase II would test specific hypotheses related to genetic and phenotypic commonalities among the comorbid conditions. For example, are there shared polymorphic markers and functional traits in common with the various comorbid conditions? Are there unique polymorphisms and functional pathways that drive a specific condition? It would be important to conduct basic animal studies that validate the identified risk factors as likely determinants of the disease and to ascertain the function of newly identified SNPs or haplotypes found to be in common among the comorbid conditions. Non-human animal identification of functional and genomic pathways involved in each of these overlapping conditions would utilize bioinformatic and systems approaches currently being explored for other complex diseases such as cancer, obesity, and chronic fatigue. It is recommended that a phenomic[4] strategy be utilized building upon both intermediate and endophenotypes, representing proposed risk factors and upon candidate genes identified in the Phase I GWAS studies. In this way, hypotheses specific for each of these overlapping disorders with certain shared phenotypes could be tested within and between the populations of defined comorbid conditions. The ten representatives of patient advocacy groups that participated in this meeting showed enthusiasm for providing affected subjects and phenotypic data maintained on their extensive databases.

It will be important in Phase II studies to utilize both classic and novel bioinformatic tools to enable the identification of key genetic and phenotypic risk factors and determinants for specific subclusters of chronic pain groups. One important goal of these analyses will be to reduce or minimize the number of phenotypes and genotypes required to define, with a high degree of sensitivity and specificity, the factors and subclusters of chronic pain groups that would lead to diagnostic tools in clinical practice and the identification of therapeutic targets for each factor and cluster. A second important goal is to identify specific biological pathways that define each chronic pain subcluster. Emerging pathway analysis tools are likely to assist with this endeavor. Finally, a third major goal will be to identify the key environmental, behaviorial, and genetic risk factors and determinates that lead to the onset of the chronic pain and its chronicity.

The results of these studies would transform and dramatically change the nature of biomedical research in the next decade. Supporting chronic pain research would be relevant to the mission of the NIH. Considering the many

chronic pain conditions, the large number of affected individuals, and the economic and societal cost of those afflicted — *can the NIH afford NOT to support this research?*

C. **Building Teams …**

Another key recommendation that emerged from the meeting was to develop innovative approaches required for the successful creation and operation of the interdisciplinary and multi-disciplinary team required for Phase I and Phase II studies. It was proposed that strategies be put in place to reward data sharing and cross-fertilization of ideas to counter the prevailing scientific culture which currently rewards individual scientists and laboratories. Whether from first or second tier research universities, superb investigators who could advance this field should be sought and included in a virtual consortium of scientists and patient advocacy groups. Mechanisms to create a suitable environment for multi- and interdisciplinary research should be explored (e.g., Programs for Genomic Application (PGA) grants, Specialized Centers of Research (SCOR) grants; new Clincial and Translational Science Award (CTSA) initiatives focusing on "Medically Undiagnosed Diseases").

D. **…and Tools**

Presently there are gaps in phenotyping tools, particularly with respect to capturing aspects of comorbidity and environmental risk factors. It will be important to apply and develop as needed standardized measures of signs and symptoms that define these disorders and enable the clearest possible characterization of the natural history of these conditions. Improved versions of existing tools with better resolving power are needed for phenotyping, along with the application of novel technologies such as those emerging in the fields of genomics, proteomics, and non-invasive imaging and spectroscopy. Implementation of a virtual (public domain) databank of comprehensive symptom presentation, suitable for advanced mathematical modeling approaches, is needed to undertake Phase II of the recommendations.

References:

[1] National Institute of Dental and Craniofacial Research, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institute of Biomedical Imaging and Bioengineering, National Institute of Diabetes and Digestive and Kidney Diseases, National Institute on Deafness and other Communication Disorders, National Institute on Drug Abuse, Office of Rare Diseases, and Office of Research on Women's Health.

[2] A trait which maps to the same region of the genome as the primary trait of interest (such as a chronic pain QTL) but not correlated with chronic pain.

[3] A hereditary trait that is normally associated with some condition but is not a direct symptom of that condition.

[4] Phenome: a set of all phenotypes expressed by a cell, tissue, organ, organism, or species; a phenome includes phenotypic traits due to either genetic or environmental influences.

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