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TMJ Science

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In This Issue…

TMJ Science

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Third Scientific Meeting of The TMJ Association

Advancing Diagnostic Approaches for TMJ Diseases and Disorders

In This Issue…

Preface

The TMJ Association convened its Third Scientific Meeting, May 6-7, 2004, to address pathways for advancing the limited clinical armamentarium of approaches for diagnosing TMJ diseases and disorders. The meeting brought leading experts in several basic and clinical disciplines together with patients for the purpose of discussing opportunities for bringing additional focus to research on diagnosing TMJ problems. It is the hope of the Association that these meetings will bring better definition to the clinical and laboratory needs of the TMJ patient and result in stimulating new and established investigators to enter this important field of inquiry.

The participants noted that TMJ diseases and disorders remain an enigma, with little understanding of their etiology. Patients usually present to a clinic or doctor's office because of TMJ pain. The participants all noted the lack of clinical definitions and evidenced-based information for making the proper diagnosis for developing a therapeutic strategy that will relieve their pain and restore TMJ mobility. The need for novel imaging and other diagnostic approaches was a major theme of all the presentations.

There is a clinical imperative to change the paradigms of existing practice. There are few hypotheses to understanding the biological basis of TMJ diseases and disorders. The field is also hampered by a lack of capacity. Points of view expressed at this Meeting suggest that existing imaging methods could be used for studying factors such as TMJ metabolism and inflammation, which might hold promise for beginning to unravel some of the mysteries of TMJ diseases and disorders. Seed grants, modest in support and duration, were suggested as the means to stimulate the use of imaging for developing diagnostic approaches for TMJ diseases and disorders. Patients deserve a concerted effort by funding agencies to seed programs that will develop diagnostic guidelines that result in alleviating their pain and dysfunction. The Association is to be congratulated for the hard work and perseverance that is necessary to facilitate these biennial scientific and engineering meetings.

John T. Watson, Ph.D.
Associate Director, von Liebig Center
and Professor, Bioengineering
University of California, San Diego

The TMJ Association

The TMJ Association is a national, non-profit organization whose mission is to improve the diagnosis, care and treatment of everyone affected by TMJ diseases and disorders through fostering research, education and other activities with the ultimate goal of preventing TMJ problems.

"We have this new model – the human."

"We heard a lot about education or lack thereof..."

"I really wonder what the true barriers are...where are the new and exciting ideas?"

"Can we create a team that is truly multi-disciplinary to take what the next step needs to be in order to solve this thing?"

"I encourage you to take the challenge, particularly for those of you outside this field...what we honestly need is an infusion of new talent. That's what we really need..."

"Take the challenge – send in grants that are so elegant, so cutting edge, so spectacularly new, that we have no choice but to fund them."

"I congratulate The TMJ Association for yet another outstanding conference....I think by working together we will eventually be able to overcome this...and we all look forward to when we won't have to worry whether medical and dental students are learning about this – it will be something in the text books about history."

Lawrence Tabak, D.D.S., Ph.D., Director
National Institute of Dental and Craniofacial Research

Excerpts from closing remarks at The Third Scientific Meeting of The TMJ Association

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THE THIRD SCIENTIFIC MEETING OF THE TMJ ASSOCIATION RESEARCH RECOMMENDATIONS

Advancing Diagnostic Approaches for TMJ Diseases and Disorders

The following are key recommendations that emerged from the meeting and discussions:

Recommendation 1.
Use currently available noninvasive imaging technologies, including CT 3D X-ray, Micro CT, PET, MRI, fMRI, MRS, and thermography, to establish, validate, and standardize the clinical diagnostic criteria for TMJ diseases and disorders and as clues to understanding the etiology of these conditions and the mechanisms underlying the symptoms of chronic pain and dysfunction.

Recommendation 2.
Integrate findings from interdisciplinary studies of the structure, mechanical function, metabolism, and blood flow of bone, joints, and muscles with studies of central and peripheral neural pathways, and the endocrine, paracrine, and cytokine factors that impact upon these craniofacial structures, as means to understanding the underlying cause(s) of TMJ pain and dysfunction.

Recommendation 3.
Establish a cohort database to assess the risk for the development of TMJ disorders in subjects that present with pain in the TM region compared with a cohort of normal subjects who have not exhibited any clinical manifestations of TMJ dysfunction. Develop protocols which include self-reported health status, as well as physical examinations by experts qualified to diagnose co-morbid conditions and the general health status of the TMJ patients.

Recommendation 4.
Conduct prospective longitudinal studies of the most vulnerable populations to establish where on the distribution time curve intervention and therapy is appropriate and at what point associated risk factors and co-morbid conditions emerge.

Recommendation 5.
Conduct genetic linkage studies to map the phenotypes defined by standardized imaging strategies (described above), or by other technologies, to identify subgroups particularly vulnerable to pain associated with TMJ disorders. Efforts should be made to reduce population heterogeneity in order to increase the statistical power of research studies.

Recommendation 6.
Develop novel therapeutic approaches that can provide joint assistance to improve the range of motion and reduce the pain of joint movements and if necessary, can be used for joint replacement as required.

Recommendation 7.
Expedite the transfer of science information and research findings on the TM joint and joint disorders to all health professional schools and practitioners.

Christian Stohler, **D.M.D.**, **Dr. Med. Dent.**, recommended development of a registry for TM joint-and muscle-related animal model systems, to provide a resource that could be used to elucidate human joint problems. The registry would include knockout models or animals that overexpress genes related to TM tissues and functional pathways...he further endorsed adding TMJ phenotyping to genetic population studies that are currently established in order to utilize the broad array of already available phenotypes to provide considerable added value to the mapping and identification of polymorphisms related to TMJ diseases.

David Altobelli, **D.M.D.**, **M.D.**, recommended that new algorithms and diagnostic approaches be used to establish a classification system and framework of understanding and treatment of TMJ diseases...he saw the need to make available current imaging and diagnostic tools to "frontline" dentists and physicians to enable them to define the stages of disease development to facilitate early diagnosis and treatment...he recommended that the NIH support the development of a centralized national patient database where this information could be correlated and mined to establish the algorithms for diagnosis and treatment.

Stephen Feinberg, **Ph.D.**, **D.D.S.**, **M.S.**, recommended development of a virtual reality model of TMJ (anatomy, kinematic studies, and biomechanics) that could be utilized for teaching, research and treatment... he emphasized the need to improve education in dental and medical schools and the importance of recruiting medical clinicians in studies involving technical advances.

Randell Wilk, **D.D.S.**, **Ph.D.**, **M.D.**, recommended that imaging parameters be established for different stages of the disease and that imaging techniques be used not only for diagnosis, but also for outcome analysis of specific interventions.

John Watson, **Ph.D.**, recommended that algorithms be developed to better quantify and define joint motion and mechanics (the "equations of motion" of the TMJ)...he further recommended the use of thermal imaging to define inflammation in craniofacial structures and regions of the body...he emphasized the need for more affordable approaches to biological imaging (for material properties, mechanics, inflammation, and other diagnostics) in order to obtain special, quantitative characteristics of the joints and muscles...advanced designs in technology are needed to improve patient safety by reducing X-ray radiation in imaging modalities and longitudinal studies by 80 percent...he proposed a 10-year prospective study in which the difficulty and cost of various diagnostic approaches be compared to determine what is predictive of TMJ disorders...in terms of mechanisms available in the NIH grant system, he recommended the use of R21 exploratory grants and proposed an annual research meeting that would bring together clinicians, grantees, contractors, and patients.

Third Scientific Meeting of The TMJ Association

Advancing Diagnostic Approaches for TMJ Diseases and Disorders

The Third Scientific Meeting of The TMJ Association was stimulated by the critical need to establish improved research and diagnostic criteria for temporomandibular diseases and disorders. Clinicians and scientists interested in studying these conditions have been handicapped by an absence of standardized and accepted diagnostic criteria. To address this need, we have assembled outstanding basic and clinical scientists who are familiar with specific aspects of temporomandibular joint diseases and disorders as well as with the underlying pathology and co-morbid conditions of the patients. While many conferences are devoted to highly focused topics within already established disciplines and diseases, it is the goal of the organizers of this meeting to bring basic and clinical scientists from a number of disciplines together with experts in physics, bioengineering, bioimaging, computational biology, and modeling with an eye to attracting their talent and expertise in an effort to expand the knowledge base needed to advance the field.

The specific aims of this meeting are:

1. To provide an understanding of the needs and challenges currently faced in the diagnosis of TM diseases and disorders.
2. To assess current methods and explore new ways to define the TMJ vulnerable population through the utilization of new and emerging technologies provided through bioengineering, bioimaging, and computational biology.
3. To promote the participation of young scientists through a travel award program.
4. To stimulate interest among young investigators to provide a multidisciplinary approach to research on temporomandibular diseases and disorders.

We believe the scientific meeting will make an important contribution to the development and utilization of advanced technologies for application to temporomandibular joint diseases and disorders. In so doing, we believe that new or improved approaches for diagnosing these complex conditions will emerge that can lead to the prevention or delay of the onset or progression of these conditions, thereby improving the quality of healthcare and life for the millions who are suffering.

THE THIRD SCIENTIFIC MEETING
OF THE TMJ ASSOCIATION
Advancing Diagnostic Approaches for TMJ Diseases and Disorders
Hyatt Regency Bethesda, Bethesda, MD
May 6-7, 2004

Thursday, May 6, 2004

8:00 – 8:10 a.m. **Welcome**
Terrie Cowley, President, The TMJ Association, Milwaukee, WI

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

Henning Birkedal-Hansen, D.D.S., Ph.D., Acting Deputy Director, National Institute of Dental and Craniofacial Research, Bethesda, MD

Belinda Seto, Ph.D., Acting Deputy Director for the Office of Extramural Research, National Institute for Biomedical Imaging and Bioengineering, Bethesda, MD

Session 1 - TMJ Diseases and Disorders and the Need for Innovative Diagnostic Tools

8:10 – 9:00 a.m. **TMJ Diseases and Disorders: Difficult but not Impossible to Solve**
Christian S. Stohler, D.M.D., Dr. Med. Dent., University of Maryland Dental School, Baltimore, MD

9:00 – 9:30 a.m. **Patient Presentations – TMJ Diseases and Disorders: Symptoms – Mild to Severe**
Moderated by Stephen B. Milam, D.D.S., Ph.D., University of Texas Health Science Center, San Antonio, TX

Session 2 – Current and Future Methodologies of Imaging for TMJ Diseases and Disorders (Including X-Ray, MRI, fMRI, PET, NMRI, Ultrasound, and Thermography Imaging)
Discussion Chair Leaders – Thomas F. Budinger, M.D., Ph.D., University of California, Berkeley, CA
Tore A. Larheim, D.D.S., Ph.D., University of Oslo, Oslo, Norway

9:30 – 9:55 a.m. **Current Radiographic Approaches for Assessment of TMJ Disease Progression**
Sigvard Kopp, D.D.S., Ph.D., Institute of Odontology at Karolinska Institutet, Sweden

9:55– 10:20 a.m. **fMRI of Jaw Motion**
James S. Hyde, Ph.D., Medical College of Wisconsin, Milwaukee, WI

10:20 – 10:35 a.m. Break

10:35 – 11:00 a.m. **3D X-Ray/PET Imaging Approaches and Uses in Neurovascular Diseases**
Kieran Murphy, M.D., Johns Hopkins Hospital, Baltimore, MD

11:00 – 11:25 a.m. **Evolving Techniques for the Investigation of Muscle Bioenergetics and Oxygenation**
Russell S. Richardson, Ph.D., University of California, San Diego, La Jolla, CA

THE THIRD SCIENTIFIC MEETING OF THE TMJ ASSOCIATION COMMENTS OF PARTICIPANTS

Advancing Diagnostic Approaches for TMJ Diseases and Disorders

Stephen Milam, **D.D.S.**, **Ph.D.**, addressed the need for continued NIH support of TMJA Scientific Meetings...and recommended further studies to characterize the biomechanics of the TM joint and muscle and the use of these approaches for diagnosis and prognosis...**Allen W. Cowley, Jr.**, **Ph.D.** added that these biomechanical studies should include patient-specific anatomically based computational models (such as finite element analysis) that would characterize the structures of the bone and fibrous tissue, neuromuscular units, metabolism and blood supply, and relevant sensory and motor regions of the central nervous system... Further, there will be a need for experimental and clinical validation of these models, utilizing imaging technologies such as fast CT 3D X-ray, micro CT, PET, MRI, fMRI, MRS, thermography, and any other non-invasive technologies that can capture the required data...**Milam** further recommended that population studies be conducted to determine the role of genetic and environmental factors in etiology. Ideally, a uniform infrastructure should be established and standardized, affordable phenotyping methodologies used to permit the recruitment of a broad spectrum of subjects, from normal to severely diseased...**Milam** concluded that it should now be possible to develop new clinical criteria for defining TMJ diseases and disorders, given the current availability of remarkably fast and sensitive imaging technologies as demonstrated at the meeting. The many discussions throughout the meeting made it clear that the there are now means of imaging joint-muscle-blood flow-oxygen level and inflammation; of observing structures during active motion, conducting longitudinal studies, etc. It should be possible to pinpoint, on the distribution time curve, when intervention is recommended and at what point associated risk factors emerge.

Thomas Budinger, **M.D.**, **Ph.D.**, recommended studies to determine if routinely carried out body scans using FDG PET techniques (for diagnosis of tumors) could be used for detection of jaw muscle (e.g., pterygoid) metabolic activity (e.g., TMJ-bone/joint stress)...he suggested a way to begin would be by mining the data from whole body scans already available at many institutions to obtain preliminary data, and then designing prospective studies using routine PET scans that could be extended to routinely include the head and neck regions...possibly at a cost of about $450 per person...He also recommended testing to determine if high resolution ^{18}F (ionic) PET techniques could be used to characterize changes in TM bone blood flow.

Sigvard Kopp, **D.D.S.**, **Ph.D.**, recommended using a combination of imaging techniques and chemical markers to determine the mechanisms behind the pain in TMJ and the relationship of pain in the TM joints and muscles to other body pain...such studies should illuminate the relationship of pain to the ongoing bone and soft tissue destruction (e.g., cytokine and TNF-alpha focus) in order to predict future destruction of the TM joints...**Milam** added that he thought that nanoparticle technology could be used to image local regions of inflammation that would be related to cytokine responses...**Budinger** proposed the use of "pinpoint" fluorescent or isotopic techniques to image inflammatory regions in joints just as they are used to detect vascular plaques...Prospective studies based on the above strategies were proposed that could lead to early diagnosis and treatment.

Jon-Kar Zubieta, **M.D.**, **Ph.D.**, recommended that fMRI and PET scanning techniques be employed to evaluate the complex neurobiological pathways in both normal and TMJ disease states...he also proposed prospective longitudinal studies of vulnerable populations such as young Caucasian women who have not exhibited any clinical manifestations of TMJ dysfunction, but who may be at risk for TMJ disease...Further screening of TMJ patients using the recommended brain imaging technologies might yield means of stratifying patients for more extensive phenotyping and genotyping studies.

In addition, the Institute supports research on the physiology and pathology of TMJ disorders and the mechanisms underlying them. Among them are environmental and genetic factors that increase the risk for TMJ disorders, the use of lasers and microarray technologies for profiling TMJ structures, the use of genomic and proteomic analyses for comparing normal and diseased joint tissues, the application of new imaging technologies in evaluating TMJ disorders, and monitoring the outcomes of treatments.

Speakers at the meeting discussed some of the databases on TMJ disorders that would benefit from reanalysis. The NIDCR has a program for this, Tabak noted. "I would hope that some of you will take up the challenge and take advantage of some of these very robust data sets."

The Institute also funds curriculum development efforts and provides grants to fund conferences, both aimed at improving education. "Keep those R13's coming," he said, citing the designation under which the Institute funds such programs—including the very scientific meeting he was addressing.

He called for new and exciting ideas and issued a challenge to The TMJ Association to "storm into my office and say: 'How dare you not fund this latest and wonderful thing.' Bring in research [proposals] that are cutting edge and so startlingly new that we have no choice but to fund them."

And with hats off to The TMJ Association he concluded, "I congratulate this organization on an outstanding conference. Working together we will eventually overcome this problem."

11:25 – 11:50 a.m. **High-Resolution Ultrasonography of the TM Joint - Sonography Versus Magnetic Resonance Imaging**
Rudiger Emshoff, M.D., D.M.D., University of Innsbruck, Austria

11:50 – 12:20 p.m. Discussion – The speakers in this session will lead a general discussion of relevant questions.

12:20 – 2:00 p.m. Lunch/Poster Session

Session 3 – Methodologies for Brain Imaging Related to TMJ Diseases and Disorders
Discussion Chair Leader – Jon-Kar Zubieta, M.D., Ph.D., University of Michigan, Ann Arbor, MI

2:00 – 2:25 p.m. **Why Look in the Brain for Answers to TMJ Pain?**
Joel D. Greenspan, Ph.D., University of Maryland, Baltimore, MD

2:25 – 2:50 p.m. **Neural Correlates of the Subjective Experience of Pain**
Robert C. Coghill, Ph.D., Wake Forest University School of Medicine, Winston-Salem, NC

2:50 – 3:15 p.m. **Interindividual Variations in the Neurochemical Regulation of Temporomandibular Pain**
Jon-Kar Zubieta, M.D., Ph.D., University of Michigan, Ann Arbor, MI

3:15 – 3:45 p.m. Discussion - The speakers in this session will lead a general discussion of relevant questions.

3:45 – 4:00 p.m. Break

Session 4 – Applications of Nanotechnologies for Imaging and Targeted Joint Therapy
Discussion Chair Leader – Thomas F. Budinger, M.D., Ph.D., University of California, Berkeley, CA

4:00 – 4:25 p.m. **Targeted Nanoparticle Emulsions For Molecular Imaging and Drug Delivery**
Samuel A. Wickline, M.D., Washington University School of Medicine, St. Louis, MO

4:25 – 4:50 p.m. **Potential of MRI and PET in Early and Presymptomatic Characterization of TMJ Disease**
Thomas F. Budinger, M.D., Ph.D., University of California, Berkeley, CA

4:50 – 5:20 p.m. Discussion - The speakers in this session will lead a general discussion of relevant questions.

Friday, May 7, 2004

Session 5/Part A: Clinical Research Use of Imaging Technologies for TMJ Diseases and Disorders
Discussion Chair Leader – Stephen B. Milam, D.D.S., Ph.D., University of Texas Health Science Center, San Antonio, TX

8:00 – 8:25 a.m. **Role of MRI in Clinical Diagnosis of the Temporomandibular Joint**
Tore A. Larheim, D.D.S., Ph.D., University of Oslo, Oslo, Norway

8:25 – 8:50 a.m. **TMD Symptoms and Specificity - A Longitudinal Clinical TMJ Study**
Jos Dibbets, D.D.S., Ph.D., Philipps University, Marburg, Germany

8:50 – 9:15 a.m. **Imaging Tools – Lessons from the Knee Joint**
Carl S. Winalski, M.D., Brigham and Women's Hospital, Boston, MA

Session 5/Part B: Computational Approaches for Modeling of TM Joint Mechanics and Morphology

Discussion Chair Leaders – Luigi M. Gallo, P.D., University of Zurich, Switzerland
Susan W. Herring, Ph.D., University of Washington, Seattle, WA

9:15 – 9:40 a.m. **Mechanical Actions of Different Partitions of Masticatory Muscles**
Arthur W. English, Ph.D., Emory University School of Medicine, Atlanta, GA

9:40 – 10:05 a.m. **TMJ Mechanics (Condyle, Capsule, and Disc)**
Susan W. Herring, Ph.D., University of Washington, Seattle, WA

10:05 – 10:20 a.m. Break

10:20 – 10:45 a.m. **Modeling of TMJ Function Using MRI and Jaw Tracking Technologies-Mechanics**
Luigi M. Gallo, P.D., University of Zurich, Switzerland

10:45 – 11:10 a.m. **Anatomically Based Modeling of the Human Jaw and Face**
Peter Hunter, D. Phil., University of Auckland, Auckland, New Zealand

11:10 – 11:35 a.m. **Multifactorial Modeling of Temporomandibular Anatomy and Orthopaedic Relationships in Normal and Disc Displaced Joints**
Andrew Pullinger, D.D.S., M.Sc., University of California, Los Angeles, CA

11:35 – 12:05 p.m. Discussion - The speakers in this session will lead a general discussion of relevant questions.

12:05 – 1:00 p.m. Lunch/Poster Presentations

Session 6 – Interactions Between Technical and Applied Users to Develop Recommendations for Diagnostic Criteria for TMJ Diseases and Disorders

Chair/Moderator – Stephen L. Gordon, Ph.D., Cognate Therapeutics, Bethesda, MD

1:00 p.m. – 3:00 p.m. **Development of Recommendations:**

This session will be divided into two discussion panels, each with the goal of leading a general discussion aimed at developing a set of recommendations to the NIH regarding the application of these technologies in the TMJ research field. The invited panelists who will lead these discussions will be provided with abstracts/summaries of presentations prior to the meeting.

The panelists in Part A will assess the current detection limits, technological barriers, and limits of the current non-invasive imaging technologies and develop a summary document of recommendations whereby currently available technologies could be immediately used to establish standardized methods for the diagnosis of temporomandibular diseases and disorders.

Another important purpose of the model is to obtain a picture of the way the muscles are innervated. The goal is to determine how neural activity is distributed in various parts of the muscle in order to control the distribution of activation potentials throughout the muscle. "We have been doing this by activating cables that represent the muscle fibers embedded within the muscle," Hunter said.

Hunter summarized the present status of his studies: "We are in the process of validating dynamic and static simulations, but more work is needed on more detailed models, particularly on the neural side. As regards the TMJ, we are beginning to create a detailed model of the joint itself, using the material properties of the cartilage and coupling that to the jaw muscle model."

Meanwhile, computational formulas and high performance computers are certainly up to the task of dealing fully with the anatomy. "Any of these models can usually be tailored to individuals based on magnetic resonance imaging or computerized tomographic observations," Hunter said. "We've done it with the heart; there's no reason that it can't be done with the TMJ."

TMJ: the sum of the parts. To predict with reasonable reliability which patients have significant TMJ disorders requires taking into account a number of different variables. If prediction is to be meaningful and useful, no single variable can be relied upon. "We need to look at the whole system," said Andrew Pullinger of the University of California in Los Angeles. In his report he identified temporomandibular hard tissue relationships that distinguished between patients with unilateral disc displacement, either with or without reduction, as compared with normal asymptomatic individuals.

He has developed what he terms a "multifactorial classification tree" that incorporates a number of different tomographic measurements of TMJ anatomy and uses this to compare patients with TMJ disc displacement with normal persons. Analysis of the data enables him to distinguish normal joints from those with disc displacement. For instance, in the normal joints the fossa sizes and shapes were less extreme and the condyle positions were more centered, than they were in the joints with disc displacement.

Again, even when the condyles in the normal joints were not in perfect concentric position, they had, on average, normal fossa size and shape compared with the condyles of the diseased joints, which were also more likely to have non-concentric positions and more extreme fossa shapes.

Depending on the position of the condyle and the width and depth of the fossa, the classification tree could differentiate deranged from normal joints.

There were differences in the fossa walls and joint spaces between those with disc displacement who did not have reduction or clicking joints, compared with those with disc displacement that did. Thus, although orthopedic organization is significant, there are additional factors such as articular and disc soft tissue qualities that are important in the development of TMJ disc disorders, said Pullinger.

He emphasized that the TMJ and its associated disorders must be studied as complete systems using multifactorial analyses that can then provide useful predictive values. However, orthopedic observations do not tell the whole story; it is necessary to look at additional soft tissue factors, gender differences, trauma, and treatment history.

Dr. Pullinger's paper concluded the formal presentations at the meeting. Ample time was included for discussions of the needs for basic and clinical research on the TMJ and associated tissues, and the development of recommendations. A summary of the discussions and the emerging recommendations follow this text.

At the conclusion of the meeting, Dr. Lawrence Tabak, Director of the National Institute of Dental and Craniofacial Research, presented closing remarks. He noted that NIDCR spends about $12 million for research on temporomandibular disorders. "Take advantage of these funding opportunities," he urged. He went on to describe some of the programs currently supported by the Institute. "We have a program announcement for research on the natural history of TMJ disorders—exactly what many of you were talking about. Hopefully, some of you will be applicants for this," he said.

Noting that the collagenous tissues deformed 15 percent or more during normal function means, as Herring put it, they "are clearly moving a lot," and so are probably liable to injury. "More attention should be given to ways to strengthen or reinforce the capsule, since it is probably key to both bony movements and discal integrity," she suggested.

Virtual imitation of TMJ movements. A combination of three-dimensional computer reconstructions of the anatomy of the Temporomandibular joint (TMJ) and jaw motion recordings obtained by magnetic resonance imaging is opening the way to computer modeling of joint movements and their relationship to anatomic structures.

The reconstructions allow dynamic, noninvasive analysis in three dimensions of the variations between the articular surfaces and the study of degenerative joint disorders. Since they are based on measurements taken on real persons, studies of both normal subjects and patients with TMJ disorders are feasible. The aim is to quantify the kinematics—the motion of the jaw—to "understand how the human jaw is loaded, and to try and explain some of its failures," said Louis M. Gallo of the University of Zurich, Switzerland.

As an example of the type of studies that can be performed with this system, Gallo cited the variations of the joint space between the condyle and the fossa during mastication.

These indicate that both temporomandibular joints are loaded during chewing, with a greater load on the balancing joint than the working joint. Changes were also observed when the subject was chewing hard food compared with soft food and on jaw closing compared with jaw opening.

There is good visualization of the movement of the TMJ condyles in their respective fossa. This helps to improve understanding of the complexity of condylar and mandibular movements in general, and can help explain what goes wrong in degenerative joint diseases, providing clues to the origins of internal derangements and perhaps helping to identify individuals prone to the development of craniomandibular disorders.

Other models. Modeling is widely used in biological studies to enlarge understanding of the structure and function of living organisms. It was this approach that Watson and Crick used to depict the double helical structure of DNA, for example.

At the scientific meeting, Peter J. Hunter of the University of Auckland in New Zealand described the development of a computational model of the human jaw, teeth and the chewing system. Until recently much of his work has been with the heart and the knee joint. "So it's early days for us as regard the TMJ," he said. The initial purpose is to simulate mastication and to calculate the force on the teeth. "Eventually, he added, the plan is to use the model as a basis for further research on jaw structure and function."

The model consists of anatomically realistic representations of the bony parts of the jaw, the mandible, maxilla (the upper jaw bone), the zygomatic arch, teeth, and temporal bones. In addition, all four pairs of the masticatory muscles (the masseter, temporalis, and the medial and lateral pterygoid) have been put into the model to capture the muscular anatomy and its fibrous structure.

To simulate muscle forces, the positions of the condyles and the teeth were fixed, and forces applied directly to regions of the mandible. The results show realistic deformation and reaction forces on the teeth, said Hunter. He also used these anatomical muscle models to simulate muscle contractions and has shown that the muscles are capable of both passive and active contractions.

Hunter and his associates are also working with a group of Australian investigators who developed a mechanical chewing machine. They have named it "Lecter" after the book and movie character, Hannibal Lecter, of notorious oral appetites.

The elaborate device consists of cables that represent the muscle fibers, fitted with strain gauges and force transducers to measure the forces in the muscle cells and the forces between the teeth. The device is able to simulate passive and active contraction of muscles, Hunter said.

The panelists in Part B will address novel investigative approaches that could open up new avenues of research or be applicable to the development of new or improved instruments and technologies for use in research and clinical diagnostics, and preventive strategies. Recommendations will be derived from these discussions regarding how to move beyond the technological limits of current approaches.

1:00 – 2:00 p.m. **Session 6/Part A: Clinical Discussions**

Panel Members:

1. Stephen Feinberg, Ph.D., D.D.S. M.S., University of Michigan Medical Center, Ann Arbor, MI
2. Sigvard Kopp, D.D.S., Ph.D., Institute of Odontology at Karolinska Institutet, Sweden
3. Stephen B. Milam, D.D.S., Ph.D., University of Texas Health Science Center, San Antonio, TX
4. Randall Wilk, D.D.S., Ph.D., M.D., Louisiana State University, New Orleans, LA

2:00 – 3:00 p.m. **Session 6/Part B: Research Discussions**

Panel Members:

1. David E. Altobelli, D.M.D., M.D., DEKA Research and Development, Manchester, NH
2. Thomas F. Budinger, M.D., Ph.D., University of California, Berkeley, CA
3. Stephen L. Gordon, Ph.D., Cognate Therapeutics, Bethesda, MD
4. Christian S. Stohler, D.M.D., Dr. Med. Dent., University of Maryland Dental School Baltimore, MD
5. John T. Watson, Ph.D., University of California, San Diego, La Jolla, CA
6. Jon-Kar Zubieta, M.D., Ph.D., University of Michigan, Ann Arbor, MI

3:00 - 3:15 p.m. **Closing Remarks**
Lawrence A. Tabak, D.D.S., Ph.D., Director, National Institute of Dental and Craniofacial Research

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National Institute of Arthritis and Musculoskeletal and Skin Diseases
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Rabbit model of TMJ function. Precisely how the muscles work to regulate movements about the TM joint is the subject of an ongoing investigation by Arthur W. English of Emory University School of Medicine in Atlanta. Working with the masseter muscle of the rabbit, he pointed out that internal tendons and branches of the nerves of this muscle are divided into 20 or 25 neuromuscular compartments. "We wanted to see if these anatomically distinct compartments were functionally distinct as well," he said. It turns out that they are and their action depends on the position of the jaw.

He attached a force movement sensor to the animal's jaw that measured the forces in three planes simultaneously. Indwelling electrodes stimulated the muscles and electromyograms (EMGs) recorded muscle activity.

English studied nine different neuromuscular compartments, noting that each showed a unique mechanical action and produced a different turning force, or torque, dependent on the position of the jaw—open and closed (up and down), pitch and roll. When the compartments were activated together they produced mechanical actions that were the sum of the actions of the contributing compartments.

When the region of the brain that controls chewing is electrically stimulated, it activates the chewing muscles. "Since the mandibles are fixed to the measuring apparatus, we don't actually see chewing movements, but what we do see is alternating EMG activity: jaw opening and closing movements. We call this rhythmic activation." Using "principal component analysis," a mathematical construct for expressing two or more variables as a single factor, he showed that the timings of the activation of the different compartments were grouped in different ways with different behaviors.

"We think the masticatory muscles are compartmentalized, each producing unique mechanical actions, their function dependent on the position of the mandible. The mechanical actions come in reasonably predictable ways and, during production of different oral behaviors, are used in different combinations," English said. "We conceptualize the muscle as a series of small actuators, each with a different mechanical action that can be combined in different ways to produce different movements."

Pig model of TMJ function. In the other animal study, involving miniature pigs, Susan Herring of the University of Washington in Seattle showed that chewing exerts significant strain on both bone and collagen. However, bone is not usually the first joint tissue to show injury. This occurs later, after the softer collagenous tissues such as the disc or joint capsule have been damaged. These soft tissues maintain the integrity of the jaw when it moves, the ligaments in the joint capsule guide or limit movement, and the disc may also play a role in distributing loads to the joint.

Arguing that pigs are the best animal models for studying human TMJ function, Herring placed strain gauges on the squamosal bone near the TMJ (a bone roughly equivalent to the human temporal bone), on the neck of the condyle, and on the mandible. To measure strains on the joint capsule and the disc, she placed semiconductor pressure transducers on both sides of the joint capsules. While the pig chewed, the strains on the bone, the deformation of the ligaments and electrical activity of the masseter and pterygoid muscles were recorded.

In all the animals, chewing resulted in tension on the squamosal bone and compression in the other sites. The disc tissue echoed the movements of the mandible, but on a smaller scale, indicating that it was possibly tethered to the squamosal bone and tissue deformation rather than bodily movement.

During chewing the joint capsule elongates, as much as 15 percent during the power stroke, particularly on the balancing side compared to the working side, where the elongation was about 8 percent. Surprisingly, the disc strain during mastication was opposite to what was expected. It elongated more on jaw closure and more on the balancing side (16 percent) than on the working side (8 percent). This may reflect compressive loading rather than movement of the condyle. In sum, collagenous joint tissues undergo considerable strain, caused not only by movement but also by loading.

These findings show that the disc is attached to the joint capsule around its perimeter including the bony attachments. When the capsule is injured, the disc must inevitably be affected, Herring said.

Existing studies tracking glucose metabolism using a radioactive glucose analogue, fluorine ^{18}F fluorodeoxyglucose (FDG), and positron emission tomography (PET), have detected increased metabolic activity in muscle following stress or exercise. “It is a fantastic marker for detecting increased transport of glucose,” Budinger said.

Budinger reported a pilot study in individuals who showed high uptakes of FDG in one of the muscles of the jaw, the lateral ptyergoid, following increased muscle activity. So Budinger proposed a systematic study of the pterygoid muscle or other associated muscles in such individuals, using FDG and PET, when the subjects were chewing gum or otherwise exercising the muscle, as a way of detecting any inflammation associated with muscle activity.

He also suggested studying TMJ patients with FDG-PET before and after correcting the bite with a splint to see if there was a decrease in glucose accumulation. Then he suggested studying patients who have unusually high uptakes of FDG in the ptyergoid and other muscle groups to see if they have symptoms of TMJ diseases and disorders.

“That an abnormally high uptake of FDG is related to TMJ disease symptoms is yet to be proved,” he said, “but PET might be an important modality in the characterization of TMJ disease and potentially more sensitive to muscle stress and pathologies than MRI.”

Imaging in Clinical Research

A soft cartilaginous disc in the TM joint acts as a shock absorber between the rounded head (called the condyle) of the mandible, the lower jaw bone, and a depression in the temporal bone of the skull called the fossa. Displacement of the disc from its normal position is quite common; it occurs in asymptomatic individuals as well as in TMJ patients, so questions have been raised about its clinical implication in TMJ disorders. Tore A. Larheim and his associates at the University of Oslo in Norway have used comparative magnetic resonance imaging studies of TMJ patients and asymptomatic individuals to conclude that the disc displacement seen in TMJ patients is different from the kind of displacements seen in asymptomatic individuals.

The Oslo group studied TMJ patients and compared them with a group of healthy volunteers with no history of TMJ pain. Both groups were examined by MRI with their mouths closed and open. They found that over three quarters of the patients had evidence of disc displacement compared with about one-third of the normal volunteers.

Complete disc displacement was seen in 40 percent of the TMJ patients compared with less than 3 percent of the asymptomatic volunteers. Two types of complete disc displacement, anterolateral and anterior, occurred frequently in patients, but seldom in volunteers. Only minor differences were found between other types of disc displacement when prevalence in patients was compared with that of volunteers.

The disc returned to the normal position in all the joints of the volunteers when they opened their mouths. By comparison, in the TMJ patients two-thirds of those with a displaced disc did not normalize when they opened their mouths. Another difference noted was that disc displacements in the joints of asymptomatic volunteers were less frequent bilaterally, and more often partial, compared with patients with TMJ pain and dysfunction. “The fact that some categories of disc displacement seem to have a greater tendency to be associated with pain than others should be helpful when images of patients with TMJ pain and dysfunction are evaluated,“ Larheim said.

One important conclusion from these studies is that clinical findings of abnormalities in the TMJ may not be related to patients’ symptoms at all and there is no need of treatment for asymptomatic abnormalities.

Modeling TMJ Mechanics

In the course of chewing, a battery of muscles coordinates the sliding and rotating movement of the temporomandibular joints. The chewing muscles coordinate their motions to move the joints, control the positions of the teeth in three dimensions, and adjust the forces applied to those teeth when chewing.

Two animal studies, reported at the meeting, one on the rabbit and the other on a species of miniature pig, illustrate the complexity of the musculature and the forces on the jaw that are involved in mastication.

Advancing Diagnostic Approaches for TMJ Diseases and Disorders

By Charles Marwick

Temporomandibular Diseases and Disorders—The Problem

Temporomandibular diseases and disorders are complex medical conditions that affect the jaw (the temporomandibular joint or TMJ), the muscles that control chewing, and adjacent tissues. Increasingly the concept is emerging that these disorders encompass a broad range of problems that reflect a variety of causes and pre-disposing factors, including injury, arthritis, autoimmune disorders, genetic susceptibility, environmental agents, and risk-conferring behaviors.

Clearly, there is no one cause or unique biological explanation for TM disorders. Moreover, symptoms vary widely in extent and severity. There is pain in the face or jaw while involvement of the jaw muscles can lead to restricted mouth opening, with some patients experiencing difficulties in breathing and speech, and in chewing and swallowing—in some cases restricting eating to a liquid diet. Some patients report headaches, earaches, and dizziness. Others experience few significant signs or symptoms, while still others may suffer intractable pain and severe dysfunction.

TMJ conditions are common, affecting some 10 million people in the U.S. Women, typically in their childbearing years, are affected more than men, and the female to male ratio increases among those seeking treatment. For those who progress to chronic pain and dysfunction, the female-to-male ratio is as high as 9 to 1.

While the problem will resolve itself over time in many cases, “it is estimated that between 1.5 and 3 million people in the U.S. seek treatment every year, a remarkable number. Literally, billions of dollars are expended in treatment and loss of income associated with these debilitating disorders,” said Stephen B. Milam of the University of Texas Health Science Center in San Antonio, speaking at the Third Scientific Meeting of The TMJ Association, May 6-7, 2004, held in Bethesda, Maryland.

In some cases patients are found to have developmental anomalies or other conditions which have been relatively well characterized and can either be treated effectively or resolve themselves over time. “But many patients experience immense suffering,” Milam said and introduced one such patient, Marsha Love, of Kalamazoo, Michigan, who gave a first-hand account of her experience. “There are many others, perhaps thousands, who could relate similar stories,” he said.

Ms. Love recited a series of harrowing experiences dating from 1982, when at the age of 31 she was first diagnosed with TMJ disease. Over the years she underwent batteries of tests, including several arthroscopic procedures and magnetic resonance imaging (MRI) scans. Oral splints and physical therapy were prescribed in an attempt to improve her jaw motion. She had her bite adjusted and underwent multiple surgeries and a jaw implant device all to no avail. “My jaw muscles had atrophied, I could no longer put a spoon in my mouth, pain was a problem, and the drugs to relieve the pain were causing me stomach problems,” she said.

At this point, various specialists presented Ms. Love with a series of options. Six recommended surgery, but there was no agreement on which procedure. “It’s overwhelming when you’re a patient and you find that there’s no science. I was confused and wondered what I was going to do. I couldn’t wait for science any longer. I had to make a decision. She appealed to her audience: “The hope for TMJ patients lies in the science.”

Allen W. Cowley, Jr., of the Medical College of Wisconsin and Chairman of the meeting’s Program Planning Committee, reinforced Ms. Love’s message. “What struck me most about TMJ disorders, when I first learned about them, was how little was really known about them, about the underlying etiology, and how little real science had been done in the field,” he said. He described the conference as an effort to develop a “mixing bowl” of scientists to create a field that has not existed in any organized way.

Cowley said the meeting reflected a widespread recognition of the need to improve the diagnosis of TMJ disorders—preferably with noninvasive techniques. "We aimed, first, at providing information about what the current technologies offer, and, secondly, to bring in other specialties, a group of world-class engineers, computational biologists, basic investigators, and clinical scientists from around the world with expertise in other fields, such as arthritis and inflammation."

Advances in Imaging Technologies

New technologies and improvements on existing imaging techniques used as diagnostic tools such as radiographs, functional magnetic resonance imaging (fMRI), and computerized tomography (CT) scans open the way for an improved understanding of temporomandibular joint disease, said Christian S. Stohler of the University of Maryland Dental School, Baltimore. We need to find better ways to capture individual patient characteristics as signs of the pathogenesis of the disease and we need to improve understanding of regulatory processes, including the role that an individual's genetic endowment may play in amplifying symptoms, he said. He called for improvements in imaging that would allow distinctions between normal variation and progressive disease. In turn, this could lead to improved case characterization and protect patients from numerous uninformative tests.

But radiographic studies, by themselves, may not be sufficient to assess active progression of disease. Sigvard Kopp of the Institute of Odontology at the Karolinska Institutet in Sweden pointed out that while existing radiographic procedures can assess the progression of bone destruction in the TMJ over time, radiography should be correlated with analyses of blood and synovial fluid (the fluid inside joints) in search of inflammatory markers and mediators. This would enable providers to estimate current disease activity, since bone destruction is frequently due to inflammation.

He cited studies in which inflammatory markers were found in synovial fluid and plasma, along with inflammatory cytokines (regulatory molecules generated by the immune system). Activation of thrombocytes (blood coagulating factors) is also an important part of joint inflammation and erosion of the joint is associated with high numbers of circulating thrombocytes and correlates with progression of bone loss.

Kopp began his talk by asking three questions:

1. Can radiography determine the inflammation associated with TMJ disease?
   His conclusion: Maybe.
2. Can current radiographic approaches be used to follow the development of disease and the extent of destruction? His answer: Yes.
3. Can radiography be used to predict the development of disease? His answer: No.

One fMRI imaging hurdle overcome. A serious difficulty in using functional magnetic resonance imaging of the brain to study jaw motion seems to have been overcome, noted James S. Hyde of the Medical College of Wisconsin. Functional MRI works by detecting changes in blood flow to specific areas of the brain, "lighting up" those areas that reflect an increase in blood flow, as for example, when a muscle is moved. But studies involving the jaw joint have been stymied because of motion-induced artifacts when chewing or speaking. The movement of the jaw changes the magnetic field and is not synchronized with the change in oxygenated blood flow detected by the technique. The chewing motion is instantaneous, but the increase in blood oxygenation is delayed by about 5 seconds. The result is an anatomic distortion in the images and a decrease in fMRI intensity, said Hyde. Vinai Roopchansingh, one of Hyde's students, solved the motion-induced artifact problem by creating magnetic field maps for each fMRI scan when the subject is chewing and not chewing. "On each of these images the magnetic field is slightly different and provides a way of making a magnetic field map of every single shot in the time course. When you know what the local magnetic field is in the brain you can make a mathematical correction to straighten out the artifacts."

Two other refinements, based on averaging responses in repeated trials, added further improvements to the technique, enabling a suppression of artifactual signals, Hyde explained.

"It looks like one can sort out the various muscles of the jaw and make some real progress in understanding this whole process—not only the control of the joint, but also in perception," Hyde said. The resolution of this technical problem now makes it possible to study normal volunteers and

The women were studied at a time in their menstrual cycle when their levels of estrogen and progesterone were at their lowest, the early follicular period (none were using birth control pills). What would be the response if they were given estradiol, one of the estrogens? To find out, the Michigan group scanned healthy women once during this early follicular phase and then again in the following month after they had been given estradiol, which increased their estrogen levels to those normally seen during the later phases of the menstrual cycle.

Now, in PET scans made after the pain stimulus, there was a striking difference in the activation of the μ-opioid system. During the normal early follicular phase, there had been little or no activation of the μ-opioid system. But under high estrogen conditions, the same women had a marked increase in the activation of the μ-opioid receptors and the effect was seen in brain areas involved with the perception and regulation of pain and other stress. Thus, estrogen has a powerful effect on the response to pain and stress, Zubieta concluded.

"These examples," Zubieta said, "demonstrate the complexity of the regulatory mechanisms engaged during sustained pain as well as the factors that contribute to the inter-individual variations in responses to temporomandibular pain. They also show the effectiveness of neurochemical PET as a tool to integrate psychophysical, genetic, endocrine, and neurochemical function to achieve a mechanistic, systems-level understanding of human physiological and pathophysiological processes such as TMD."

Nanotechnology Imaging and Targeted Drug Delivery

Nanotechnology is the building of molecules atom by atom to study or change natural structures (nano is from the Greek word for dwarf). Since a nanometer is a billionth of a meter—1,000 times smaller than a micrometer—the assembly of "nanoparticles" is science and engineering at an infinitesimal scale. The technology is already beginning to play a fundamental role in research and in drug delivery.

"We're involved in molecular imaging and related targeted therapeutics," said Samuel A. Wickline, of Washington University School of Medicine in St. Louis. "What we do is something you probably won't be able to use for at least five years. Our work has nothing to do with the jaw, but there's a lot going on with nanotechnologies that is going to be applicable to noninvasive diagnostics, to inflammatory diseases, and to localized therapeutics. Nanoparticles can be injected into the human body. "They go where you tell them to go, get there, stay there, and do something. They have to be small enough to do that, yet large enough to pack a punch, deliver a payload," he said.

Loaded with contrast agents that can be detected with standard imaging equipment, these nanoparticles target specific molecules and provide information at the cellular and molecular level that is useful for early diagnosis and more accurate characterization of disease. Nanoparticles can detect organ or cellular malfunctions even before the first anatomical changes occur, which helps in selecting treatment strategies and in measuring their effects.

One type of nanoparticle Wickline described is a perfluorocarbon suspended in an emulsion, like salad dressing. "You can attach things to it, such as contrast agents for MRI, or drugs, or radionuclides. Then you put a targeting signal on it, with the molecules of your choice--monoclonal antibodies or a specific molecule--depending on how you arrange the molecular 'zip codes' on it."

Such nanoparticles are a million times more sensitive than currently available MRI contrast agents. Since they zero in on the desired target cells, they can detect blood clots, unstable deposits of plaque in arteries, atherosclerotic lesions, and tumors, along with the growth of new blood vessels (angiogenesis) that can feed a tumor. They can also localize the molecular factors involved in response to injury. For example, anti-cancer drugs and therapeutic radionuclides can be incorporated into nanoparticles for direct delivery to tumors. Drug toxicity is lowered since the drug goes directly to where it is wanted and is not distributed in the circulation. In turn, that means the therapeutic payload can be increased.

Spotting stressed jaw muscles. The pain TMJ patients experience is a reflection of abnormal stress on the jaw muscles. Thomas F. Budinger of the University of California in Berkeley suggested that one way to identify when this stress occurs early on, before the patient experiences pain, is by measuring the uptake of glucose, a source of the body's energy.

the possibility that cognitive factors may account for a substantial portion of these inter-individual differences," he said.

There are clinical implications of these findings, Coghill noted. It is potentially possible to screen patients for their pain sensitivity. Those with a high level of sensitivity could have their pain managed more aggressively, even at the risk of higher side effects and costs. Alternatively, those with a low level of pain sensitivity could be managed less aggressively and thus spare the patient the side effects of pain medication.

At the same time, the pain expectation data suggest that it is possible to enhance analgesic efficacy. Coghill's advice when presenting a patient with a new drug, is to avoid a negative presentation and strike a positive note. Creating a positive expectation might amplify the pharmacologic effect that the drug is going to have.

Gender, genes, and pain. How we experience pain is mediated by neurochemicals acting throughout the nervous system from the periphery to the brain. The action of these neurochemicals depends on their structure and abundance in the system and these are under genetic control. Thus, the way we perceive pain has a genetic component and explains in part why pain responses vary from one person to another.

To examine the action of these neurochemicals on the brain's pain centers, Jon-Kar Zubieta and his associates at the University of Michigan selected one of the body's pain- controlling molecules, the μ-opioid receptor to exert a powerful analgesic effect. It is one of several opioid receptors in the nervous system that use chemicals that are the body's natural counterpart to morphine-like drugs. The activation of the receptor is controlled by a protein, the enzyme, catechol-O-methyltransferase or COMT. The enzyme metabolizes neurotransmitters known as catecholamines that modulate responses to pain. Several genetic variants of the COMT gene exist. One that is particularly abundant, substitutes one amino acid, valine, for another, methionine. This substitution leads to a three-to-fourfold reduction in the activity of the COMT enzyme. Individuals carry two copies of the COMT gene, one from each parent. Some people have two copies of the methionine gene, others have two copies of the valine gene. They are homozygous for either the methionine gene or the valine gene. Others have one copy of each of the two genes, the methionine gene and the valine gene, and are heterozygous.

Using this as a way of studying response to pain, Zubieta and his associates enlisted a group of young, healthy volunteers. The subjects were randomized in a double blind trial in which they were given an injection of a radioactive tracer that binds to μ-opioid receptors. They then subjected the volunteers to moderate levels of sustained pain meant to simulate TMD pain by injecting their jaw muscles with a 5 percent saline solution. Another group received 0.9 percent saline solution and served as controls. The subjects rated their pain every 15 seconds and the saline infusions were controlled to keep the pain constant.

The brains of the subjects were then scanned using positron emission tomography (PET) in which areas with activation of μ-opioid receptors would light up in response to pain.

The subjects who were homozygous for the methionine gene had a more pronounced reaction to pain as revealed by the PET scan, compared with those who carried both the methionine gene and the valine gene the heterozygous individuals. Conversely, those who were homozygous for the valine gene were able to withstand more pain. The heterozygous individuals had a pain tolerance between the two groups.

Women experience chronic pain syndromes more frequently than men and are more sensitive to the effects of opiate drugs, Zubieta noted. Also, as noted, more women than men are affected by TMJ disorders and also fibromyalgia. "This may be due to a difference in their capacity to activate their pain response systems when estrogen levels are low," Zubieta said. He reported some evidence for this observation.

Using the same study design, Zubieta and his associates looked at the differences in μ-opioid activity between the sexes. A group of 14 men and 14 women were given the pain stimulus and a PET scan. While the sample size was small, the results showed significant sex differences in the activation of the μ-opoid system to the same levels of pain intensity compared with placebo controls. Men had larger magnitudes of μ-opioid activation than did the women, Zubieta reported.

TMJ patients while chewing, correlating motor regions of the jaw and tongue with the sensory regions in the brain, such as the somatosensory cortex that perceive these motions. Moreover, studies of TMJ patients can determine the responses of major brain areas involved in pain, not only the somatosensory cortex, but the thalamus, insula and anterior cingulate, and perhaps extend it to the limbic system and pick up signals from the amygdala that are associated with the emotional aspects of pain—its "suffering" component.

"There's a vast literature of fMRI in pain research that can be mined, once these technical problems are solved," he said. Hyde did not, however recommend immediately studying patients. Rather, "We should take advantage of this opportunity and study the normal TMJ in great depth."

New CT scanners to image TMJ disorders. New developments in computerized tomography offer the potential for improvements in visualizing the temporomandibular joint, said another speaker, Kieran Murphy of The Johns Hopkins Hospital in Baltimore. Traditional CT scanners use one beam detected by one series of x-ray detectors; the latest generations of these scanners have between 4 and 32 detectors and even larger arrays of detectors—up to 256—have been designed. "These machines will provide new diagnostic and therapeutic opportunities," he predicted.

Murphy, who specializes in brain and spine interventions and who described himself as a "plumber", is a radiologist who does close to 2,500 examinations a year, involving cardiac and vascular aneurysms.

He showed one CT scan of the temporomandibular area, but his principal message was to highlight new developments in multi-detector CT scanning that would enable us to "get wonderful 3-D fluoroscopy definitions of the entire temporomandibular joint, the mandible, and the skull base." There is a downside, however, in the increase in radiation exposure and the risk, though low, of a reaction to the ^{131}iodine contrast media. Radiation exposure is particularly important when focusing near the orbit of the eye.

Muscles at work. There are newer applications of magnetic resonance imaging in terms of muscle bioenergetics and function, said Russell S. Richardson of the University of California, San Diego.

"For the jaw to function, you need to be sure that muscles are working adequately. If you don't use a muscle for a period of time it will atrophy. So if there is inadequate jaw movement, you are going to end up with muscle-associated problems." Richardson said.

In his talk Richardson outlined a number of noninvasive techniques employing MRI and magnetic resonance spectroscopy (MRS) to assess the physiology and biochemistry of muscle. MRI scans show the joint in space; MRS indicates what chemicals are at work. "MRI gives you a map; MRS gives you a quantitative content of the chemical you are interested in. We use both," Richardson said.

Richardson described MRS studies of myoglobin, the protein in muscle that acts as an intracellular storage site for oxygen, to assess the intracellular partial pressure of oxygen. "Oxygen is obviously important. So if we can noninvasively assess how much oxygen is in a muscle at any given time, we have a pretty powerful tool," he said.

To gain an insight into the metabolic capacity of skeletal muscle both at rest and at work, Richardson studied volunteers who used their quadriceps muscle in the leg to extend the knee, taking blood samples from the radial artery and femoral vein to measure oxygen consumption in the muscle in the course of movement. These invasive studies are combined with the noninvasive studies, Richardson said, "to get a good handle on what's going on."

He then combined spectroscopy with other sophisticated techniques to assess blood flow metabolism. This enables you "to get at something very elusive: how do blood flow and metabolism match in muscle? You can have a perfectly adequate blood flow but inadequate metabolism, and vice versa, and you can be in trouble either way."

Although his studies involved the knee muscle, Richardson noted that the muscles that control jaw function are also skeletal muscles and their function is similar. As oxygen is essential for life and normal physiological function, the noninvasive MRS assessment of intracellular oxygen tension offers a unique view of muscle function and can easily be applied to the muscles that control jaw function, he said.

Brain Imaging of Pain in TMJ Disorders

While the pain that patients with temporomandibular disorders experience is often considered to be the end result of injury to the TMJ or the surrounding tissues, "there is considerable evidence that patients with TMJ diseases and disorders are intrinsically more sensitive to pain than healthy subjects. They experience a higher intensity of pain and a lower pain threshold," said Joel D. Greenspan of the University of Maryland in Baltimore.

Furthermore, there is also the well-known sex difference in patients with TM disorders. More women seek medical care for the problem than men, and women are more likely than men to report ongoing pain. "There may be physiological differences in pain signal processing that may explain the differences," he said.

Greenspan reported results from a study comparing TMD patients and healthy subjects. The study examined 25 female TMD patients, 25 healthy men, and 25 healthy women, age matched with a mean age of 39 years. The TMD patients had jaw and facial muscle pain lasting for at least 3 months, a pain frequency of 2 days a week, and a pain intensity of 2 on a scale of 0-10. Patients with a history of acute trauma, infections, joint disease, or other conditions were excluded.

The subjects' fingers were compressed using a small, computer-guided mechanical probe, which did not penetrate the skin. Threshold studies were done to determine the minimum force necessary to evoke pain in each individual. The probe was then applied repetitively, and subjects were asked to rate the pain intensity from the first to the fifth to the tenth sequence in the series, as well as their after-sensations.

There was a slightly lower threshold in women than men, but the difference was not significant. What interests Greenspan is the cumulative effect of repeated stimuli over a period of time—the temporal summation of stimulation. In this respect healthy women showed an increase in pain intensity compared to healthy men, but there was an even larger and significant difference in the TMD patients' temporal summation. "This enhanced temporal summation of pain suggests changes in the central nervous system processing of nociceptive (pain) signals potentially at the level of the spinal cord, brain stem, thalamus, or cerebral cortex," Greenspan said.

When the stimulus interval was increased from two seconds to five seconds and then to ten seconds, temporal summation decreased in all three groups. But it was still higher in the TMD patients than in the healthy subjects. If the interval was increased to 20 seconds, no one reported temporal summation.

"So we're demonstrating that there's some level of stimulation where we're not getting temporal summation; but also a difference in temporal summation and in the time course that occurs within the central nervous system," said Greenspan.

Ratings of after-sensations—how intensely subjects feel a lingering sensation of pain 15 seconds after a train of 10 stimuli—also revealed differences across the groups. While some men reported lingering sensations of pain, there was a small but significant increase in after-sensations experienced among the healthy women; but a much greater and significant increase in after-sensations in the TMD patients.

This suggests there is a general hyperexcitability in the nociceptive receptor system in the TMD patients, which we believe is happening early on, following the nociceptive input at the level of the spinal cord and brain stem, Greenspan said. This hyperexcitability likely contributes to the development or at least the maintenance of chronic pain in TM diseases and disorders, as well as the likelihood that other chronic pain problems might occur, he concluded.

In short, "If there is a sex difference and the women are showing greater temporal summation of pain, then it's easier for them to be upregulated to a pathologically hyperexcitable state—if that's a reasonable description of what we're seeing—and that would make them part of a more vulnerable population, those that are more sensitive, easily switched or upregulated into a condition where minimal amounts of pain are amplified so that you develop a chronic pain problem.

"But," Greenspan added, "I'm also obliged to point out that other regulatory factors are definitely involved in how people experience pain, including how their life experiences affect their perceptions of pain. As well, there's a sort of mutual effect of

local factors influencing nervous system processing and the pain experience that affects the various factors themselves. We've been focusing on one part of the story. It's an important part, but surely not the only part."

Pain and the brain. Pain is a personal experience. Different individuals exposed to the same level of pain rate the experience differently, and this raises the question: How can an outside observer, such as a doctor, appreciate the pain the patient experiences and how one patient's pain can be distinguished from another's?

With the help of functional magnetic resonance imaging, Robert C. Coghill of Wake Forest University School of Medicine in Winston Salem, NC, has provided an answer. He reported a study on 17 normal volunteers, eight women and nine men with no history of psychiatric or neurologic disorders. Each volunteer was subject to a heat stimulus of 49 degrees C on the back of the leg while fMRI scans were made of their brains. "What we found was a huge range in their reports of pain intensity. The most sensitive subjects rated it at 8.9 on a 10 point scale; the least sensitive rated it at 1.05 on the same scale, yet they had received exactly the same stimulus," Coghill said.

He then compared the fMRI scans of the brain regions that play a role in the processing of pain, including the primary somatosensory cortex (which responds to the location and intensity of the pain), the anterior cingulate, and prefrontal cortex, and found dramatically different responses between the two groups. Of the six individuals in the highly sensitive group, four activated the primary somatosensory cortex, whereas none of the six least sensitive individuals did. "They're probably activating it, but at a magnitude insufficient for us to detect," Coghill said.

Similarly, Coghill found that the anterior cingulate, associated with emotional responses, was activated in all six of the highly sensitive individuals, but in only one or two of the relatively insensitive group.

In the prefrontal cortex (associated with thinking and judging) the effect is somewhat less pronounced, but a significantly greater number of individuals in the highly sensitive group activate this area. What is important is that the magnitude of the activation is significantly greater in the highly sensitive groups than in the least sensitive group, Coghill said.

One surprise was that there was no significant difference between the two groups, either in the magnitude of the frequency or in the activation of the thalamus, a subcortical brain area which received signals from all the sensory systems of the body except olfaction. This suggests that a lot of the reported differences in individuals' experiences of pain happens beyond the thalamus at higher brain levels.

Again using the heat stimulus, Coghill manipulated subjects' expectations of pain by training them to expect a specific stimulus after a set time interval. They were told that the longer the time delay the more intense would be the stimulus; after 30 seconds they were told to expect a 50 degree C stimulus; after a 15 second interval a 48 degree C stimulus.

Two-thirds of the time, the subjects were given a 50 degree C stimulus after 30 seconds; one-third of the time, however, they received a 50 degree C stimulus after only 15 seconds. In these instances the subjects, expecting a 48 degree C stimulus but actually getting the 50 degree C stimulus, all reported a significantly lower pain response. This kind of experiment illustrates one way the placebo effect is assumed to work. Giving individuals a dummy or sugar pill and telling them it may make them feel better, may indeed have that effect because their expectations have been manipulated.

Interestingly, when the investigators looked at the fMRI scans of the volunteers, they found that the brain areas activated matched the level of pain reported. When the subjects were exposed to a 50 degree C stimulus after 30 seconds, there was robust activation of pain areas. But when they were given the 50 degree C stimulus after only 15 seconds—in the context of a decreased expectation of pain—there was no detectable activation in these areas. "So all of these areas are responding to a manipulation of the subjects' experience of pain," Coghill said.

"Individuals who report similar pain sensitivity exhibit similar patterns of brain activation. Given the fact that the differences we see between these individuals, combined with this expectation data, suggest that a lot of these individual differences rise above the levels of the thalamus and raises