



...changing the face of TMJ

TMJ Science

Joan Wilentz, Editor
Terrie Cowley, Contributing
Editor
Deanne Clare, Production
Manager

Copyright 2003 by TMJ
Science

TMJ Science is intended solely as an information resource for people with TMJ diseases and disorders. It does not constitute medical advice, nor is it a substitute for medical advice. Always consult your physician before starting treatment. The TMJ Association does not provide physician referrals.

The Association does not endorse any particular medical professional specialty or organization, nor do the opinions of a medical professional or organization referred to in *TMJ Science* reflect the opinions of The TMJ Association.

Send correspondence to:
Editor, *TMJ Science*
P.O. Box 26770
Milwaukee WI 53226-0770
Phone: 414-259-3223
Fax: 414-259-8112
Web site: www.tmj.org
E-mail: info@tmj.org

The TMJ Association is a non-profit tax exempt organization.

Photocopying the contents without permission is a violation of copyright laws. If you would like to reprint an article appearing in *TMJ Science*, please write to The TMJ Association and request permission.

Second Scientific Meeting of The TMJ Association

Joint and Muscle Dysfunction of the Temporomandibular Joint

In This Issue...

Preface.....	i
Scientific Meeting Program.....	1
TMJA Scientific Meeting Summary <i>Damaris Christensen</i>	5
Second Scientific Meeting of The TMJ Association Recommendations	17

Preface

The TMJ Association convened a superb conference in May 2002, bringing together investigators from many disciplines to focus on temporomandibular muscle and joint dysfunction. Their presentations and discussions took us a step closer to broadening the scope of scientific inquiry into TMJ disorders.

Another noteworthy aspect of the conference was the opportunity it gave investigators to hear firsthand the perspective of patients who suffer pain and dysfunction from TMJ disorders. Equally important was the opportunity for patients to hear firsthand the discussions by scientific experts.

While there remain more questions than answers about TMJ disorders and their management, I am confident that equation will be reversed. The National Institute of Dental and Craniofacial Research has begun building the research infrastructure needed to allow multidisciplinary teams of scientists to tease out the molecular and physiological basis of these complex disorders. Once we understand their biological basis, it will become possible to devise rational and targeted approaches for controlling and alleviating the pain and dysfunction that people with TMJ disorders confront on a daily basis.

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

Second Scientific Meeting of The TMJ Association

Joint and Muscle Dysfunction of the Temporomandibular Joint

The first national scientific meeting of The TMJ Association (Bethesda, Md. May 22-23, 2000) was designed to bring together an outstanding group of TMJ and non-TMJ scientists to focus on TMJ diseases/disorders. The intent of the organizers was to bring new perspectives and fresh ideas to the field, aware that there is no coherent body of knowledge on the etiology and pathogenesis of TMJ diseases, and hence little in the way of evidence-based treatment guidelines. The presenters reviewed the state of the science and developed a research agenda with an eye to attracting new talent and expertise from many disciplines to the field. The proceedings of the meeting were summarized in *TMJ Science*, the journal of The TMJ Association, and detailed in the journal, *Cells, Tissues, and Organs*, Vol. 169, No. 3.

It was evident to the attendees that TMJ problems should not be considered the sole province of dentists, oral surgeons or ear, nose, and throat specialists, but require the attention of experts in chronic pain, neuromuscular disorders, bone and joint disease, chronic immune and inflammatory diseases, endocrinology, genetics, development, bioengineering, and biomaterials. It was also evident that no single scientific meeting on TMJ could encompass the many basic and clinical disciplines needed to advance the field. Instead, the organizers agreed that future meetings should focus on selected aspects of TMJ disorders, while remaining committed to maintaining an integrated, broad-based, interdisciplinary approach to TMJ science. Accordingly, this second TMJ Association-sponsored scientific meeting has selected as its focus the role that osteoarthritis and muscle mechanics play in temporomandibular joint diseases/disorders.

Scientific Meeting Planning Committee

Chairman

Allen W. Cowley, Jr., Ph.D.
The Medical College of Wisconsin

Robert E. Baier, Ph.D., P.E.
University at Buffalo

Kenneth M. Baldwin, Ph.D.
University of California, Irvine

Kenneth D. Brandt, M.D.
Indiana University

Arthur W. English, Ph.D.
Emory University School of Medicine

Louis C. Gerstenfeld, Ph.D.
Boston University School of Medicine

Stephen L. Gordon, Ph.D.
Toucan Capital Corporation

Vincent C. Hascall, Ph.D.
Cleveland Clinic Foundation

Andrew H. Kang, M.D.
University of Tennessee

Stephen B. Milam, D.D.S., Ph.D.
University of Texas Health Science
Center, San Antonio

Christian S. Stohler, DMD, Dr. Med. Dent.
University of Maryland Dental School

The Second Scientific Meeting of The TMJ Association

Joint and Muscle Dysfunction of the Temporomandibular Joint

FASEB Conference Center
Chaired by Dr. Allen W. Cowley, Jr.
May 6-8, 2002

Welcome

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

Introduction and Opening Remarks

Terrie Cowley, President, The TMJ Association

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

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

Keynote Speaker - Clinical Perspective on TMJ

Stephen B. Milam, D.D.S., Ph.D., University of Texas Health Science Center, San Antonio

The Neurobiology of Craniofacial/Deep Tissue Persistent Pain: Report from a Pre-Conference NIH Symposium held in connection with the American Pain Society Meeting in March 2002

Ronald Dubner, D.D.S., Ph.D., University of Maryland Dental School

Session 1 - Osteoarthritis and Inflammatory-Immune Processes in Joints

Chairperson, Stephen B. Milam, D.D.S., Ph.D. University of Texas Health Science Center, San Antonio

Etiology and Management of Osteoarthritis

Kenneth D. Brandt, M.D., Indiana University School of Medicine

Nitric Oxide in Experimental Joint Inflammation: Benefit or Detriment?

Sharon M. Wahl, Ph.D., National Institute of Dental and Craniofacial Research

Genetics of Bone Development and Predisposition to Osteoarthritis

Bjorn R. Olsen, M.D., Ph.D., Harvard Medical School

Session 2 - Cartilage Degradation (Mechanics/Biochemistry/Metabolism)

Chairperson, Louis C. Gerstenfeld, Ph.D., Boston University School of Medicine

The Role of Friction and Adhesive Forces in TMJ Dysfunction

Dorrit W. Nitzan, D.M.D., The Hebrew University-Hadassah School of Dental Medicine, Jerusalem, Israel

Glycosaminoglycan Profiling by FACE – Monitoring Joint Tissue Degeneration and Repair

Anna H.K. Plaas, Ph.D., Shriners Hospital for Children, University of South Florida, Tampa

Molecular Mechanism of the Induction of Metalloproteinases 1 and 3 in Human Fibroblasts by Calcium Phosphate Crystals - Role of Calcium-Dependent Protein Kinase C- α
Herman S. Cheung, Ph.D., Miami VA Medical Center and University of Miami

Subchondral Bone and Bone Resorption in the TMJ: Is There a Role for Anti-resorbing Agents such as 17-Beta-Estradiol?
Helen E. Gruber Ph.D., Carolinas Medical Center

Subchondral Bone, Microdamage, and Trabecular Microfracture
David B. Burr, Ph.D., Indiana University School of Medicine

Session 3 - Microvascular Structure/Function of Synovial Joints and Mechanisms/Implications of Angiogenesis for Arthritis
Chairperson – Chris M. Storgard, M.D., Mayo Clinic, Rochester, Minnesota

Angiogenesis in Arthritis
Alisa Erika Koch, M.D., Northwestern University Medical School

VEGF and Bone
Ellen H. Filvaroff, Ph.D., Genentech, Inc.

The Role of Genetic Factors in Angiogenesis
Andrew S. Greene, Ph.D., The Medical College of Wisconsin

Angiogenesis: Necessary and Sufficient for Inflammatory Arthritis?
Chris M. Storgard, M.D., Mayo Clinic, Rochester, Minnesota

Session 4 - Clinical Symptoms and Current and Emerging Therapeutic Approaches
Chairperson – Sigvard Kopp, D.D.S., Ph.D., Institute of Odontology at Karolinska Institutet, Sweden

Mediator Mechanisms Behind Symptoms and Signs of Temporomandibular Disorders in Chronic Arthritis
Sigvard Kopp, D.D.S., Ph.D., Institute of Odontology at Karolinska Institutet, Sweden

Pathophysiological Mechanisms in Osteoarthritis Lead to Novel Therapeutic Strategies
Charles J. Malesud, Ph.D., Case Western Reserve University

Osteoarthritis of the Temporomandibular Joint: Bringing Research Findings to Clinical Practice
Howard A. Israel, D.D.S., Weill Medical College of Cornell University

Mesenchymal Stem Cells and Their Use for Regenerating TMJ Tissues
Arnold I. Caplan, Ph.D., Case Western Reserve University

Analgesic Effect of Elastoviscous Hyaluronan Solutions and the Treatment of Arthritic Pain
Endre A. Balazs, M.D., Matrix Biology Institute

Gene Therapeutic Targets in the Treatment of TMJ Arthritis
J. Edward Puzas, Ph.D., University of Rochester School of Medicine and Dentistry

Session 5 - Skeletal Muscles and the Jaw - Fatigue and Remodeling in Response to Loading

Chairperson, Kenneth M. Baldwin, Ph.D., University of California, Irvine

Sex Differences in Masseter Muscle Function

Arthur W. English, Ph.D., Emory University School of Medicine

How Do Hind Limb Skeletal Muscles Adapt to Chronic Increases in Mechanical Stress?

Kenneth M. Baldwin, Ph.D., University of California, Irvine

IGF-I Restores Satellite Cell Proliferative Potential in Immobilized Old Skeletal Muscle with Aging

Frank W. Booth, Ph.D., College of Veterinary Medicine, University of Missouri-Columbia

Human Extraocular, Jaw-closing and Laryngeal Muscles: How Different are they from their Counterparts in Limb and Abdominal Muscle?

James J. Sciote, M.S., D.D.S., Ph.D., University of Pittsburgh School of Dental Medicine

Neuromuscular Strategies for Control of Tongue Movement

Alan J. Sokoloff, Ph.D., Emory University School of Medicine

TMJ Patient Presentations

William Wright, spouse of a TMJ patient, Virginia

Leslie Wright, Virginia

Linda Hoover, Ohio

Marion Blackburn, North Carolina

Kevin Clark, spouse of a TMJ patient, Wisconsin

Gerry Segelman, New York

The TMJ Association gratefully acknowledges the following agencies, corporations, and individuals for their support of the Second Scientific Meeting of The TMJ Association.

National Institute of Dental and Craniofacial Research

The National Institute of Arthritis and Musculoskeletal and Skin Diseases

The National Institute of Biomedical Imaging and Bioengineering

The National Heart, Lung and Blood Institute

Office of Research on Women's Health (NIH)

Federation of American Societies for Experimental Biology (FASEB)

Procter & Gamble Company

Shaker Family Foundation

The TMJ Association would like to thank Dr. Martin Frank, Ms. Linda Allen, and Ms. Aira Sumpter for their assistance to the Association in coordinating this meeting at the FASEB Conference Center, and the TMJ patients who made presentations as well as the many for whom the conference offers hope through research.

Support for this research was provided from grant 1R13DE014542-01 from the National Institute of Dental and Craniofacial Research PI, Dr. Allen W. Cowley, Jr., Ph.D.

JOINT AND MUSCLE DYSFUNCTION OF THE TEMPOROMANDIBULAR JOINT

By Damaris Christensen

Introduction

Constant pain, an inability to open her mouth wide enough to eat, migrainous headaches, repeated surgeries, and defective jaw implants make Linda Hoover a model for many patients who suffer from serious jaw disorders. At one point, the constant pain made her suicidal, she said at a recent conference. Surgery to replace her defective jaw implants with rib grafts solved some of her problems, and, despite continued pain, Linda can now eat and continues to teach.

Disorders and diseases of the jaw are estimated to affect some 10 million adults in the US. Most of those who seek treatment are women in their reproductive years. The condition can be relatively mild and resolve over time or it can progress to severe jaw malfunction and intractable pain. Diagnosis is typically based on signs and symptoms ranging from occasional discomfort in the temporomandibular joint (TMJ) and surrounding tissues to debilitating pain and, as in Linda's case, severely compromised jaw function. Since the jaw is involved in such vital activities as breathing, talking, chewing and swallowing, serious cases can lead to severely restricted diets, disrupted sleep, and pain. The combination of pain and dysfunction can force patients to quit work and withdraw from normal social activities.

A diagnosis of temporomandibular diseases/disorders, commonly referred to as TMJ, can encompass a multitude of signs and symptoms, including persistent pain in the face, jaw joint area, or associated muscles, limited mouth opening, grating sounds when opening and closing the jaw, dizziness, and other complaints. This wide range of presentations makes simple definitions of temporomandibular diseases/disorders almost impossible and, to most researchers, suggests that "TMJ" actually represents a family of disorders with overlapping but not identical features. Trauma or arthritic conditions underlie some cases of TMJ disorders, but many other cases have unknown causes.

Scientists and patient advocacy organizations like the Milwaukee-based TMJ Association are pressing for better understanding of these disorders. In part to accomplish this goal, and specifically to try and understand the role that osteoarthritis and muscle disorders may play, The TMJ Association sponsored its second scientific conference, held May 6-8, 2002, at the campus of the Federation of American Societies for Experimental Biology in Bethesda, Md.

"Triumph is 'try' plus 'oomph,' Linda told the scientists assembled at the meeting. "We'll continue to try, and hope that you can provide us with the scientific 'oomph'

we need to get better treatments and overcome this problem.”

* * *

TMJ Clinical Perspectives

“The temporomandibular joint is an extraordinary joint about which we know extraordinarily little in terms of pathology and normal function,” said Allen W. Cowley, Jr., chairman of the meeting and a professor at The Medical College of Wisconsin.

The temporomandibular joint is the only joint in the body that can slide and also work as a hinge, said keynote speaker Stephen B. Milam, of the University of Texas Health Science Center at San Antonio. It is also the only paired joint. The left TMJ works in tandem with its counterpart on the right, linked by the U-shaped bone of the lower jaw, the mandible. Milam summarized what is known about the normal joint and about TM diseases and disorders. The biochemistry and immunohistochemistry of the bones and tissues in the TM joint have largely been elucidated, he noted, but many scientists are unaware of the existence of such data—which is why it is important to bring non-TMJ scientists to meetings like this one, he added. In addition to the joint’s unique movement capability, Milam noted the presence of estrogen receptors in joint tissue, as well as in joint-related areas of the central nervous system. Some researchers believe that these receptors may account for the apparent preponderance of women as sufferers of painful TMJ disorders.

The TM joint is exceptional also with regard to an inherited disorder called Hunter-Thompson chondrodysplasia, in which the vertebral segments of the spine and the jaw joints are spared, while all other joints are significantly abnormal. “This suggests that the TM joint might differ significantly from other joints in the body with respect to its development and response to injury,” Milam said. The jaw also has considerable adaptive capacity,

as compared, for example, to the hip joint, and at least in young people, has been shown to regenerate. He cited the example of a 10-year-old whose mandibular condyle (the lower bony component of the TM joint) was seriously displaced as a result of a fracture sustained in an accident. Within four years, the displaced joint segment dissolved and was replaced by normal structure. However, because relatively few tissue samples have been collected during procedures to treat TMJ problems, and because of a lack of good animal models for TMJ disorders, researchers trying to understand what might go wrong in the TMJ must rely largely on information about osteoarthritis gathered from other joints.

Osteoarthritis Perspectives

And that may be folly. “What we know about knee osteoarthritis can only be transferred to other joints, like the TMJ, with considerable danger,” cautioned Kenneth D. Brandt of the Indiana University School of Medicine. Major risk factors for osteoarthritis include female sex, obesity, and increasing age, along with injury to the joint, repetitive stress, and some developmental defects. “Osteoarthritis is the most common joint disease in mankind,” he said. He stressed that osteoarthritis should be considered an *organ* disease—involving joint cartilage, the joint capsule, which contains synovial fluid and is lined by a synovial membrane, and associated tendons, ligaments, and muscles.

Pain not correlated with pathology. The key to therapy for osteoarthritis today, Brandt emphasized, lies in non-pharmacologic measures, including educating the patient in ways to protect the joint, exercises to increase the joint’s range of motion and strengthen muscles, weight loss in the case of obesity, and palliative measures, such as applications of heat. He noted that drugs used to treat arthritis pain and reduce swelling, even the newer selective anti-inflammatory agents, decrease pain by only 20 to 25

percent and are not risk-free. He suggested that they be kept as secondary options. Moreover, researchers studying osteoarthritis have been unable to correlate joint pain—the primary reason people seek help from their doctors—with progressive loss of cartilage over weight-bearing areas, bone loss, or inflammation. Interestingly, cartilage tissue does not contain nerve endings, so the pain of arthritis originates elsewhere in the joint.

Inflammation and Immune Responses

The arthritic conditions that develop in the TMJ, and in any other joint, may be based on local or systemic inflammatory processes that may cause tissue destruction as well as pain. Local nerves responding to painful stimuli in the TMJ can release chemicals that contribute to swelling and inflammation. A pain-associated neurotransmitter called neuropeptide Y has been found in the synovial fluid of the temporomandibular joint of patients with TMDs, said Sigvard Kopp of the Institute of Odontology at the Karolinska Institute in Sweden. Increased concentrations of this neuropeptide seem to be associated with increased pain, reduced joint mobility, and decreased blood flow, along with signs of bone destruction, he said. Other compounds found that seem to be linked to more severe disease include higher concentrations of TNF-alpha, an immune signaling molecule or “cytokine” that can lead to inflammation, and the neurotransmitter serotonin, which can sensitize nerve endings to pain. In one study a drug that blocks TNF-alpha reduced joint pain among 19 patients with TMD, he said, and it is possible that blocking these other compounds might also help patients.

Preventing programmed cell death. At the molecular level, osteoarthritis can be characterized as an imbalance between signaling factors that cause cartilage destruction and those that stimulate cartilage synthesis, said Charles J. Malemud of Case Western Reserve

University School of Medicine in Cleveland. He noted that when cartilage is stressed by mechanical forces, the cells that compose the cartilage tend to produce chemicals—such as caspases and the cytokines TNF-alpha and IL-1 beta—that ultimately trigger programmed cell death, a process called apoptosis. He too suggested that blocking these chemicals with drugs or other compounds might benefit TMJ patients. Similar strategies have already helped patients with rheumatoid arthritis, he added.

Role of nitric oxide. Recently, researchers using animal models have implicated higher-than-normal levels of an immune system mediator, nitric oxide, with increasing joint pain. This enzymatic chemical messenger is released in response to injury or inflammation and can help to destroy infectious bacteria. Nitric oxide also serves as a signaling molecule in inflammation. It can be produced by three different enzymes, one called endothelial nitric oxide synthase (eNOS), another called neuronal nitric oxide synthase (nNOS), and a third called inducible nitric oxide synthase (iNOS). In animal models of osteoarthritis, inhibiting iNOS worsened symptoms, but inhibiting eNOS and nNOS reduced swelling, inflammation, and tissue breakdown in the joints. Tissue cultures of cells taken from diseased temporomandibular joints show increased iNOS, but no one has yet looked for eNOS and nNOS, and these enzymes might play a role in the progression of TMD, said Sharon M. Wahl of the National Institute of Dental and Craniofacial Research in Bethesda. “It is certainly a place for additional research,” she said.

Genetic Factors and Susceptibility

Each end of the jaw bone is rounded into a mandibular “condyle,” which fits into a depression in the temporal bone of the skull called the temporal fossa. Both the condyle and the fossa are covered with cartilage, composed largely of a fibrous connective tissue protein, collagen, which comes in different forms. A fibrocartilaginous oval

disc further acts as a shock absorber between the condyle and the fossa.

Research suggests that genes can predispose people to osteoarthritic disease, said Bjorn R. Olsen of the Harvard School of Dental Medicine in Boston. Mice with one defective version of a gene that codes for a component of a collagen 11 protein show signs not only of knee osteoarthritis, but of jaw joint problems as well. Conceivably, such mice might be useful animal models of human temporomandibular diseases. In addition, he noted that patients with mutations of the collagen 11 gene suffer joint disorders called Stickler-like syndromes. It's possible, he said, that people with Stickler-like syndromes also have previously unrecognized involvement of the temporomandibular joint. If osteoarthritis of the human TMJ is caused by underlying defects in collagen, treatment strategies that minimize the effects of these defects may help ward off symptomatic disease.

I. Recommendations: Clinical Perspectives, Immunology, and Genetics

Clinical Perspectives

- Study the cellular and molecular composition of the articular tissues of the TMJ.
- Develop accurate means of assessment and categorization of patients using standardized techniques to enable comparisons of patients.
- Establish a National TMJ Registry of TMJ patients with appropriate privacy safeguards, to serve as a source of clinical data and of patient volunteers for clinical studies.
- Develop mutant, transgenic, chemical or trauma-induced animal models of TMDs and osteoarthritis to determine how these varied derangements affect cellular, biochemical, and molecular changes in joint tissues and signaling pathways.

Inflammation and Immunology

- Determine the turnover dynamics of the cartilage in a normal TMJ and that of patients with dysfunction.

- Explore the role of apoptosis in cartilage degeneration of the TMJ.
- Determine the roles that nitric oxide formation and the generation of reactive oxygen and nitrogen species play in TM joint and muscle inflammation.
- Explore cytokine-modulating therapeutic strategies that have proven clinically efficacious in rheumatoid arthritis for use in treating TMD and osteoarthritis (OA).

Genetics

- Study genetic mutations, such as those affecting various forms of collagen, as risk factors for TMJ diseases.

Note: Recommendations for other types of genetic studies are found in other sections of this report.

* * *

TMJ and Deep Joint Pain

As in the case of osteoarthritis patients, it is the chronic and persistent pain in and around the temporomandibular joint that drives patients to seek medical help. Pain is a huge issue in TMJ, noted Ronald Dubner of the University of Maryland Dental School. He reported on the findings from a satellite symposium on the neurobiology of craniofacial and deep tissue persistent pain held in conjunction with the annual meeting of the American Pain Society (APS) in March 2002. The symposium was sponsored by the APS, the National Institute of Neurological Disorders and Stroke, and the Office of Rare Disorders of the National Institutes of Health.

"Persistent pain involves changes that take place both at the site of injury and in the central nervous system, a combination of peripheral sensitization and central sensitization," he said. Cutaneous pain is localized, typically involves tissue damage, and is rarely referred to other areas, while deep tissue pain is diffuse, aching, or burning, often triggered in response to innocuous stimuli, and may be referred to skin sites. Much more is known about the molecules

and mechanisms underlying cutaneous pain than about deep tissue pain, Dubner noted, including the existence of descending pathways in the brain and spinal cord that can inhibit cutaneous pain. These pathways are less operative in deep tissue pain which, in contrast, can spread to other sites producing co-morbid painful conditions. Such facilitation of pain might account for the clinical observation that some TMD patients report low back pain, fibromyalgia, irritable bowel syndrome, or pelvic pain. To address the research challenge, pain researchers are using a variety of models of deep muscle pain to shed light on pain associated with TMD. These include repeated injections of saline and short-term injections of mustard oil, carrageenan, and Complete Freund's Adjuvant, all of which can induce excessive pain or hyperalgesia.

The potent neurotransmitter glutamate seems to be more active and triggers greater nerve cell activity signaling pain in these models than in models of cutaneous pain. Scientists have also reported a number of other biological signals associated with chronic deep pain. For example, nerve growth factor (NGF) seems to play a role in the maintenance of persistent pain. NGF is elevated in the synovial fluid of arthritic joints, in the spinal fluid of fibromyalgia patients, in inflamed muscle tissue, and in the carrageenan pain model in animals. Immune system proinflammatory cytokines are elevated in people with TMD, bone cancer, and neuropathic pain, and these molecules can directly excite nerve endings. A lowered pH, indicating an increase in acidity, is associated with inflammation and pain in deep tissues, Dubner said, noting that there is new interest in acid-sensing channels and a class of receptors sensitive to heat and pH levels.

Gender differences. Diseases that involve chronic pain, including arthritis and TMD, are more common in women than men, and animal studies have confirmed that there are sex as well as genetic differences in how males and

females of various species respond to pain. Human studies indicate that men and women also differ in response to various forms of opiate drugs given to control pain. Some sex differences may be related to the estrous cycle, but researchers are also teasing out other cellular and molecular responses to pain that may account for women's increased sensitivity to chronic deep tissue pain. "These sex differences are real, and they play an important role in deep pain situations," Dubner said.

Scientists at the pain symposium reported on different techniques for imaging the brain's responses to painful stimuli. These studies demonstrate that the experience of pain stimulates areas of the brain well beyond the sensory-motor areas to include sites associated with motivation, attention, cognition, and emotion.

The Role of Jaw Muscles

More sex differences? Muscles are made up of tiny individual fibers, called myofibrils, bundled together and separated from larger bundles by tendons and nerves. The fibers come in a variety of slightly different shapes and compositions, which, interestingly, may differ in composition in some animals depending on whether the animal is male or female, said Arthur W. English of Emory University School of Medicine in Atlanta. During activation of the chewing muscles of the jaw, the masseters, the teeth, jaws, and temporomandibular joints in male rabbits experienced higher pressures, or loading, than did the teeth, jaws, and temporomandibular joints in females, he reported.

It is not clear whether that is the case in people, because it is very difficult to measure loading of the temporomandibular joints. In terms of the main fiber types making up human masseters, normal jaw muscles look a lot like atrophied limb muscles, said James Sciote of the University of Pittsburgh School of Dental Medicine. The size of muscle fibers varies greatly from person to person, and

even from patient to patient, he noted. It's possible that the profound human variability in muscle types affects a person's susceptibility to TMD and other jaw disorders, but even then it is not clear whether the variation is a cause or an effect of normal function or malfunction.

If hind limb muscles in animal models are subjected to higher-than-normal stress, the total protein content increases over time, while the concentration of myofibrils was initially reduced but eventually rebounded to normal, said Kenneth M. Baldwin of the University of California, Irvine. He suggests that initial trauma might impair the myofibril's ability to respond to stress. If the structure and function of jaw muscles contribute to joint stability, he said, then the possibility exists that strengthening jaw muscles might protect the joint. He proposed further studies to see if exercises could relieve pain or improve muscle function.

Muscles that are not used atrophy, but with renewed use, muscle mass can be restored, more so in younger animals and people than in older ones. Frank W. Booth of the University of Missouri-Columbia and his colleagues showed that directly applying a growth factor, insulin-like growth factor 1, onto atrophied leg muscles in rats rescued up to half of the muscle mass lost by immobilization, and increased the ability of muscle cells to divide.

Each muscle fiber is innervated by a particular neuron. This pairing of a neuron with its muscle fiber is called a motor unit. Typically, movement is thought to be controlled through the selection and activation of individual muscles, said Alan J. Sokoloff of Emory University in Georgia. Studies of independent movement of regions of the tongue suggest that motor units can be activated based on location rather than fiber type or muscle compartmentalization. "There are probably multiple different ways of organizing motor units," Sokoloff said. Understanding how jaw muscles are controlled will help researchers understand what might be going wrong in

patients with temporomandibular disorders and potentially lead to new treatments.

II. Recommendations: Deep Tissue Pain and the Role of Jaw Muscles

Deep Tissue Pain

- Elucidate the basic mechanisms of persistent TMJ pain and develop biomarkers of pain.
- Refine and test diagnostic approaches to allow electrical detection thresholds in the region of the TMJ to differentiate pain originating from the joint versus the muscle.
- Apply pain-imaging techniques to the study of TMJ patients.
- Explore the basis of co-morbidity of pain disorders in TMJ patients.
- Study the role of Nerve Growth Factor in chronic pain conditions.
- Study the role of newly cloned peripheral pain receptors in muscle and joint inflammation.
- Explore the use of proinflammatory cytokines as biomarkers of injury-associated TMJ pain.
- Determine the role of central nervous system glial cells in central sensitization associated with deep tissue injury.
- Conduct studies to confirm observations that there is no correlation between joint pain and cartilage degeneration. If confirmed, explore reasons for this dissociation.

Role of Jaw Muscles

- Refine methods to measure the forces exerted by the jaw muscle to determine how heavily the temporomandibular joint is loaded.
- Develop animal models to address how jaw structure and load affect muscle remodeling and may contribute to disease.
- Study the role of cytokines and other inflammatory processes in TMJ muscles during trauma.
- Determine if human masseter muscle types vary by sex and according to clinical characteristics.
- Conduct studies of the regulation of various motor units within cranial muscles such as tongue and masseters

and determine how this control is integrated centrally.

- Determine the extent to which pain contributes to the recruitment of motor units and whether distortions of masseter muscles, tongue, and larynx contribute to pain in TMJ patients.
- Determine whether information about other joints such as the knee and hip with respect to associated muscle remodeling can be applied to the TMJ.

* * *

Altered Blood Flow in Arthritis

The growth of new blood vessels—angiogenesis—in joints characterizes many rheumatic diseases, such as rheumatoid arthritis. The increased blood vessel density may allow additional inflammatory mediators, including white blood cells, to populate the joint, leading to increased swelling and pain. In animal studies and in people, higher blood concentrations of markers for compounds that induce angiogenesis such as vascular endothelial growth factor, or VEGF, or that mediate blood vessel growth, such as the alpha v beta 3 integrin, seem to predict later disease progression. In animal models, compounds that block angiogenesis, such as the immune signaling molecule interleukin 4 (IL-4), seem to decrease the severity of arthritis, said Alisa E. Koch of Northwestern University Medical School in Chicago.

Inhibiting the alpha v beta 3 integrin marker and regulator of angiogenesis alleviates disease severity in both early and late arthritic disease in a rabbit model of arthritis, said Chris M. Storgard of the Mayo Clinic in Rochester, Minn. In fact, blocking alpha v beta 3 integrin reduced symptoms more than treatment with the potent immunosuppressant, cyclosporine, which reduces the presence of white blood cells in the diseased joint, he said. “Angiogenesis may be necessary for and sufficient to induce arthritis,” he concluded.

“There is a highly developed system of blood vessels that serves the

temporomandibular joint,” said Andrew S. Greene of The Medical College of Wisconsin. He pointed out that many of the same factors associated with TMDs, such as female sex, injury, joint stress or mechanical factors, also are associated with increased angiogenesis. “Does genetic susceptibility to angiogenic stimuli play a role in susceptibility to TMD?” Greene asked. While he could not answer the question directly, Greene has shown that in rat models, components of a signaling pathway that regulates blood pressure affect compounds that trigger new blood vessel growth. “We need to be very clear not only to concentrate on agents that are important in angiogenesis in other tissues and conditions, but also look for additional factors,” he said.

All these studies suggest that inhibiting angiogenesis might benefit patients with arthritic disease of the TMJ. “However, there’s a trade-off if you try to inhibit VEGF or other compounds that stimulate angiogenesis,” cautioned Ellen H. Filvaroff of Genentech, a biotech company in South San Francisco. She and her colleagues have found that inhibiting the growth of new blood vessels also inhibits new bone growth. In animal models, blocking VEGF slowed or completely inhibited bone repair after fractures or bone damage. However, in mice and rabbits, slow release of VEGF near sites of fracture or bone damage accelerated wound repair. The trick will be in developing ways of increasing angiogenesis in bone but not in cartilage or in the fluid surrounding the joint, Filvaroff said.

* * *

III. Recommendations: Microvasculature and Angiogenesis in Joint Disease

- Determine if angiogenesis plays a role in TMJ disorders and the development of arthritis in this joint.
- Test whether anti-angiogenesis agents offer a therapeutic benefit in inflammatory arthritis of the TMJ.
- Elucidate the mediators of angiogenesis in TM joints.
- Determine the vascular phenotype in TMJ.

- Determine if angiogenic markers can predict disease progression in TMJ patients.
- Explore whether genetic susceptibility to angiogenic stimuli plays a role as a risk factor affecting the TM joint and related musculature.

* * *

Current and Future Therapies

Many speakers proposed therapies for TMDs on the basis of clinical observations of various pathophysiologic changes. Some of these approaches are in use today; others await further research, development, and clinical testing.

Arthrocentesis. The synovial fluid in the joint cavity between the mandible and temporal bone is composed of phospholipids and hyaluronic acid, a medium that enables almost frictionless sliding between the disc and the fossa, noted Dorrit W. Nitzan of the Hadassah School of Dental Medicine in Jerusalem. If this lubrication system fails, perhaps because of high oxidative stress, friction causes the disc to lag behind and separate from the condyle. Over time, this can lead to disc displacement. In some cases of temporomandibular disorders, individuals are completely unable to move their jaws, she said. Such serious symptoms may be due to a very thin film of fluid that causes adhesive forces to bind the flexible disc to the fossa. Simply flushing the joint area with saline and then removing the excess fluids (a process called arthrocentesis) can result in dramatic improvements in jaw motility, she said.

Glucosamine treatment. The body has a number of mechanisms to repair damage to the soft tissues in joints—which includes complex molecular components of cartilage such as proteoglycans (PG), and of synovial fluid, such as hyaluronic acid (HA). However, if these normal, healthy responses to injury become chronic, they can lead to severe and irreversible tissue destruction. In particular, the chemical composition of

PG changes in response to a number of factors, including stress on the joint, and may serve as a marker for early arthritic disease, said Anna H.K. Plaas of the University of South Florida in Tampa. She reported on a method of quantifying the contents of these complex tissue molecules. In animal studies, injury to the knee joint typically leads to a marked increase of PG containing chondroitin sulfate and dermatan sulfate. If the injured animals were fed glucosamine, however, these responses could be blunted, resulting in a tissue composition closer to the pre-injury normal state. She conjectured that these findings might explain the anecdotal evidence of the effectiveness of dietary glucosamine in treating human OA. However, the long-term effects of glucosamine on joints and joint function were unclear and might even be detrimental, she cautioned.

Calcification. In many forms of osteoarthritis, the soft tissues in the joint become calcified, or filled with calcium-containing crystals, said Herman S. Cheung of the University of Miami. This calcification may be as common in the TMJ as in other joints, he suggested, giving rise to pain and promoting further joint degeneration. Cheung and his colleagues have worked out two independent molecular pathways through which calcification can trigger joint pain and degradation. Understanding such underlying pathways might ultimately lead to ways of preventing or treating joint damage.

Increased bone density. Most clinical findings show an association between degenerative joint disease and increased bone density, said David B. Burr of Indiana University School of Medicine in Indianapolis. The denser the bone, or the more calcified the overlying cartilage, the more stress seems to be placed on the cartilage, he said, perhaps predisposing the joint to damage. His studies have shown that calcified cartilage may even be denser and stiffer than the bone underneath, Burr said. “Now that flies in the face of tradition.” He notes that

cartilage can overlies several different types of bone and that each type of bone may respond differently to stress. Tiny cracks or "microdamage" in the layer of bone underlying the cartilage and in calcified cartilage may accelerate the normal process of bone resorption and formation, and such stimulation has been linked to bone degradation. Indeed, while it had been thought that microfractures in spongy bone did not play a role in joint degeneration, studies now indicate that calcified cartilage and microdamage may be highly significant and should be explored in greater detail.

Emerging evidence suggests that damage to the bone just underlying cartilage may actually precede damage to the cartilage itself, both in arthritis and in temporomandibular disorders, said Helen E. Gruber of the Carolinas Medical Center in Charlotte, N.C. In the process of normal turnover, bone is constantly being resorbed by cells called osteoclasts and reformed by cells called osteoblasts. However, as many as half the patients with temporomandibular disorders may have severe destruction of bone in the condyle and fossa, suggesting that the balance between osteoclasts and osteoblasts has swung in favor of destruction. Osteoporosis, a degenerative disease characterized by low bone density, seems to be a risk factor predisposing people to TMD, and patients with osteoporosis are less likely to have good outcomes after surgery to improve joint function, she said. A number of anti-resorption agents, including the hormone estradiol, merit further study to see if they can benefit patients with TMD, Gruber concluded.

Hyaluronan derivatives. Some studies indicate that joint injections of solutions of high-molecular-weight hyaluronan, one of the proteoglycans in synovial fluid, can control pain in arthritic joints of animals and people, said Endre A. Balazs of the Matrix Biology Institute in Ridgefield, N.J. Hyaluronan and related compounds have been approved for use in the U.S. to treat arthritic knee pain, though not all scientists are convinced that hyaluronan

has a beneficial effect. Recently, scientists have shown that another elastoviscous solution containing hylan, a derivative of hyaluronan, decreases activity of ion channels and can desensitize pain receptors so that it too might offer some benefits to TMJ patients, Balazs said.

Tissue engineering. Work in tissue engineering raises the hope of regenerating, rather than repairing, damaged bone and cartilage in adults, said Arnold Caplan of Case Western Reserve University. In adults, so-called mesenchymal stem cells can divide and give rise to bone and cartilage, among other cells. Mesenchymal stem cells can be grown in culture, but in order to grow them as tissues, researchers need to develop the appropriate scaffolds to get the cells to cluster into the needed shapes. An Italian company called Fidia Advanced Biopolymers is using hyaluronan and related compounds to make scaffolds that will break down in the body yet, in culture, provide a frame for and induce these stem cells to turn into cartilage and bone. In goats, such systems can heal damage induced by wear and tear on an injured joint, Caplan said. He cautioned, however, that the composition of cartilage is different in every joint area and it isn't clear exactly what type of cartilage these mesenchymal cells will differentiate into.

Gene therapy. Finally, treatment insights may come from gene therapy and research on animal models of TMD, said J. Edward Puzas of the University of Rochester School of Medicine in Rochester. A mouse engineered to produce large quantities of the human gene for TNF-alpha seems to undergo changes that mimic arthritic TMD, he said. These transgenic animals have higher than normal concentrations of proteins that break down connective tissue and bone in their joints. Puzas and his colleagues found that they could interfere with this cycle and prevent bone loss by blocking a compound called NF κ B. So far, mice treated with gene therapy to block

NF_KB have shown no side effects, though it is too early to see if the treatment was effective in reducing tissue degradation and pain, Puzas said.

* * *

IV. Recommendations – Current and Future Therapies

- Study the reputed *in vivo* effectiveness of chondroitin sulfate and glucosamine hydrochloride therapy in human degenerative TMJ disorders to determine efficacy and underlying mechanisms of action.
- Determine the role of subchondral bone loss in the natural history of TMD. New approaches and techniques are required to study the events associated with condylar resorption.
- Determine if osteoporosis is an added risk factor in TM disease and detail the relationship between bony degenerative changes and TMD symptomatology.
- Determine if agents that reduce bone resorption have a place in TMD therapy.
- Study the biochemistry of mineral deposition involved in calcification of joint soft tissues.
- Detail the causes and effects of the accumulation of microdamage and microfractures in subchondral bone on joint degeneration.
- Apply principles of tissue engineering using mesenchymal stem cells to regenerate bone, cartilage, muscle and tendon, and develop ways to deliver these cells for the repair or regeneration of injured temporomandibular structures.
- Expand efforts to develop material suitable for the reconstruction of diseased TMJs.

* * *

Educating Health Professionals

Treatment of TMJ has been beset with failures, said Howard A. Israel of the Weill College of Medicine at Cornell University. In the 1970s and 1980s, many physicians surgically treated patients with TMJ to move discs back into place. Since then, however, it has been shown that disc

derangement is not necessarily linked to symptoms of disease and may be common in asymptomatic people. Similarly, surgeries to replace defective jaw joints led to terrible outcomes for many patients whose implants failed. Understanding such failures is important before trying to put new therapies in place, Israel said. Using osteoarthritis as a model, researchers are beginning to think that the mechanical problems of the TMJ follow, rather than cause, the cartilage and bone destruction.

“It is critical to establish the diagnosis before treatment,” he said. “A damaged joint can do any one of three things: have pain, a limited range of movement, or clicking. Regardless of the pathology, the end result is going to be very similar.”

Future treatments, Israel said, would probably rely on tissue engineering rather than on total joint replacement. Minimally invasive therapies like arthroscopy or arthrocentesis and using drugs to block pathologic mechanisms also hold promise. “Clinicians must make decisions based on sound science,” he emphasized.

V. Recommendations: Educating Health Professionals

- Develop new approaches for information transfer including ways to enrich health professional school curricula and continuing education programs with state-of-the-science knowledge on the TM joint and its diseases and disorders to meet the critical need at this time.
- Evaluate for safety and efficacy current treatment approaches for TMDs, especially invasive and irreversible procedures such as surgical disc repositioning and joint replacement.

* * *

What the Patients Said

Many of the patients who spoke at the meeting discussed their difficulties dealing with physicians who were either unaware of the science or—as in the case of the defective joint implants—who were

providing the standard of care at that time, only to find that the solution turned out to be worse than the initial problem. Both patient advocates and scientists speaking at the meeting highlighted the need to establish a foundation of quality science to translate into clinical practice as soon as possible.

“What’s unique about this meeting is the participation of patient advocates,” said Lawrence Tabak, director of the National Institute of Dental and Craniofacial Research in Bethesda. “I think that will add an element that will be very important. It is important for investigators to hear from patients and for patients to hear from investigators,” he said, and that happens at relatively few medical meetings.

Among the urgent research needs for people with TMJ are standards for pain management, clinical and basic science to gain an understanding of TMJ diseases/disorders, and suggestions for proper nutrition, said William Wright, husband of a woman who has suffered from TMJ problems for more than a decade. Many patients have difficulty eating and even those who can eat normal foods often must chew strangely and are embarrassed to eat in public. The odd diet of many patients seems to promote weight gain and metabolic abnormalities, he said.

“I was lucky and sidestepped over-treatment,” said Marion Blackburn of Greenville, N.C., whose pain and dysfunction are largely under control. “But many patients do not. There is no standard to test and identify these disorders, no standard of care, and pitifully few studies of appropriate quality to guide treatment decisions,” she said. “Your work will likely have a clear and immediate impact . . . to lead the way to a brighter future for TMJ patients.”

“I’m really hopeful that some day there will be cures,” agreed Gerry Segelman, who has had TMJ for 15 years, has experienced severe chronic pain, and undergone multiple surgeries, including

various implants. “For us, it’s a matter of getting through not only the pain but mourning the loss of our health and our great lives. . . . We really need to focus some serious time and some serious money on education of primary care doctors and dentists. It’ll help both the patients and doctors.”

“The reality of TMJ is not understood by people who do not live it,” said Terrie Cowley, founder of The TMJ Association. “This is a complicated, multifaceted disease that takes a toll on the sufferer and society. The hope of the patients is in quality science that will unravel the mysteries of TMJ and yield safe and effective treatments which will improve the quality of health care and lives of TMJ patients, and ultimately lead to a cure and prevention.”

* * *

THE SECOND SCIENTIFIC MEETING OF THE TMJ ASSOCIATION – RECOMMENDATIONS

Joint and Muscle Dysfunction of the Temporomandibular Joint

I. Recommendations: Clinical, Immunology, Genetics

Clinical Perspectives

- **Determine the unique features of the TMJ that may contribute to understanding basic mechanisms of disease and lead to the development of effective therapies, including the design of prostheses.** Studies are needed to characterize the cellular and molecular composition of the articular tissues of the TMJ, which appear to differ significantly from other load-bearing joints. Developmental regulation as well as responses to injury may also distinguish the TMJ significantly from other load-bearing joints. The extent to which these differences contribute to disease susceptibility is unknown and should be explored.
- **Use advanced technology to collect baseline data on the composition of the soft tissue components in the normal human TM joint and changes associated with aging.** Methods for obtaining normal human tissue need to be developed. Rapid sampling and processing of cadaver tissue are required and advocacy efforts are needed to improve collection and delivery of tissue. These studies can make use of techniques such as Fluorophore-based carbohydrate electrophoresis (FACE) to quantify the tissue composition of key molecules: glycosaminoglycan (GAG), chondroitin/deratan sulfate, keratan sulfate proteoglycans, and hyaluronan, and compare these quantities with data gathered from tissues from diseased joints.
- **Develop accurate means of assessment and categorization of patients using standardized techniques to enable comparisons of patients.** Diagnostic criteria currently used cannot distinguish patients according to different pathophysiologic processes. As a result, poorly categorized patient groups confound clinical studies.
- **Establish a National TMJ Registry of TMJ patients, with appropriate privacy safeguards, to serve as a source of clinical data and of patient volunteers for clinical studies.** The Registry should include family history and provide facilities for storing biological samples to permit meaningful genetic and pathophysiological studies. Insofar as subtle phenotypic differences may be related to genetic mutations, clinical descriptions of various forms of TMJ disease are needed so that genetic association studies can be conducted. Patient data should include assessments of other joints, as well as eyes, ears, autonomic and endocrine function, and the presence of co-morbid conditions.

- **Develop animal models (mutant, transgenic, chemically or trauma-induced) of both TMDs and osteoarthritis** to determine how these varied induced derangements affect cellular, biochemical, and molecular changes in joint tissues and signaling pathways. While each system (e.g., mouse, rat, rabbit) can provide valuable insights regarding multiple pathophysiologic changes in human TMJ conditions, none can completely mimic human OA or TMJ dysfunction. Nor can animal models substitute for the study of surgical interventions or disease progression. Likewise, it is not clear how surgically induced disease in rabbits, sheep, goats, and pigs relates to people. There are no good animal models for testing TM joint prostheses.

Inflammation and Immunology

- **Determine the turnover dynamics of the cartilage in a normal TMJ and that of patients with dysfunction.** Replenishment of the cartilage matrix involves the synthesis and degradation of proteoglycans, various collagen isoforms, and accessory proteins. The types of collagen and their regulation in association with chondrocyte differentiation in the growth plate of the TM joint needs to be determined, including the role of growth factors, binding proteins, and factors involved in matrix degradation such as interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-alpha). In addition, signaling pathways involving mitogen-activated protein kinases (MAPKs), whose activity appears critical for metalloproteinase expression in fibroblast-like synoviocytes locally in the synovium and for inflammation in general, need to be explored in the OA process. Synthesis of larger aggrecans and chondroitin sulfate as well as genes that encode them need to be explored. Gene expression studies can contribute to these studies. In addition, signaling pathways that activate cells in the joint capsule to release destructive enzymes and are involved in inflammatory processes in general need to be explored in osteoarthritic processes.
- **The role of various inflammatory and anti-inflammatory cytokines in TMJ pain and arthritis need to be explored in human subjects.** It is important to determine if synovial inflammation accelerates joint degenerative changes and progressive loss of cartilage in the TMJ, which represents a weight-bearing joint in the body of great significance for daily living and quality of life. The knee and hip joints have distinctly different patterns of degradation. These characteristics need to be specifically characterized for the TM joint. There is evidence that cytokines, among them tumor necrosis factor alpha (TNF-alpha) and interleukin 1-beta (IL-1 beta), participate in the development of pain and tissue destruction in the TMJ. Other elements of the inflammatory pathways need to be explored, such as 5-HT-1, 2,3 receptors, PGE₂, and LTB₄. The peripheral nerve terminals of primary afferent nociceptors release neuroendocrine peptides that could mediate neurogenic inflammation in the TMJ region. The contribution of these mediators needs to be explored.
- **The role of apoptosis in cartilage degeneration of the TMJ needs to be explored.** An understanding of this process may help identify the pathogenic mechanisms occurring in these joints. Chondrocytes are normally resistant to apoptosis. What stimuli change them to make them more susceptible? Caspase inhibitors could be explored as a means of inhibiting apoptosis in the chondrocytes.

- **Determine the role that nitric oxide (NO) formation and the generation of reactive oxygen and nitrogen species (ROS and RNS) play in TM joint and muscle inflammation.** The inducible NOS isoform (NOS II) has been found to be elevated in giant cells obtained from TMJ explants. As well, serum levels of metabolic byproducts—nitrites/nitrates—have been found in a limited number of patients. The constitutive forms of NOS (NOS I and III) have not yet been examined in the TMJ. Such studies could logically lead to the development of new therapeutic targets and strategies aimed at inhibiting NO and ROS production in temporomandibular joints.
- **Explore cytokine-modulating therapeutic strategies that have proven clinically efficacious in rheumatoid arthritis for use in treating TMD and OA.** Interventional drugs that block pathogenic mechanisms e.g., role of doxycycline as an inhibitor of collagenase and gelatinase, matrix metalloproteinases that cause tissue destruction, could be explored in this context. Potential therapeutic use of caspase inhibitors, IL-1 receptor antagonists, TNF-alpha neutralizing agents, and glucosamine to inhibit NF κ B, hyaluronic acid and chondroitin sulfate to enhance NF κ B need to be explored as well as a green tea fraction that induces apoptosis in selected tumor cells and which inhibits apoptosis induced by IL-1 beta in human chondrocytes. If the details of the pathways through which TNF-alpha works were known, they might provide better targets for the treatment of arthritis.

Genetics

- **Study genetic mutations as risk factors for TMJ diseases.** It is believed that early-onset osteoarthritis, associated with an underlying chondrodysplasia, is genetic, as are metabolic bone diseases such as crystal-associated arthropathies. The influence of genetic mutations, including polymorphisms, on susceptibility to TMJ disease is unknown. These studies should include the genetic contribution of connective tissue elements as well as immune factors. The temporomandibular joints of transgenic animals developed for the study of early-onset OA and metabolic bone disease should be examined for evidence of pathology.

II. Recommendations: Deep Tissue Pain/Role of Jaw Muscles

Deep Tissue Pain

- **Elucidate the basic mechanisms of persistent TMJ pain and develop biomarkers of pain.** Study the sensory neurons in masseter muscles and tendons to understand the origins of deep pain. Use microarrays to determine which genes are differentially expressed in masseter muscle pain.
- **Refine and test diagnostic approaches to allow electrical detection thresholds in the region of the TMJ to differentiate pain originating from the joint versus the muscle.**
- **Apply functional imaging techniques to the study of TMJ patients.** PET and fMRI technology need to be more fully explored to define identifiable changes in cortical sites associated with deep tissue pain (as distinguished from cutaneous pain). Changes in activity of CNS cortical sites that activate descending systems and modify the pain experience via attention and cognition (e.g., anterior insula, SI, SII, and anterior cingulate) need to be identified.

- **Explore the basis of co-morbidity of pain disorders in TMJ patients.** Why do some individuals with TMJ also have fibromyalgia or other pain conditions?
- **Study the role of Nerve Growth Factor in chronic pain conditions.** There is evidence of an increase of Nerve Growth Factor (NGF) in synovial fluid in TMD which may contribute to pain and also represent a biomarker of pain. NGF may be important in chronic inflammatory conditions.
- **Study the role of newly cloned peripheral pain receptors in muscle and joint inflammation.** Expression of these receptors in TMJ-associated tissues (muscle and joint) may serve as a biomarkers of pain. For example, it has been learned that changes in pH are important since the newly discovered ASIC3-acid sensing channel (shown in cardiac tissue) is very sensitive to lactate and may be very important in muscle and/or joints after inflammation when pH decreases. Also, a vanilloid receptor (VR1) has been shown to be importantly involved in heat and pH sensing, and the role of this receptor in muscle and joint inflammation needs to be explored.
- **Determine the role of glial cells in the central nervous system in central sensitization associated with deep tissue injury.**
- **Conduct studies to confirm observations that there is no correlation between joint pain and cartilage degeneration.** If true, explore reasons for this dissociation.

Role of Jaw Muscles

- **Develop methods to measure the forces exerted by the jaw muscle to determine how heavily the temporomandibular joint is loaded, or stressed.** Clinical measures such as cartilage indentation tests might be of use to answer these questions.
- **Develop animal models to address how jaw structure and load affect muscle remodeling and contribute to disease.** Models are needed to examine the consequences of changes in masseter muscle strength and activity upon the TM joint. Does skeletal muscle structure/function contribute to TMJ stability? Can strengthening TMJ muscles serve a preventive role in certain disorders? Do muscle strengthening exercises impact TMJ dysfunction in the same manner as seen in limb joints? Studies of how the cranial muscles are innervated and controlled could lead to better understanding of the kinds of muscle abnormalities present in patients with TMDs and whether these abnormalities are caused by or contribute to pain and loss of function in the joint.
- **Study the role of cytokines and other inflammatory processes in TMJ muscles during trauma.**
- **Determine if human masseter muscle types vary by sex and according to clinical characteristics. Are the muscle clinical signs the cause or the consequence of the various clinical problems found in patients with TM joint diseases? Are there clinical markers in muscle for TMJ or markers that would point to potential complications with routine orthodontic/surgical treatments?**

- **Conduct studies of the regulation of various motor units within the cranial muscles (masseter, tongue, etc.) and how this control is integrated centrally.**
- **Determine the extent to which pain contributes to the recruitment of motor units and whether distortions of masseter muscles, tongue, and larynx contribute to pain in TMJ patients.** Conversely, since in the absence of pain, the destruction of the joint still leads to abnormal use of muscles in order to protect the joints, how do these changes affect muscle and joint function? Does too much jaw muscle activity such as bruxing lead to pathology? The effects of pain on function and remodeling/plasticity of muscle need to be explored. Models of chronic jaw closing need to be studied with regard to jaw muscle, jaw pain, and effects on joint.
- **Can information about other joints (knee, hip) and muscle remodeling around them be applied to the TMJ?** Some investigators believe that muscle pain in TMJ patients originates at the ends of the muscle in the tendons, and may be disrupted with local anesthetic. Accordingly, it would be of value to determine how modulation of various ion channels may be involved in this pain.

III. Recommendations: Microvasculature/Angiogenesis in Joint Disease

- **Determine if angiogenesis plays a role in TMJ disorders and the development of arthritis in this joint.** Is angiogenesis a pathologic feature of TMJ pathology? Is it selectively associated with specific TMJ disease subsets?
- **Test whether anti-angiogenesis agents offer a therapeutic benefit in inflammatory arthritis in the TM joint.** Anti-angiogenic agents which may prove useful include strategies which target VEGF such as antibody antagonists, soluble receptor antagonists, and small molecules which block VEGF-mediated cell signaling. Additionally, targeting the angiogenesis-associated integrin alpha v beta 3, which has shown efficacy in inhibiting angiogenesis and ameliorating arthritic disease in rheumatoid arthritis models, should be assessed for efficacy in TMJ disease.
- **Elucidate the mediators of angiogenesis in TM joints.** Multiple angiogenic cytokines have been associated with arthritis pathology; however whether the angiogenic cytokine profile in TMJ is similar or different from the angiogenic cytokines in other joints is unknown.
- **Determine the vascular phenotype in TMJ.** Immunohistochemical characterization of the vasculature should focus on angiogenic markers (e.g., alpha beta 3 adhesion molecule expression (ICAM, VCAM, E-selectin) and matrixmetalloproteinase expression.
- **Determine if angiogenic markers can predict disease progression/severity in TMJ patients.** Determine if clinical symptoms can be correlated with changes in vascular morphology. A cohort study of rheumatoid arthritis indicated serum sVCAM-1 and PECAM-1 (CD31) predicted disability. Known markers of angiogenesis should be screened to determine which could be used for indexes of inflammatory and non-inflammatory joints.

- **Explore whether genetic susceptibility to angiogenesis plays a role as a risk factor affecting the TM joint and related musculature.** It is known that in rats the genetic background determines the angiogenic responses of skeletal muscle and this may be the case in the TM region. Genomic manipulation in rats (consomic and congenic rat models) has been used to clarify several important angiogenic pathways. Such models should be used to evaluate angiogenesis in the TM joints and musculature. (Several existing congenic inbred strains of rats have shown an important association between activation of the renin-angiotensin system and VEGF expression.)

IV. Recommendations: Current and Future Therapeutic Approaches

- **Study the reputed *in vivo* effectiveness of chondroitin sulfate and glucosamine hydrochloride therapy** in human degenerative TMJ disorders to determine what may be the underlying mechanisms of action.
- **Determine the role of subchondral bone loss in the natural history of TMD.** New approaches and techniques are required to study the events associated with condylar resorption. Animal models should be used to carry out a comprehensive analysis of bony changes that occur in the temporal and condylar sites during both normal development and with aging. **Idiopathic condylar resorption** is a poorly understood progressive disease that affects the TMJ with bone destruction that can be severe. There is evidence that subchondral bone changes may precede cartilage changes in TMD and in arthritis. Methods, including improved imaging techniques, are needed to detect increased resorption before bone loss is evident radiographically.
- **Studies are needed to determine the role of osteoporosis as an added risk factor in TM disease and to detail the relationship between bony degenerative changes and TMD symptomatology.** Presence of osteoporosis may jeopardize TMJ surgical outcomes.
- **Determine if agents that reduce bone resorption have a place in TMD therapy.** Osteoporosis poses a threat for nearly 55 percent of the US population aged 50 and older.
- **Study the biochemistry of mineral deposition involved in calcification of joint soft tissues.** The role of crystalline Ca pyrophosphate dihydrate (CPPD) and basic Ca phosphate (BCP) in TM joints needs to be explored to determine if therapeutic approaches can be developed to inhibit crystal formation in TMJ disorders. Each of these phosphate molecules occurs frequently in OA joints, including the TMJ, and in the case of BCP crystals, may cause acute attacks of pseudo gout. These crystals can activate protooncogenes and metalloproteinases that cause tissue breakdown and are also involved in a destructive cascade using protein kinase C signaling pathways. The effects of PKC inhibitors on these events should be evaluated.

- **The cause(s) and effects of the accumulation of microdamage and trabecular microfractures in subchondral bone on joint degeneration need to be fully explored.** Microdamage occurs in both subchondral bone and in calcified cartilage and may increase bone stiffness and contribute to the pathogenesis or progression of TM joint diseases.
- **Apply principles of tissue engineering using mesenchymal stem cells to regenerate bone, cartilage, muscle and tendon, and develop ways to deliver them for repair or regeneration of injured temporomandibular structures.** A number of questions should be addressed. Are there stem cells left in the TMJ? Are there tissue-engineering constructs that could generate cells in specific regions? Articular cartilage is a single unified structure to resist mechanical/physical stress: how can cells transplanted into these tissues (of rabbits, for example) be integrated in a way that the load-specific architecture is achieved? Exercise and loading is required for normal cartilage health, but there are few data on the TMJ regarding the stresses and tissue modeling by loading.
- **Expand efforts to develop material suitable for the reconstruction of diseased TM joints.** Conduct further studies of tissue healing and autologous grafts, e.g., costochondral grafts, as well as bone/cartilage growth factors.

V. Recommendations: Educating Practitioners and Researchers

- **Develop new approaches for information transfer to meet the critical need at this time. TMJ should be included in all health professional school curricula.**
- **Current treatment approaches (e.g., surgical disc repositioning and joint replacement) need to be re-evaluated.** Are they needed in conditions other than a tumor and major trauma?

The *TMJ* Association

Board of Directors

Terrie Cowley, President
Milwaukee, WI

Kevin D. Clark, Vice President
Milwaukee, WI

C. Polly Ellingson, J.D., Secretary
Milwaukee, WI

Charles M. Sturm, Treasurer
Milwaukee, WI

Joan B. Wilentz
Chevy Chase, MD

James M. Wozniak, CFP, CIMC
Milwaukee, WI

Diana M. Zuckerman, Ph.D.
Washington, D.C.

Scientific Advisory Board

Robert E. Baier, Ph.D., P.E.
University at Buffalo
State University of New York
Buffalo, NY

Ronald Dubner, D.D.S., Ph.D.
University of Maryland
Baltimore, MD

Julie Glowacki, Ph.D.
Harvard Medical School and
Harvard School of Dental Medicine
Boston, MA

Stephen L. Gordon, Ph.D.
Toucan Capital Corp.
Bethesda, MD

Stephen B. Milam, D.D.S., Ph.D.
University of Texas
Health Science Center
San Antonio, TX

Christian S. Stohler
D.M.D., Dr. Med. Dent.
University of Maryland
Baltimore, MD

Special Advisor

Allen W. Cowley, Jr., Ph.D.
The Medical College of Wisconsin
Milwaukee, WI

*Volume 2, Number 1
January 2003*

The logo features the letters 'TmJ' in a large, dark red serif font. The 'm' is lowercase and positioned between the 'T' and 'J'. A horizontal purple bar with a thin red vertical line in the center passes behind the letters. Below the 'J' and the bar, the word 'Science' is written in a purple, italicized serif font.

Science

the journal of The TMJ Association