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TMJ Science

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TMJ Science

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With this issue we are launching *TMJ Science*, a TMJ Association publication designed to provide readers with information directly and indirectly related to TMJ. The journal format will allow us to cover material at greater breadth and depth than we can do in the newsletter, *TMJ Communiqué*. The TMJA Board of Directors and Scientific Advisory Board have discussed the need for such a publication in recent meetings and in strategic planning sessions, emphasizing that the articles should be accessible to a lay audience. For this debut issue it seems most appropriate to present a summary of The TMJ Association's first-ever scientific research meeting held at the headquarters of the Federation of American Societies for Experimental Biology, May 22-23, 2000, in Bethesda, Maryland. That meeting, which was co-sponsored by components of the National Institutes of Health and private industry, was intended to bring experts from other areas of research together with scientists who have focused on TMJ to exchange ideas and build an innovative research agenda. This issue reprints the program for the workshop, provides a summary of the scientific papers presented, and concludes with the recommendations that emerged from the breakout sessions. In addition to circulating this material to TMJA members, we will use this first issue as a document to distribute to the research community, allied health voluntary organizations, health professional societies, foundations, government agencies, members of Congress, and others interested in the conduct and support of research and research training.

In the next few months we expect to build a *TMJ Science* Editorial Board to provide review and oversight over the contents of the journal. To the extent possible, we will review the peer-reviewed scientific literature and ask authors of TMJ-related papers to work with us to provide lay summaries of their findings. We will also ask colleagues at the NIH to describe relevant activities and meetings, provide summary listings of new and ongoing research grants in areas relevant to TMJ, and furnish updates on the activities of the TMJ Interagency Working Group. This group was established by Congress to further collaborative basic and clinical research on TMJ problems and develop a research agenda. Members include major components of the NIH as well as other agencies, such as the Food and Drug Administration, the Agency for Healthcare Research and Quality, the Centers for Disease Control and Prevention, and the TMJA itself.

We have indicated our ideas for the contents of future issues of *TMJ Science*. Together with the *TMJ Communiqué* and the regularly updated TMJA Web site, our goal is provide comprehensive coverage of what's happening in the world of TMJ. As always, we welcome your feedback. By working together we can *change the face of TMJ.*

Joan Wilentz, Editor

First Annual Scientific Meeting of The TMJ Association

...moving TMJ Research into the 21st Century

The meeting will explore basic science topics relevant to understanding deep joint and muscle pain and dysfunction, as exemplified by temporomandibular joint diseases and disorders.

The organizers of this event are cognizant of the lack of a coherent body of knowledge on the etiology and pathogenesis of TMJ diseases and disorders and the resultant lack of evidence-based treatment guidelines. This first meeting will be an interdisciplinary gathering bringing together experts in arthritis, TMJ pathology, bone, joint, and muscle physiology, neuroscience, pain, genetics, endocrinology, immunology, and tissue repair/engineering. The goal of this and future meetings is to build a solid scientific basis for TMJ research and define future directions of research.

At the same time, the meeting is designed to bring together and enrich the pool of investigators directed to TMJ research by attracting experts from other fields and by stimulating the interest of young investigators in this emerging field of research. We have assembled an outstanding and influential group of scientists as speakers for this first meeting.

The TMJ Association recognizes that the hopes of a better future for the millions of TMJ patients must be built upon basic scientific principles and is committed to sponsoring annual scientific meetings to advance this field.

Scientific Meeting Planning Committee

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Papers from the workshop will be published in the June 1, 2001 issue of The Special Topics Issue of Cells, Tissues, Organs entitled "Moving Tempormandibular Joint Research into the 21st Century."

First Annual Scientific Meeting of The TMJ Association …moving TMJ Research into the 21st Century

FASEB Conference Center
Co-chaired by Drs. Andrew H. Kang and Ronald Dubner
May 22 and 23, 2000

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

Welcome/Patient Presentation
Terrie Cowley, President, The TMJ Association

Remarks
Harold Slavkin, D.D.S., Director, National Institute of Dental and Craniofacial Research

Introduction/ Multi-Disciplinary Model
Andrew H. Kang, M.D., The University of Tennessee College of Medicine

Introduction/Meeting Goals
Ronald Dubner, D.D.S, Ph.D., University of Maryland Dental School

Clinical Perspectives on TMJ
Christian S. Stohler, D.D.S., Dr. Med. Dent., University of Michigan

Session 1 - Tissue/Structure-Function

Chairperson, Stephen L. Gordon, Ph.D., Osiris Therapeutics, Inc.

BONE

Loading of the TMJ: Anatomical and in Vivo Evidence from the Bones
Susan W. Herring, Ph.D., University of Washington

Bone Response to Joint Degradation and Repair
D. Rick Sumner, Ph.D., Rush Medical College

DISC

Experimental Tools for Studying TMJ Cell Biology
Regina Landesberg, D.M.D., Ph.D., Columbia University

What can Intervertebral Disc Degeneration Teach about the TMJ?
Theodore R. Oegema, Jr., Ph.D., University of Minnesota

MUSCLE

Androgen-Mediated Gender Differences in the Rabbit Masseter Muscle Arise During a Critical Period of Postnatal Development
Arthur W. English, Ph.D., Emory University School of Medicine

Hormonal and Activity Influences on Skeletal Muscle Plasticity
Kenneth M. Baldwin, Ph.D., University of California, Irvine

Session 2 - Neural/Endocrine

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

NERVOUS SYSTEM

Peripheral Mechanisms of Hyperalgesia and Development of Novel Analgesics
Kenneth M. Hargreaves, D.D.S., Ph.D., The University of Texas Health Science Center, San Antonio

Afferent Neurons Innervating Joint Capsules
Peter Grigg, Ph.D., University of Massachusetts Medical School

Activity-Induced Plasticity in the Nervous System Following Tissue or Nerve Injury
Ronald Dubner, D.D.S., Ph.D., University of Maryland

ENDOCRINE SYSTEM

TMJ and Hormones in Women
Michelle Warren, M.D., Columbia University

Genetic Predisposition To Pain: from Mice to Molecules
Jeffrey Mogil, Ph.D., University of Illinois Urbana

Gender Differences in Brain Stem Neural Activation after Injury to the TMJ Region
David A. Bereiter, Ph.D., Brown University School of Medicine

Session 3 - TMJ Pathology

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

DEGRADATION PATHWAYS

Pathogenesis of TMJ Degenerative Diseases
Lambert G. M. de Bont, D.D.S., Ph.D., University Hospital Groningen, the Netherlands

TMJ Pathology and Biochemical Markers
Anthony Ratcliffe, Ph.D., Advanced Tissue Sciences, Inc.

BIOCHEMICAL DEGRADATION PATHWAYS

Why is Special Study of the TMJ Warranted?
Stephen B. Milam, D.D.S., Ph.D., University of Texas Health Science Center, San Antonio

Cytokine Mediated Pathways for Disc Degeneration in the TMJ: Lessons Learned from a Transgenic Mouse Model
J. Edward Puzas, Ph.D., University of Rochester School of Medicine and Dentistry

INFLAMMATORY PROCESSES

Orofacial Deep and Cutaneous Tissue Inflammation and Trigeminal Neuronal Activation: Implications for Persistent Temporomandibular Pain
Ke Ren, M.D., Ph.D., University of Maryland Dental School

Inflammation and Bony Changes at the TMJ
Mark C. Horowitz, Ph.D., Yale University School of Medicine

Drug Target Discovery and Validation
Mark E. Nuttal, Ph.D., SmithKline Beecham

BIOMECHANICAL/BIOCHEMICAL PROCESSES

Mechanical Loading and Chondrocyte Gene Expression
Robert Lane Smith, Ph.D., Stanford University School of Medicine

Mechanical Regulation of Cellular Response
Al J. Grodzinsky, Sc.D., Massachusetts Institute of Technology

Novel Materials for Tissue Repair and Engineering
Kristi S. Anseth, Ph.D., University of Colorado

Session 4 - Tissue Repair

Chairperson, Ronald Dubner, D.D.S., Ph.D., University of Maryland

ANGIOGENESIS

Role of Angiogenesis and Angiogenic Factors in the Development of the Nervous System
Peter J. Polverini, D.D.S., D.M.Sc., University of Michigan School of Dentistry

Hormonal Control of Bone Blood Flow
John T. Fleming, Ph.D., University of Louisville, KY

CONNECTIVE TISSUE GROWTH & REPAIR

Signaling Network Regulating Mandibular Development
Mina Mina, D.D.S., Ph.D., University of Connecticut

Impaired Intramembranous Bone Formation During Bone Repair in the Absence of TNF Signaling
Louis C. Gerstenfeld, Ph.D., Boston University School of Medicine

TISSUE ENGINEERING

Engineered Cartilage, Bone and Joints
Julie Glowacki, Ph.D., Harvard Medical School and Harvard School of Dental Medicine

Engineering Complex Tissues: Oral Mucosa and TMJ
Stephen E. Feinberg, D.D.S., Ph.D., University of Michigan Medical Center

Session 5 - Breakout Sessions

Chairperson, Stephen L. Gordon Ph.D., Osiris Therapeutics, Inc.

WRAP-UP SESSION/FINAL RECOMMENDATIONS

Group 1 **–** Tissue/Structure-Function
Drs. Susan W. Herring and Kenneth M. Baldwin

Group 2 **–** Neural/Endocrine
Drs. Kenneth M. Hargreaves and Jeffrey Mogil

Group 3 – TMJ Pathology
Drs. Anthony Ratcliffe and Stephen B. Milam

Group 4 – Tissue Repair
Drs. Julie Glowacki and Stephen E. Feinberg

Final Comments
Drs. Andrew H. Kang and Ronald Dubner

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Ms. Beverly Miller
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The TMJ Association would like to thank Dr. Martin Frank, Ms. Linda Allen, and Ms. Cheryl Wright for their assistance to the Association in coordinating this meeting at the FASEB Center.

MOVING TEMPOROMANDIBULAR JOINT RESEARCH INTO THE 21st CENTURY

By Damaris Christensen

THERE are few things more frustrating than having a disease that can barely be diagnosed, much less treated, yet that frustration confronts thousands of Americans who suffer from diseases and disorders of the temporomandibular (jaw) joint and surrounding tissues. Further, some of the treatments they have received to alleviate their painful symptoms have failed, leaving their joints in far worse shape than they were before "treatment."

Little research has explored these problems. To spark progress, The TMJ Association, a national patient advocacy group based in Milwaukee, organized a meeting to assess the current state of the science and provide directions for future research. Scientists working in arthritis, temporomandibular jaw pathology, physiology, neuroscience, pain, genetics, endocrinology, immunology, and tissue repair and engineering compared notes on how their knowledge might illuminate the problems of the temporomandibular joint and associated tissues.

This first Association-sponsored scientific meeting on temporomandibular joint diseases and disorders was held May 22-23, 2000, at the Federation of American Societies of Experimental Biology campus in Bethesda, Md.

A wondrous joint

The temporomandibular joint is a complicated, poorly understood network of nerves, muscles, cartilage, fluids, and bone. It is also one of the most complex joints in the body, performing multiple vital functions. It lets the lower jaw, or mandible, move up and down, side to side, and forwards and backwards as a person does such wondrous things as speaking, biting, chewing, swallowing, smiling, laughing, and frowning.

The mandible connects with the temporal bone at the side of the skull near the ear. Each end of the mandible has a rounded structure called the 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. The space between the bones is further cushioned by an oval disc of cartilage, which acts as a shock absorber.

All forms of temporomandibular diseases and disorders[1] are characterized by pain in the jaw, temples, face, and the area just

[1] The terms "diseases and disorders" reflect the multiple causes of jaw problems. For the sake of brevity, the word "disorders" will be used throughout this report.

in front of the ear. Many patients also complain of noises in their jaw, are unable to open their mouths fully, or perceive that their teeth are not coming together properly. The disorder can be relatively mild and resolve over time or progress to severe jaw malfunction and intractable pain.

Current classification systems separate disorders that involve the joint from those involving the muscles used to open and close the jaws, although, of course, there is a significant overlap between the two groups. The severity of pain, the extent of pain, and the presence of musculoskeletal disease affecting other parts of the body vary from patient to patient. More than two-thirds of patients seeking care from specialists report pain in the head and face, while some report more widespread pain. There are no formal criteria for diagnosing temporomandibular problems.

Based on a national survey conducted in 1989 by investigators at the National Institute of Dental and Craniofacial Research (NIDCR) of the National Institutes of Health, an estimated ten million people in the United States have signs of temporomandibular disorders. In community studies, women are slightly more represented than men among those reporting symptoms. Women are much more likely than men to seek out primary care providers for TMJ disorders and overwhelmingly more likely to see specialists.

In the 1980s, an oval disc of two laminate plastics—Teflon and Proplast—was made by Vitek, Inc. and another plastic material, Silastic, made by Dow Corning Corp., were widely used to replace natural cartilage discs that had been dislocated or damaged. However, many, perhaps most, of these interpositional implants abraded with use. The reactions triggered as a person's body was exposed to the particles of plastic led to inflammation and immune problems. These reactions, in turn, dramatically increased the deterioration of the person's jaw joints and surrounding tissues and contributed to greater pain and dysfunction.

"What we have is a disorder with no consensus on definition, cause, diagnosis, or treatment—in other words, a virtual lack of science, with the end result a huge 'medical mess,'" said Terrie Cowley, president of The TMJ Association, in a 1990 letter published in the Wall Street Journal. Further, because there is no medical specialty focused on temporomandibular joint disorders, and because practitioners have no evidence-based science to guide them in diagnosis and treatment, "the clinical picture of TMJ treatment is dismal," Cowley said.

THE STATE OF CURRENT RESEARCH

Gender differences

As many as 80 percent of patients treated for temporomandibular joint disorders are women, noted Michelle Warren, MD, of Columbia University in New York. Although women are generally more likely to seek out care than are men, the preponderance of women seeking care for temporomandibular disorders can't be completely explained by gender differences in care-seeking, she said.

According to Warren, there are two possible explanations. First, women may be more at risk for one of the varied physiologic factors thought to play a role in TM disorders, such as displacement of the disc or arthritis of the jaw joint. Second, women may experience more pain, perhaps because of hormonal or physiological factors.

Some evidence links female hormones to temporomandibular pain, said Christian S. Stohler, DDS, Dr Med Dent, of the University of Michigan in Ann Arbor. One study has shown that women taking oral contraceptives or postmenopausal estrogen supplements are 19 percent and 77 percent more likely to seek care for such disorders than control groups in each category, he said.

Jaw muscles in rabbits differ between the sexes because of androgen exposure, notes Arthur W. English, PhD, of Emory University School of Medicine in Atlanta. "We would predict that the masseter muscles of males would produce larger and faster forces than those of females," he said. "If this gender difference holds true in people, it might help explain why women seem to be more vulnerable to the disease."

Clinical studies confirm the presence of estrogen receptors in the articular cartilage of the temporomandibular joint. However, these differences have not as yet been linked to greater susceptibility to temporomandibular joint disorders.

Structure of the temporomandibular joint

A major problem in approaching research on structural abnormalities that might trigger temporomandibular disorders is that very little is known about the normal structure and function of the joint, researchers said. "We need to know what is normal before we can say what is abnormal," said Regina Landesberg, DMD, PhD of Columbia University in New York.

Most people have jawbones of different lengths that are set into their skulls at different angles. It is not clear whether people with certain jaw shapes are more prone to temporomandibular disorders. The cartilage disc between the joints is displaced or damaged in many jaw joint patients. However, it is possible that many people without such symptoms also have displaced discs, and thus that such displacement is not abnormal, said Lambert G.M. de Bont, DDS, PhD, of the University Hospital Groningen in the Netherlands.

Loading of the temporomandibular joint

An important issue is whether the articular, or facing, surfaces of the temporomandibular joint exert compressive forces on each other—in other words, whether the joint is "loaded." The belief that the TMJ was only lightly loaded is thought to be a major factor in the failure of interpositional disc implants, which were inadequately tested for their resistance to stress and strain.

Loading cannot be directly measured in people, but it is probably both significant and more complex than was previously thought, said Susan W. Herring, PhD, of the University of Washington in Seattle. Using a pig model, she and her colleagues have shown that there are compressive forces at work in the temporomandibular joint during muscle contraction, and that different parts of the jaw experience different kinds of forces at different times. For example, when one side of the jaw contracts, the other side "seems to be actually coming apart," she said.

Just how much loading the temporomandibular joint experiences and to what extent loading plays a role in TM disorders is not known. Intraoral splints—devices that may decrease loading of the jaw—are sometimes used in people to modify load on the temporomandibular joint and to reduce pain. One major concern from Herring's research is that pigs fitted with intraoral splints actually had more trouble with their jaws over the long term than pigs without such devices, she said.

Loading can cause increased bone density in a stressed joint and appears to accelerate joint disease in the hip, but cartilage changes in the ankle can occur without increased bone density, said Rick Sumner, PhD, of Rush Medical College in Chicago. Some researchers have suggested that the TMJ disc may have parallels in the vertebral discs of the spine, but such comparative studies have yet to be made.

Stress acting on the temporomandibular joint alters gene expression and can affect the rate at which cartilage is lost or replaced, noted Robert Lane Smith, PhD, of Stanford University School of Medicine in Stanford, Calif. Abnormally high loads on

the temporomandibular joint may tilt the balance away from normal and contribute to disease, he said. He suggested that researchers may eventually be able to use mechanical stimuli to accelerate repair and regeneration of an arthritic temporomandibular joint.

Questions remain on how the temporomandibular joint varies across species and what animals might be the most appropriate models for understanding TMJ disorders in people . Developing animal models is difficult because of uncertainty about the pathology of TMJ disorders, making it hard to figure out what to look for in a model.

Cartilage involvement

Most joints in the body are primarily made of flexible, semi-transparent hyaline cartilage. The temporomandibular joint is different, being composed primarily of less resilient fibrocartilage. According to research presented at the conference, the pathology of TMJ disorders may involve a number of factors, including the abnormal function of enzymes that break up and rebuild disc cartilage and arthritis of the temporomandibular joint.

Before identifying possible molecular and cellular processes that might be disrupted in people with TM disorders, researchers must first understand what the cellular processes of repair and regeneration are within the normal TMJ, said Stephen B. Milam, DDS, PhD, of the University of Texas Health Science Center in San Antonio. In order to do this, he said, researchers will need to study tissue and fluid specimens obtained from normal volunteers. Studies of cartilage cells taken from the temporomandibular joint of cows suggest that immune system regulators known as cytokines can speed up the natural process of cartilage matrix destruction, said Edward Puzas, PhD, of the University of Rochester School of Medicine and Dentistry in New York. Further, mice genetically engineered to have higher than normal rates of cartilage destruction have abnormalities in their temporomandibular joint, he said.

Human studies indicate that cytokines are implicated in the immune response, swelling, and bone deterioration that mark temporomandibular disorders. Somewhere between 60 and 100 percent of patients with TMJ disorders have high levels of the cytokine tumor necrosis factor alpha (TNF-alpha) in fluid taken from the temporomandibular joint. TNF-alpha is an inflammatory cytokine that can trigger programmed cell death. In contrast, most people without disease do not seem to have detectable levels of TNF-alpha, said Mark C. Horowitz, PhD of Yale University School of Medicine in New Haven, Conn. The amount of another cytokine, interleukin-6 (IL-6) seems to vary with the nature of the particular TM disorder, he said. People with temporomandibular problems have about four times the amount of the cytokine IL-1 beta as do people without jaw problems.

The role of bone remodeling

TNF-alpha is also believed to affect normal bone resorption in the course of "bone remodeling," a natural process in which bone loss is balanced by bone growth in healthy people. Bone resorption may be abnormal in people with TMJ disorders, said Louis C. Gerstenfeld, PhD, of the Boston University School of Medicine. He and his colleagues report that in mouse models, bone healing was slower than normal in mice genetically engineered to lack receptors for TNF-alpha. Mice without TNF-alpha receptors are insensitive to the cytokine. So far, the mouse studies suggest that TNF-alpha is responsible for destroying damaged cartilage cells rather than bone cells, Gerstenfeld said; other factors must be involved in triggering bone growth and loss.

Drugs that inhibit bone resorption may eventually offer some benefit to people with TMDs, said Mark E. Nuttall, PhD, of SmithKline Beecham Pharmaceuticals in King of Prussia, Pa. Similar drugs that block the destruction of cartilage are also under development, he said.

Proper blood flow is essential for normal bone growth, bone remodeling, and fracture repair, said John T. Fleming, PhD, of the University of Louisville in Kentucky. Researchers at the conference noted that hormones such as norepinephrine and vascular endothelial growth factor (VEGF) may play roles in regulating blood supply to joints, including the temporomandibular joint. If these processes are not working properly in some people with TMJ disorders, they may benefit from drugs that restore normal blood flow and facilitate bone healing, he said.

The factors regulating angiogenesis, the growth of new blood vessels, to damaged tissues may also be out of balance in people with TMJ disorders, said Peter J. Polverini, DDS, DMSc, of the University of Michigan School of Dentistry in Ann Arbor. Studies in mice confirm that VEGF hormones are involved in the growth of nerve cells and of new bone as well as angiogenesis, he said. All of these processes might be disrupted in patients with TMJ disorders.

Chronic pain

Pain research has shown that nerve cells can become more responsive to pain after injury. "After a peripheral injury, stimuli that were ordinarily not painful now produce pain," a phenomenon called allodynia, said Kenneth Hargreaves, DDS, PhD, of the University of Texas Health Science Center in San Antonio. Another dramatic response to pain is hyperalgesia, a condition in which a person becomes extremely sensitive to painful stimuli. Both responses may play roles in TM pain and other conditions of chronic pain, he said. Researchers hope that if they can tease out the mechanisms that underlie the nervous system's varied responses to pain, they will be better able to measure a person's pain. Eventually, such research may lead to drugs that work selectively on various aspects of the pain that patients experience in temporomandibular disorders and other chronic pain conditions, Hargreaves said.

Pain of so-called deep tissues such as the temporomandibular joint or the muscles of the jaw is often diffuse and difficult to localize. Further complicating the picture, such pain may be referred—appear to be localized—at surface areas, and may lead to hyperalgesia, said Ke Ren, MD, PhD, of the University of Maryland Dental School in Baltimore. In studies of mice, TMJ injury seems to induce long-lasting changes and increased susceptibility of the nociceptive (pain) pathways of the trigeminal nerve, the major nerve supplying the temporomandibular joint region.

It is possible that initial pain cues are triggered when the joint is overextended or inflamed, said Peter Grigg, PhD, of the University of Massachusetts Medical School in Worcester. Most pain is protective and serves to warn against possible tissue damage, he said. Chronic pain probably begins as a protective pain but persists long after any apparent injury has been healed, and changes may involve nerves at the injury site as well as the central nervous system, noted meeting co-chair, Ronald Dubner, DDS, PhD of the University of Maryland Dental School, Baltimore.

Since pain is a primary symptom of TM disorders, researchers at the conference said it would be helpful to understand why pain sometimes outlasts the underlying injury. In other words, Dubner asked, what makes these nerve pathways change from protective to pathologic? He also noted that at this stage, there is no good evidence that the pathways of pain transmission from the injured site in the jaw to the central nervous system differ between genders.

Possible treatments for TMJ problems

Basic research may eventually offer clinicians the ability to intervene earlier in the disease process. For those people who have already suffered significant damage to their temporomandibular joint, however, advances in tissue repair and engineering may offer more immediate hope.

Using parts of a rib to replace the lower jaw has been one option offered to people whose jaw problems are severe enough to warrant replacement, with mixed results. New plastics that rapidly polymerize after being exposed to laser light—known as photopolymers—may allow surgeons to use biodegradable implants that may serve as scaffolds for growing tissues, said Kristi S. Anseth, PhD, of the University of Colorado in Boulder.

While true biological joints are far in the future, advances in cell-based therapies for reconstituting bone and cartilage may become available to the clinician in the next few years, said Julie Glowacki, PhD of the Harvard School of Dental Medicine in Boston. These novel tissue engineering techniques offer exciting alternatives to the alloplastic and non-biologic materials commonly used to treat TMJ disorders.

Still much to learn

Researchers at the conference acknowledged that TM disorders remain a field in which there are more questions than answers. Indeed, just defining the disease is difficult, the scientists agreed. "TMD … is a catch-all phrase for pain, discomfort, and/or disability associated with the temporomandibular joint," said Warren.

TM disorders "are not a single disorder, but rather groups of disorders" including muscle conditions, internal derangements of the jaw joint, or arthritis-related conditions, Stohler said. At the moment there are no accepted diagnostic tests to further classify TM disorders. And even though these conditions seem to share common symptoms, there is no reason to assume that all forms of temporomandibular disorders share a common cause, researchers said.

Biologic, familial, biochemical, physical, occupational, and psychosocial factors may all play a role in causing temporomandibular disorders, Stohler said. However, at this point there is little data in support of any proposed model of causation.

Although there are suggestions that hormones may affect TMJ disorders and that estrogen receptors are found in the temporomandibular joint, "there's not enough research … to draw meaningful conclusions as to why more temporomandibular disease cases are women," Warren said.

Ideally, researchers would like to identify TMJ disorders early in the progression of disease, when it might be easier to treat. However, that might be easier said than done, said Anthony Ratcliffe, PhD, of Advanced Tissue Sciences in La Jolla, Calif. In osteoarthritis—swelling and stiffness caused by wear and tear on the joints—biochemical markers of swelling and inflammation have not been linked to impaired function of the jaw or to pain, he said. "From a clinical point of view, [these markers] haven't acted as a marker for a disease process," Ratcliffe said.

PROPOSED RESEARCH GOALS

A major goal of the TMJ meeting was to propose a series of research priorities based on the assessment of current research as well as major unknowns about the temporomandibular joint. The researchers proposed studies to address a number of fundamental topics, including the following:

***What can be learned from people with TMJ disorders*?**

Registries and Tissue Banks. A registry of TMJ patients should be developed as soon as possible in order to trace the progress of various surgeries and determine appropriate interventions for patients whose implants have failed or are failing. Recovery of failed implants for study as well as collection of tissue biopsies might shed light on the factors driving tissue destruction in reaction against implants. Surgical attempts to remove the affected tissues and to reconstruct the joint have not been consistently successful. Typically, tissue destruction caused by immune responses continues, while the patient does not

regain normal jaw function and remains in debilitating pain.

Epidemiology. There is a great need for better epidemiological studies to characterize the symptoms and traits TMJ patients share. The hope is that understanding common traits will help scientists better identify subtypes of TMJ disorders, the characteristics that predispose people to a problem, and the contributions of gender and genetic factors to the development and progression of TMJ disorders. In addition, such studies are needed to link basic science and clinical research and to aid in the development of appropriate clinical models for TMJ disorders.

Prospective studies. Researchers called for a prospective, observational study of patients to evaluate sex differences, aging, the relationship of temporomandibular disorders to pregnancy, hormone replacement, surgery, or trauma, genetic susceptibility and co-existing conditions such as fibromyalgia. These studies should help researchers define the relationship between myofascial pain and dysfunction in the temporomandibular joint. In addition, the studies should attempt to develop markers of TMJ disorders and disease progression. Modern imaging technologies should be explored to identify common pathologies of cartilage, disc, bone, muscle, and the nervous system associated with TMJ disorders.

What goes wrong in people with TMJ disorders?

A key aspect of research is to define the primary mechanisms of injury and disease. Scientists have only a limited understanding of the molecular, cellular, tissue and mechanical features of the temporomandibular joint. As yet, researchers have not been able to determine whether disease results from patient susceptibility, direct injury, or a combination in addition to unknown causes. By defining mechanisms of disease researchers could further classify patients into groups with similar symptoms and, presumably, similar responses to treatment.

Comparative studies. One possible approach is to collect joint fluid and tissue biopsies from people with TMJ disorders and people without such disease, to see if inflammatory mediators, growth factors, tissue history, cell morphology, and the patterns of gene and protein expression differ between groups. Non-invasive imaging technologies may help researchers compare TM joint structures and tissues between people with and without disease. Again, researchers will look for measures that correlate with clinical symptoms in TMJ patients.

TM joint compared to other joints. Another step is to compare the molecular, cellular, and mechanical features of the temporomandibular joint to other joints, to see which mechanisms are in common (and thus what other joints might serve as models) and which features are unique, and to look for pathogenic changes in these mechanisms. Understanding joint mechanics will contribute to understanding possible mechanisms of disease, and provide an important database for the development of prostheses and tissue repair.

Sorting pain mechanisms. Clinical tests based on mechanistic characterization of pain may help classify patients and indicate effective treatments, researchers said. To better understand the pain associated with TM disorders, epidemiological studies should incorporate tests of hyperalgesia in deep tissues, referred pain, and sympathetic involvement, based on models of peripheral and central mechanisms of plasticity associated with persistent pain.

Are there appropriate models of TM disorders?

Basic research into temporomandibular joint disorders will be enhanced if researchers can develop — and standardize — models to study the development and normal

mechanisms governing jaw function, as well as pathologic processes, musculoskeletal pain, and the effects of therapies. Most researchers agreed that in vitro and animal models will be used, that a variety of models may be needed, and that clinical testing is necessary to establish the validity of animal models and to address aspects of TM disorders such as the emotional qualities of pain. The arthritic knee should be explored as a model for the arthritic temporomandibular joint, since, in humans, the knee is easier to study.

Transgenic models. While cows, pigs, rabbits, rats, and mice may serve as appropriate models for the normal function of the temporomandibular joint in humans, transgenic mice can be developed that manifest signs and symptoms of TM disorders. The animals would not only provide a model of disease, but also offer insight into possible underlying genetic factors. Researchers may also be able to induce disease in animals by manipulating mechanical, inflammatory, or immunologic features. Ideally, researchers would like to develop both short-term and long-term models of TMDs and use the models to assess the effects of interventions.

Biomarkers. Researchers should look for biological markers to help monitor the progress of joint repair following treatment, perhaps by testing joint fluid and tissue biopsies from an animal model and looking for changes in inflammatory mediators, growth factors, and tissue expression of proteins and genes.

Tissue culture. Methods of tissue culture will enable researchers to study explants of disc, cartilage, synovial tissue, and isolated connective and neural cells of the jaw joint. Cell isolation and separation procedures are needed to generate models for biochemical and molecular analysis.

Repair systems. Researchers should identify model systems to investigate events in normal cartilage and bone repair. Although it is generally accepted that tissue repair during postnatal growth is similar to the developmental processes that form the jaw in embryo, regulatory cues may be different. Because this area is relatively well studied, researchers suggested the possibility of using protein or gene therapy to selectively drive cartilage formation to regenerate and maintain the disc and other cartilage at the temporomandibular joint. However, these approaches raise questions about safety and the best ways of delivering these agents to the temporomandibular joint.

What causes the pain?

Trigeminal studies. Because pain is a primary symptom of TM disorders, research to elucidate the underlying mechanisms of how pain is triggered in the trigeminal system—the paired nerves serving the face and jaw—is key to understanding TM-related pain and eventually developing effective treatments to relieve pain.

Deep pain mechanisms. Many of the clinical attributes of temporomandibular disorders—such as lowered pressure-pain thresholds of the joint and muscle and a limited range of jaw motion—can be explained as a direct consequence of pain. Therefore, researchers should develop models in which to study muscular pain, joint pain, and the effect of mechanical load on the temporomandibular joint. These models should attempt to capture the effects of inflammation, nerve injury, and mechanical load on pain, and, if possible, the effect of cognitive and emotional states on a person's experience of pain.

Although there has been a recent surge in knowledge of pain receptors in cutaneous tissue, much less is known about the role of peripheral mechanisms in the muscle and joint, especially in the trigeminal region. In addition, researchers need to examine how the central nervous system is involved in sensing and modulating

TM-related pain. Recognizing these peripheral and central mechanisms may shed light on the chronic pain experienced by those with TM disorders.

What triggers functional problems?

Sensory feedback. Researchers should evaluate the role of proprioceptive feedback—signals sent from nerves that give information on the movement and positions of the body—in regulating jaw muscle function. It is now widely recognized that somatosensory neurons, such as those that deliver pain cues, undergo changes in response to extensive activation. However, it is unclear whether proprioceptive systems undergo similar changes, and what the effect of such changes might be.

Like the somatosensory system, proprioceptive feedback might be affected by hormones and gender. One possible approach is to study molecules already implicated in changing an animal's response to pain and look for effects on proprioceptive feedback. It is easier to develop assays for jaw function in rabbits and pigs. It would be easier to genetically manipulate mice to tease out the effects of specific molecules on the proprioceptive system, however.

Does angiogenesis affect the TMJ?

Angiogenesis pathways and molecules. Research should aim to illuminate the pathways that control angiogenesis and the pathways that regulate blood flow to the bone and temporomandibular joint. These processes are likely to affect pain, inflammation, post-surgical healing and the ability of implanted scaffolds to trigger new growth. Perturbations in these pathways may cause or exacerbate TM disorders. Understanding these pathways is also critical for examining how the bone of the temporomandibular joint responds before and after intervention.

Animal and human studies should be used to monitor blood flow and metabolism, and the responses of these systems to activity, chemical signals, injury, growth, and exposure to therapeutic drugs. Isolated vessels and cell cultures can help to analyze the molecular and cellular basis for these actions, the scientists said.

Researchers should also work to define the chemicals involved in the regulatory processes, determine the significance of new blood vessel growth and new nerve cell growth, or neurogenesis, during repair or healing of the temporomandibular joint and nearby tissues. These processes seem to work using similar ligands and receptors, suggesting there may be common mechanisms that regulate both processes. Using this knowledge base, it may be possible to develop strategies to redirect angiogenesis and neurogenesis to repair the diseased or damaged temporomandibular joint, researchers said.

What kind of drugs or surgeries will be effective treatments?

Drug inhibitory effects. Researchers should conduct animal studies to determine if therapeutic agents may have an inhibiting effect on the tissue repair process. People with TM disorders are prescribed drugs to reduce pain and swelling, to relax muscles, and to act as sedatives. If such medications are obtained over-the-counter, patients may receive little direction in terms of recommended dosage and frequency of use. A patient registry might be able to answer questions about drug effects.

Biomaterials research. A pressing research need is to develop new materials and processes to repair and reconstruct the temporomandibular joint. Advances in cell-based therapies, new materials such as photopolymers, and design-manufacturing principles should be applied to the specific biomechanical and loading requirements of the temporomandibular joint. Researchers should investigate strategies of cell-based repair, develop natural and synthetic materials for scaffolds, and pursue combinations of the two approaches.

Clinical research. Testing possible treatments for TM disorders is a critical task facing clinicians and researchers. Researchers at the meeting called for the development of safer methods to reconstruct the temporomandibular joint, the development of effective therapeutics such as drugs or cytokines, and consideration of the best ways of delivering those therapeutic agents to the joint or muscle. As TM disorders are further characterized, treatments may become more targeted, researchers said.

HOPE FOR THE FUTURE

"This [TMJ disorder] is a fascinating puzzle that can be solved ... if we approach it in an open fashion," from a variety of medical disciplines, said Harold C. Slavkin, Director of the National Institute of Dental and Craniofacial Research in Bethesda, Md., one of several agencies co-sponsoring the meeting.

"The TMJ Association was pleased to host this long-anticipated meeting of patient advocates, NIH agencies, and scientists from across disciplines," said Cowley. "This interaction showed that the current state of TMJ science is poor, at best—as frustrated TMJ patients have experienced. Patients in pain visit doctor after doctor, only to go through a series of unproven, unsuccessful treatments. This meeting is providing concrete steps for future research and safer, more effective treatments."

"Although a great deal is known about temporomandibular disorders, there are still major gaps in our understanding," concluded Andrew H. Kang of the University of Tennessee College of Medicine in Memphis. "Multidisciplinary research holds the best promise for finding cures for human disease of unknown causes like temporomandibular disorders," he said.

MOVING TMJ RESEARCH INTO THE 21ST CENTURY

Recommendations from The TMJ Association's first annual scientific meeting held May 22-23, 2000 at FASEB headquarters in Bethesda, Maryland

Following a day of formal presentations, speakers met in four breakout groups to develop a research agenda to address areas of knowledge critical to advancing our understanding of temporomandibular diseases and disorders. The four breakout groups corresponded to the major subject areas covered in the meeting. Recurrent themes emphasized:

- A paucity of information on characteristics of the normal, healthy TMJ that could provide a basis for understanding joint pathophysiology.

- The lack of a TMJ patient registry as well as banks of clinical material and failed implants.

- The lack of validated diagnostic criteria for classification of TM diseases and disorders.

- The need for epidemiologic and prospective studies as aids to the development of a TM disease taxonomy, patient demographics, and disease incidence and prevalence.

- The need for in vivo, in vitro, transgenic, and computer models of the TMJ. Studies of normal human volunteers are important as well as collections of normal human tissue samples. With respect to the research recommendations presented, the following specific model needs were identified:

  In vivo: Small animal models such as rat and mouse are useful insofar as they permit larger sample sizes and unique genetic research approaches to TMJ research. The larger pig model has strong potential because the joint anatomy and function are similar to the human TMJ. Developing specific TMJ defects in pig and other large animal models may provide rigorous validation of new interventions. Existing models for other anatomical joints, such as the knee, can be a source of comparative studies of pathogenesis and treatment. Finally, it would be valuable to conduct research to validate in vitro and computational models for problems in TMJ physiology and pathophysiology. Neuroendocrine studies require models of musculoskeletal pain associated with inflammation, nerve injury and/or mechanical load. Additional models are needed that capture the effect of cognitive and emotional state on the pain experience.

  In vitro: Models based on tissue or cell culture will require the establishment and characterization of methods of tissue culture for explants of disc, cartilage, synovial tissue, and isolated connective tissue and neural cells of the TMJ. Cell isolation and separation procedures of native human and animal TMJ tissues should be developed to generate suitable in vitro models for biochemical and molecular analysis. In addition, permanent cell lines should be developed or identified that reflect the native cell populations of the TMJ.

Transgenics: The use of existing and new transgenic animal models to identify TMJ development and pathology should be encouraged. Gene deletion/addition studies and mutational analysis may accelerate the identification of critical molecules involved in the pathogenesis of some temporomandibular joint diseases. The characterization of these models will be used to study mechanisms of disease progression and the influence of mechanics on initiation and progression of disease.

Susceptible strains: Screening studies of animal species and existing animal strains should be supported to identify animals that may be susceptible to TMJ disease. Alternatively, the development and validatation of experimentally induced models of TMJ disorders (including inflammatory, immunologic and degenerative pathologies) can be considered. These approaches should be based on suspected or validated pathophysiologic processes and must be verified using relevant human markers of temporomandibular joint disease.

- The need for biomarkers of TMJ diseases and disorders. There are no objective criteria to assess the extent of TMJ tissue/cell damage, to classify the severity of joint dysfunction, or to evaluate tissue/cell repair following surgical intervention, pharmacological treatment, or gene/protein therapy. Proposals include:

  Synovial fluid and tissue biopsies collected from control and TMJ patients to quantitate the amount and biological activity of inflammatory mediators, growth factors, tissue history, cell morphology, and tissue expression of proteins/genes. Comparisons of human samples with specimens from appropriate animal models, both before and after surgical intervention, are needed to determine qualitative/quantitative similarities or differences in inflammatory mediators, growth factors, and tissue proteins/genes.

  New or improved instruments and techniques include the need for finer detailed non-invasive bioimaging technologies and tools for analyzing joint microcirculation. Biological and anatomical data can be correlated with clinical symptomology in TMJ patients to assess changes in inflammatory mediators, growth factors, and tissue expression of proteins in the natural history of the disorders.

I. TMJ Tissue Structure/Function

Evaluate the biomechanics of the TMJ

The TM joints, like other joints, subserve a mechanical function, allowing for movement and force transmission. The joint surfaces, their coordinated motions, and the neuromuscular architecture that orchestrates their motion makes these joints the most complex in the body. Biomechanical features are basic to an understanding of the development of TMJ disorders, which can arise from mechanical events (injury, dental and surgical procedures). Some in vivo recording techniques for tissue deformation are available and have been used to a limited extent. Further work is needed, using pig and other laboratory animals.

In addition to assessing the stresses and strains on articular cartilage, TMJ disc, and bone, measurements of the joint capsule and the location of sites where soft tissues

attach to bones are important, as rupture of these elements is probably a key feature in TMJ injury. Measures of synovial and other fluids must be incorporated as well. Studies in humans can use advanced bioimaging as an alternative to invasive measurements.

Knowledge gained from in vivo biomechanical studies of normal joints can be applied to study the behavior and biointegration of candidate biomaterials proposed for joint prostheses.

Clarify vascular structure and blood flow in relation to the metabolic demand of joint tissues

The regulation of blood flow to the structures of the TM region under normal conditions is poorly understood and may involve unique signaling mechanisms and pathways as well as unique responses to vascular growth factors. The control of angiogenesis and the regulation of blood flow to the bone and TMJ are major issues in relation to pain, inflammation, post-surgical healing, and the potential vascularization of prosthetic devices.

In vivo animal and human studies will be needed to define the vascular responses to activity, neuroendocrine factors, and normal growth, as well as responses to injury, therapeutic drugs. and other interventions. These studies can take advantage of laser-Doppler flowmetry, tracer washout studies, microsphere distribution studies, local fMRI, ultrasound, electromagnetic flowmetry, etc. New techniques and model systems will be required to study the microcirculation of some of these structures. Isolated vessels, primary organ, and cell culture systems should be utilized to assess the relationships between endothelial and vascular smooth muscle functions, including surface receptors, cell signaling pathways, ion channels and their physiological function. It is imperative to understand the role of tissue metabolites and oxygenation upon these levels of vascular control.

Study postnatal growth, maturation, and aging in the normal TM joint and in response to injury

The extent to which changes in the growth, maturation, or aging of joint tissues are associated with the progression of TMJ disorders is not known. Information is also lacking about the normal adaptive properties of jaw muscle, bone, disc, capsule, ligaments, and synovial structures in response to mechanical loading/unloading and the hormonal environment. The mechanisms regulating cell and matrix turnover in these tissues must be characterized in order to understand the pathogenesis and consequences of temporomandibular joint disorders (TMDs). Relatively little is known about joint regenerative capacity in response to injury—whether acute, chronic (repetitive) and/or resulting from surgical trauma.

II. TMJ Pathology

Define mechanisms of injury and disease

The pathogenesis of temporomandibular disorders is poorly understood. Disease may result from patient susceptibility or as a result of injury. Articular tissue responses to mechanical, metabolic, infectious, immunologic, and neural stimuli or insult should be examined in appropriate animal models and in studies involving human subjects. In addition, the influences of therapies on disease progression should be examined. These studies should include tissue and joint responses to drugs and prostheses.

Identification of the mechanisms of injury and disease could lead to improved diagnostics and new treatment modalities. Restricted joint function with limited mandibular range of motion may result from adhesion formation and subsequent joint fibrosis or ankylosis. Yet, the mechanisms of adhesion formation in the TMJ are currently unknown. Likewise, pain is a primary complaint of the majority of patients, yet basic mechanisms of acute and chronic TMJ pain are poorly delineated at the present time. [See Neurological/Endocrine recommendations.]

Develop diagnostic criteria based on validated physiologic models of TMJ disease

TMJ patients remain poorly characterized because current diagnostics lack specificity and are not based on physiologically validated models. There is a need for molecular markers of pathophysiologic processes implicated in the development of TMJ diseases. Such markers can also be used to monitor disease progression and treatment outcomes and can be associated with biochemical, genetic, mechanical or neurosensory processes. In addition, studies to identify a genetic basis for susceptibility to TMJ disease should be conducted. New imaging techniques will be required for correlative studies. These will include development of non-invasive imaging methodologies to identify disease of cartilage, disc, bone, muscle, and the nervous system. Dynamic, real-time imaging should be explored to couple mechanical and functional information with image analysis. Arthroscopic imaging should be improved. This method may be ultimately coupled with tissue sampling and assessment.

Pathophysiological pathway identification and development of therapeutic strategies

There is a need to design studies to identify specific mechanistic pathways involved in the development of TMJ diseases and based upon this information develop targeted therapeutic approaches that address specific pathologic mechanisms, joint dysfunction, and pain. These may include, among others, mechanisms related to cytokine function, growth factors, etc., and the development of drugs that can be targeted to tissue specific sites. Finally, new stem cell based technologies and other approaches must be utilized for the development of new biomaterials that are suitable for use in the reconstruction of diseased human temporomandibular joints. Since many patients may require TMJ reconstruction, there is also a need to develop new surgical techniques.

Characterize temporomandibular joint tissues

Studies designed to compare and contrast the molecular (matrix components, proteases), cellular (phenotype, response to soluble and cell surface expressed mediators), and genetic (cDNA libraries) features of TMJ tissues and tissues from other synovial joints should be conducted. In addition, the biomechanical properties (compressive, tensile, shear) of the TMJ tissues should be characterized. The characterization should include the study of genetic (DNA expression arrays) and cellular responses to compressive, tensile and shear loading of the tissue. Given the unique structural and functional characteristics of the human temporomandibular joint relative to other joints in the body as well as in comparison to the TMJs of other species, it is expected that unique biomechanical properties of human TMJ tissues will be discovered.

III. Neural-Endocrine Research

The vast majority of pain research has focused on cutaneous or visceral pain in non-trigeminal systems. A considerable gap in knowledge exists regarding mechanisms of musculoskeletal pain and associated hyperalgesia—particularly in the trigeminal system. Studies in the trigeminal system are more technically challenging and are more anatomically and functionally complex than comparable studies in the spinal system.

Conduct epidemiological studies

A prospective, observational, mechanistic-based epidemiologic study of TMDs is necessary, based upon our understanding of peripheral and central mechanisms of plasticity associated with persistent pain. Based upon this classification, the following potential risk factors should be evaluated: female sex, age, relationship to pregnancy, use of hormone replacement therapy, injury, surgery, genetic susceptibility, and co-morbid conditions. Mechanistic tests to be incorporated into epidemiologic studies include assessments of hyperalgesia in deep tissues, referred pain, sympathetic nerve involvement, etc. The present research classification system (Research Diagnostic Criteria or RDC) is inadequate because it does not provide information of mechanistic value

Elucidate peripheral mechanisms in TMD pain

Multiple models are required to study peripheral mechanisms of TMD pain. The appropriate model selected depends upon the experimental hypothesis and outcome measure. Although the focus of this research is upon the trigeminal system, we are also interested in research on peripheral mechanisms of other musculoskeletal pain conditions. Specific topics include:

- Autonomic involvement
- The role of peripheral plasticity in afferent fibers
- Transduction mechanisms in muscle and joint (especially mechanical)

- Paracrine interactions among bone-muscle-neuron-immune and other cells (soluble factors, e.g., cytokines, neurotrophins)
- Endocrine (hypothalamus-pituitary-adrenal axis, gonadal steroids)

Elucidate the role of central mechanisms in TMD pain

Multiple models are required to study central mechanisms of TMD pain. The appropriate model selected depends upon the experimental hypothesis and outcome measure. Although the focus of this research is upon the trigeminal system, we are also interested in research on peripheral mechanisms of other musculoskeletal pain conditions. Specific topics include:

- CNS plasticity to musculoskeletal injury
- Descending modulation of musculoskeletal pain
- Higher order processing of musculoskeletal input
- Autonomic involvement
- Central neuroendocrine or immune effects

Evaluate the role of proprioceptive feedback in regulating jaw muscle function

Plasticity in the somatosensory system has been widely studied. Both primary afferent receptor neurons and their second order partners undergo remarkable changes in response to activation. The changes are generally associated with an increase in synaptic efficacy brought about by neuropeptides like substance P or neurotrophins like BDNF. These changes appear to be more pronounced in females than in males. Proprioceptive feedback from muscle spindles, Golgi tendon organs, periodontal receptors, and other low-threshold mechanoreceptors has been proposed to play an important role in masticatory muscle function. It is not known whether plastic changes similar to those established in the somatosensory system are found among proprioceptive afferents. In particular, it is not known whether the efficacy of proprioceptive regulation of motor function in jaw movement is modulated by extensive activity of these afferent neurons, whether plastic changes in the somatosensory system have consequences for proprioceptive feedback, whether any such effects are sex-dependent, or whether such changes might underlie sex differences in masticatory muscle structure or function.

These questions can be studied in three ways. First, it is important to determine whether proprioceptive afferent neurons undergo plastic changes in response to their repetitive activation or the activation of somatosensory neurons. This could be studied anatomically as changes in the phenotype of the afferents and functionally as changes in both the response properties of the neurons and the transmission of those signals to second order neurons, both sensory and motor. The significance of such changes should be studied in different species and in both sexes, under different hormonal conditions. Second, the effects of molecules already implicated in somatosensory plasticity should be investigated for effects on proprioceptive feedback. Signaling molecules such as neurotrophins or neuromodulators such as substance P are potential mediators of plastic changes in proprioceptive feedback during oral behaviors. Third, the role of "helper" cells, such as mast cells, which might function to amplify any signals mediating plasticity, should be studied.

IV. TMJ Tissue Engineering

Determine the unique tissue repair problems in TMJ patients

TMD patients can present with a wide range of clinical findings, such as condylar overgrowth, intraarticular heterotopic ossification, excessive scars, and adhesions. Repair mechanisms may be unique in various sites and disorders. A broad series of clinical studies is required to understand repair mechanisms in the many components of craniofacial tissues and elucidate any gender-specific aspects of repair. In order to obtain diagnostic information relating to the various defects, these studies should characterize synovial fluid factors that may reflect pathology and natural repair of these tissues.

Clarify tissue changes associated with foreign body reaction caused by alloplastic TMJ implants

Thousands of patients who have failed alloplastic implants have developed a foreign body reaction that leads to local destruction of joint structures and adjacent tissues and may potentially give rise to systemic manifestations. Surgical attempts to remove the affected tissues and alloplastic materials and reconstruct the joint generally lead to a failure to stop the process, with continued tissue destruction and debilitating pain and dysfunction. A better characterization of the tissue changes and an understanding of their specific etiology can lead to more appropriate interventions to eliminate the problem. A registry for the collection of surgical biopsy materials for analysis would help to better define the condition. Basic research using a large animal model to simulate the acute and chronic phases of failed alloplastic TMJ implants would enable researchers to explore immunomodulatory factors and cytokines that influence the inflammatory process in the TMJ and help determine the success and/or failure of new alloplastic implants.

Determine the effects of therapeutic drugs on tissue repair in temporomandibular diseases and disorders

Patients use a large number of analgesic, anti-inflammatory, sedative, and muscle relaxant drugs, based on conventional as well as complementary and alternative medicine approaches, including nutritional supplements and herbal preparations. Often, these are obtained over the counter with no control of dosage or frequency of use. While some of these agents may be helpful in managing pain and dysfunction, little is know about their effects on the reparative process. There is a need to determine in controlled clinical studies whether these agents are beneficial (provide symptomatic relief), harmful (cause detrimental effects on tissue repair processes) and how they interact with each other.

Study nerve-vascular interactions to gain insight into mechanisms regulating joint growth and repair

The recent identification of shared ligands and receptors between endothelial cells and neural cells suggest that there may be common mechanisms that co-regulate angiogenesis and neurogenesis. Initially, ligands and receptors and their associated pathways for angiogenesis and neurogenesis should be demonstrated in TMJ structures using both in vitro and in vivo experiments. Next, investigators must determine the functional significance of angiogenesis and neurogenesis during the repair/healing response in the TMJ and associated tissues. Finally, scientists could develop novel strategies to redirect angiogenesis and neurogenesis in the diseased/damaged TMJ.

Evaluate novel reconstruction methodologies for temporomandibular diseases and disorders

Existing FDA-approved prostheses, materials, and biologic/mechanical processes are inadequate to meet the mechanical and biologic needs of repair and reconstruction of the TMJ. The unique anatomical features of the TMJ require precise information of the biomechanics and loading requirements. Advances in novel materials and tissue engineering should be applied to these problems. Some promising areas include cell-based therapies, new materials for biological scaffolds, and computer aided design-manufacturing principles. Advances in minimally invasive technologies offer potential applications for diagnosis, management, and treatment of TMD.

A major effort will be required to establish multidisciplinary teams to define the structure-function relationships in TMJ and improve the design and construction for joint and meniscal replacement. Development of natural and synthetic materials may require optimization of variables such as architecture, fabrication, strength, resorption, and controlled release of biological agents. Computer techniques will be necessary to assist in model simulation and fabrication. Biological technologies may include growth factor and cytokine delivery as well as cell-based therapies using a stable source of stem or osteoprogenitor cells.

Explore the potential for protein and gene therapeutic approaches to temporomandibular repair

Currently there is a wealth of data on morphogenic factors that are associated with bone and cartilage formation. The ability to selectively promote cartilage repair may provide a potential therapeutic approach for treating patients with TMD. In vivo and in vitro model systems can be developed to explore effective approaches for delivery for soluble or conjugated factors to anatomically appropriate sites. It will be critical to monitor the repair process and measure the presence of exogenous and endogenous factors. Bioactive morphogenic gene products can be delivered by gene therapy and mimetic device approaches.

Compare the processes controlling postnatal joint homeostasis with prenatal joint development

It is generally accepted that tissue repair during postnatal growth is similar to a recapitulation of events during embryogenesis. Nevertheless, the postnatal microenvironment may provide a different set of regulatory cues that must be defined to optimize tissue repair strategies. The presence of a mature inflammation system distinguishes the postnatal setting. Initially, fundamental studies of the joint are required to understand molecular and regulatory events in TM repair versus embryologic chondrogenesis. Comparative studies may be based on knowledge and techniques learned with appendicular studies. It is likely that inflammatory cells and mediators will have a key role. Transgenic mouse models may help answer some basic questions despite the small size of the model.

Develop evidence-based protocols for the management of myofascial pain (without joint involvement)

Many TMD patients present with pain and dysfunction in the absence of recognized TM joint pathology. A rational approach to the management of these symptoms should be based on an understanding of the etiology, predisposition, perpetuation factors, and the contribution of gender and genetic factors Clinical registries would help to define the issues requiring more in-depth study. Likewise, animal studies may lead to new therapies requiring clinical study. Multi-center clinical outcome studies require that an extensive infrastructure be created. All of these approaches may elucidate the relationship between myofascial pain and dysfunction and pathology in the TMJ. Association with what may be related conditions such as fibromyalgia, chronic fatigue syndrome, osteoarthritis, adult and juvenile rheumatoid arthritis, lupus, and other autoimmune conditions should be evaluated.

The *TMJ* Association

In This Issue…