Treatment of TMDs:

Bridging the Gap Between Advances in Research and Clinical Patient Management

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dedication

This book is dedicated to the memory of Dr Laszlo Schwartz, who founded the first academic temporomandibular joint (TMJ) center in the United States at Columbia University in 1949. At that time, the generally accepted viewpoint was that abnormalities in dental and jaw relationships were the major factors in the development of disorders related to the TMJ. Therefore, procedures such as occlusal adjustment or major restorative dentistry were the preferred therapies. All this eventually changed as the result of his pioneering research and his leadership. His textbook, *Disorders of the Temporomandibular Joint*, published in 1959, represented a major paradigm shift from a mechanical to a biopsychosocial approach to their treatment. Dr Schwartz's work not only had a profound influence on the future direction of research in the field, but it has also led to improved care of patients with temporomandibular disorders.

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foreword

I am very pleased to write a foreword for this textbook. My first reason for this is based on the major shift in the concepts and protocols for managing temporomandibular disorders (TMDs) and orofacial pain that I have seen in my professional career. These changes have occurred as a result of the new knowledge we have gained that has enhanced our understanding of these conditions, and the precise goal of this textbook is to bring this type of information to the clinician. Another reason that I am pleased to write this foreword is because of my admiration for both Dr Greene and Dr Laskin. Very early in the 1970s, these two individuals boldly questioned universally accepted therapies, and their efforts began a professional movement that demanded more evidence to support our TMD treatments. Acquiring such evidence is essential in offering the best care to our patients. This textbook provides the clinician with an understanding of the basic science and clinical research that supports the use of our current therapies while also pointing the way toward future treatment possibilities. These principles are fundamental to good health care.

Many years ago, a link was made by the dental profession between the occlusal relationships of the teeth and orofacial pain. Early on it was observed clinically that in some patients changes in the occlusal condition seemed to be associated with a reduction in pain. Unfortunately, at that time we had very little understanding or appreciation for the scientific method that could be used to better define this association. Instead, we made some assumptions regarding connections between what we knew (occlusion) and what we really did not know well (the pathophysiology of pain). Our early mentors taught by authority and not necessarily by reason or evidence. This seemed to fit nicely with the mechanistic model that we dentists understood and used in managing most of our patients' common dental problems. However, it eventually became obvious that there were significant inconsistencies in achieving success with our orofacial pain patients. We then began to ask more questions that would help us better understand these patients' problems.

By the late 1980s, the profession began to appreciate and embrace the concept of basing our treatment decisions on scientific studies and not just assuming that our mentors were correct. This stirred up much controversy, not only because it discredited some mentors but also because it forced us to give up concepts that we had accepted that had no scientific merit. We learned, as we have continued to learn, that it is difficult to change belief models.

By the late 1990s, the scientific method became more embraced by the profession and we began to hear the term *evidence-based medicine*. Significant research funding became available, especially for the investigation of pain. However, much of this research was in the basic science domain, leaving the clinician with little connection to the findings. Realizing the need to link these research findings to the practice of medicine and dentistry, the concept of "translational science" became a standard goal. Translational science is exactly what this text offers. It presents a state-of-the-art description of the known biology of TMDs and orofacial pain, as well as of developing concepts, in a format that can be translated into the clinical management of patients.

Another important feature that was uncovered by basic science research was that pain is pain. Although there are definitely some unique features of the masticatory structures, we have learned that the mechanism by which nociceptive impulses are initiated, transmitted, and perceived as pain is not unique to the masticatory system but in fact common to all other areas of the body. We have also learned to appreciate that dentistry and medicine blend together in the area of orofacial pain. The mechanistic model first embraced by the dental profession can no longer explain the pain our patients experience, especially as it becomes chronic. In fact, most chronic orofacial pain conditions are very similar to other chronic pain conditions managed in the medical field. Moreover, many of the chronic pain patients have two or more pain conditions simultaneously. The evidence-based research in orofacial pain has moved us away from teeth to the vast field of understanding human pain and suffering.

Although we have advanced greatly in the field of TMDs and orofacial pain, our knowledge is still incomplete. Yet every day clinicians meet patients who ask for help with their pain and suffering. We must take the best scientific evidence available and determine the most appropriate treatment for each patient. This is not always an easy undertaking, yet it is the most critical task that needs to be accomplished for the patient. This is the concept behind "best practice." This text will help clinicians make many of these very important decisions for their patients. The most essential factor to consider is to always select the most conservative approach and to do no harm. The human being is a remarkably complex organism with a great ability to adapt and recover. The most conservative approach to therapy is often adequate to enhance this recovery.

I commend Drs Greene and Laskin for their efforts in assembling this fine text. I also applaud the contributing authors, many of whom have dedicated their life's work toward gaining a better understanding of why and how our patients suffer and what can be done to help them. The true value of this book will be measured not only by the number of clinicians who read it but also by how they use this information to reduce the pain and suffering of their patients. This is the ultimate responsibility of the health care provider.

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The central theme of this book arises from a single question: What is happening in basic and clinical research today that likely will significantly impact the diagnosis and treatment of temporomandibular disorders (TMDs) in the near future? Clearly, the answer to this question must extend far beyond the traditional pain issues that have been the predominant focus of most recent research. The combination of new research tools with innovative experimental designs has produced a large body of information about musculoskeletal disorders, and much of this can be directly or indirectly applied to the temporomandibular joint (TMJ). However, many dental clinicians are unaware of this type of information because it is presented mainly in medical publications or nonclinical scientific journals. Thus, there is a significant information gap between many of the latest advances in the general field of musculoskeletal disease and their potential applications in the clinical management of patients with various TMDs. This is especially true in regard to the issues of acute versus chronic pain. It is the purpose of this book to help bridge this gap.

The book is divided into five sections, each containing numerous chapters that deal with varying aspects of the anatomy, biochemistry, neurophysiology, and psychology of the common TMDs. Chapters dealing with topics such as the biomechanics of normal and abnormal TMJ function, the complexities of TMJ and masticatory myofascial pain, diagnostic technology and markers of disease, pharmacologic management of TMDs, and tissue engineering of joint components provide a strong foundation for discussing other important issues. Each chapter discusses present knowledge in the particular field and how it may apply to the diagnosis and treatment of TMD patients. In addition, every chapter provides an overview of current new research in the field and its potential for changing future patient care. Included are such clinically relevant topics as the relation of abnormal joint function to joint pathology, the prediction of treatment responsiveness, how sleep disorders affect facial pain, and the role of comorbid conditions in pain response and management. Several chapters also deal with the evolving field of pharmacotherapeutics, including new analgesic drugs, drugs for managing neuropathic pain, and potential drugs for stopping or reversing degenerative joint disease. Because of the numerous technical terms used in this book, an appendix of abbreviations has been added.

We are fortunate to have as contributors to this book a group of international authors who are recognized as leading experts in their fields and who have contributed significantly to our current knowledge through their well-known research and publications. We wish to thank them for their time and effort in accepting the challenge of writing chapters with a focus on future clinical applications of their knowledge. Ultimately, we hope that the information they have offered in this book will provide the reader with a better understanding of the complexities of the various TMDs, which should help to make their management easier and more successful now as well as in the future.

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I Understanding Regional and Widespread Pain Phenomena

The five chapters in this section are devoted to topics that expand the understanding of orofacial and temporomandibular disorder (TMD) pain phenomenology. The authors have summarized the current research in their respective areas, and they offer projections for future applications of that research to the clinical situation. Advances in these areas are having a profound impact on both researchers and clinicians, and already many of those advances are being applied to the management of TMD patients.

In the Dubner, Ren, and Sessle chapter, the newest concepts of pain neurophysiology are well summarized in just one of their sentences: "An emerging concept is that the immune cells, glia, and neurons form an integrated network in which activation of an immune response modulates excitability of pain pathways." This is one of many fresh insights that their chapter provides regarding pain mechanisms in general and specifically musculoskeletal pain.

Benoliel, Svensson, and Eliav have reviewed the extensive literature on muscle pain, with special emphasis on masticatory myofascial pain. This review shows that many factors may be involved in the etiology and pathophysiology of such pain, including host susceptibility, genetically influenced physical traits, psychologic issues, and environmental parameters such as ethnicity, culture, and stress. Thus, this type of pain appears to be more complex than joint pain, which leads them to conclude that in the future "emerging pharmacotherapeutic targets [will] appear at various levels, including receptors, regulatory proteins, and downstream enzymes."

Emshoff brings his wide experience in the study of temporomandibular joint arthritis to his extensive review of the literature on that topic. Many of the etiopathologic features of osteoarthritis in general have been elucidated in recent years, and this has shown that detrimental changes in bone, cartilage, and synovium appear to be interconnected in the pathogenesis of this disease. These findings have led him to conclude that future therapeutic areas on which to focus should include osteochondral angiogenesis, mitochondrial dysfunction, and chondroprotection through lubrication.

The topic of comorbidity has only recently become well recognized and widely studied in the pain field. The various conditions that are found to coexist in many TMD patients (especially chronic TMD patients) not only complicate the diagnosis of their facial pain complaints but also clearly affect the management of these problems. As Velly, Schweinhardt, and Fricton point out, clinicians need to identify comorbid conditions in TMD patients early so as to provide proper therapy to manage their TMD pain. This may require collaboration with other health care providers as part of a comprehensive rehabilitation treatment program. Their chapter provides the latest information on this important topic, along with suggestions for managing such patients clinically.

Macaluso, Carra, and Lavigne have provided an overview of how the topics of sleep and pain have converged in recent years. Sleep studies of pain and non-pain patients have demonstrated important differences between them. This has led to the conclusion that sleep deprivation and fragmentation have an essential role in the way pain is perceived and exacerbated. Sleep problems can exacerbate pain, and intense pain or variable pain intensity can lead to poor sleep. All concerned clinicians must be prepared to deal with this reality.

Sensory Mechanisms of Orofacial Pain

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This chapter reviews the processes involved in orofacial sensory functions and their clinical correlates. Particular emphasis is given to temporomandibular joint (TMJ) and masticatory muscle pain and their underlying mechanisms.

Peripheral Mechanisms

The TMJ and masticatory muscles are innervated by the primary afferent (sensory) nerve fibers of the trigeminal nerve. These fibers terminate as sense organs (receptors) that respond to peripheral stimulation of the tissues.[1–3] The large-diameter, fast-conducting primary afferent nerve fibers (namely, the A-alpha [Aα] and A-beta [Aβ] afferents) end in the tissues, typically with connective tissue or epithelial cell specializations encapsulating their endings. These receptors respond to low-threshold (non-noxious) mechanical stimuli or movements. In primate jaw-closing and lingual muscles, some of these large-diameter afferent endings are associated with muscle spindles and Golgi tendon organs that respond, respectively, to muscle stretch and contractile tension; other orofacial muscles have few, if any, of these specialized endings. Some of the small-diameter, slow-conducting primary afferents (A-delta [Aδ]; C) instead terminate principally as free nerve endings, some of which can respond to non-noxious thermal stimuli (ie, warm or cold thermoreceptors). However, most free nerve endings are activated by noxious stimuli and are therefore termed *nociceptors.*

Activation of the nociceptive endings in the TMJ and masticatory muscles can ultimately lead to the perceptual, reflex, and other behavioral responses characterizing musculoskeletal pain. In contrast, the various low-threshold receptors in these tissues and their afferent inputs to the central nervous system (CNS) play a role in responses evoked by stimuli related to non-noxious joint position, movement, and muscle stretch or tension.[4,5] It has been known for several decades that the TMJ is supplied by afferents principally in the auriculotemporal branch of the mandibular nerve and that in most mammalian species the richest innervation is in the posterolateral aspect of the TMJ capsule. However, there is conflicting data on whether the articular surfaces and disc of the TMJ are innervated. The innervating fibers may not all be sensory (ie, afferents) but may include efferents of the sympathetic nervous system.[1–3,6] Free nerve endings are abundant in the TMJ and also in the masticatory muscle tissues, but more specialized receptors are sparse except for those muscles with muscle spindles and Golgi tendon organs.

About 40 years ago, the first electrophysiologic investigations were made of the response properties of TMJ and masticatory muscle afferents.[1,6–8] They documented that low-threshold non-nociceptive afferents have either slowly adapting or rapidly adapting responses to jaw movement or change in condylar position, and these responses were implicated in the sense of jaw movement and jaw position sense (kinesthesia). It became apparent, however, that other primary affer-

Table 2-1 Diagnostic criteria for masticatory myofascial pain

Myofascial pain*	Myofascial pain with or without limited opening†
Regional, dull, aching pain • Aggravated by mandibular function	**Axis I: Physical findings** Complaint of pain of muscle origin • In jaw, temples, face, preauricular, or auricular at rest or during function
Hyperirritable sites or trigger points • Frequently found within a taut band of muscle tissue or fascia • Provocation of these trigger points alters the pain complaint and reveals a pattern of referral • More than 50% reduction of pain is inducible by muscle stretch preceded by trigger point treatment with vapocoolant spray or local anesthetic injection Signs and symptoms that may accompany pain • Sensation of muscle stiffness • Sensation of acute malocclusion, not clinically verified • Ear symptoms, tinnitus, vertigo, toothache, tension-type headache • Decreased mouth opening; passive stretching increases opening by > 4 mm • Hyperalgesia in the region of referred pain	Pain associated with localized areas of tenderness to palpation in muscle Pain on palpation in more than three of the following sites and at least one of which is ipsilateral to the pain complaint (right/left [R/L] muscles count for separate sites): • R/L temporalis: posterior, middle, anterior, tendon (8 sites) • R/L masseter: origin, body, insertion (6 sites) • R/L posterior mandibular region (2 sites) • R/L submandibular region (2 sites) • R/L lateral pterygoid region (2 sites) Myofascial pain as above accompanied by: • Stiffness of muscles • Pain-free unassisted mandibular opening of > 40 mm • With assistance, an increase of ≥ 5 mm in mandibular opening
No psychosocial assessment required	**Axis II: Psychosocial comorbidity‡** Pain intensity and pain-related disability • Graded chronic pain scale • Jaw disability checklist Depression and somatization • Symptom checklist for depression and somatization (SCL-90)

*American Academy of Orofacial Pain.[2]
†Research Diagnostic Criteria for Temporomandibular Disorders.[3]
‡Other validated measures may be used.[4]

The early pathophysiologic theories offered "one cause, one disease" hypotheses involving such things as muscle hyperactivity, altered occlusion, or stress. However, these theories were largely based on cross-sectional studies that are not adequate for establishing causality or possible risk factors. Accumulated data have now indicated a more complex etiology, and the most current concepts are the multifactorial[14,15] and biopsychosocial[16] theories. Both of these theories propose a complex interaction between environmental, emotional, behavioral, and physical factors and have increased our understanding of the factors involved at a population or group level. However, specific risk factors may not be active in any given case, and therefore these concepts still do not explain why an individual patient develops MMP. Dworkin et al[17,18] approached the question of pathophysiology using prospective studies and showed early on the importance of risk factors such as the psychologic profile and the presence of pain in other sites. These and other studies have established psychosocial distress and impaired pain modulation as the two major emerging factors in understanding the etiology of persistent MMP.[19–22] It has become clear that these factors act within a milieu of further instigating or modulatory factors such

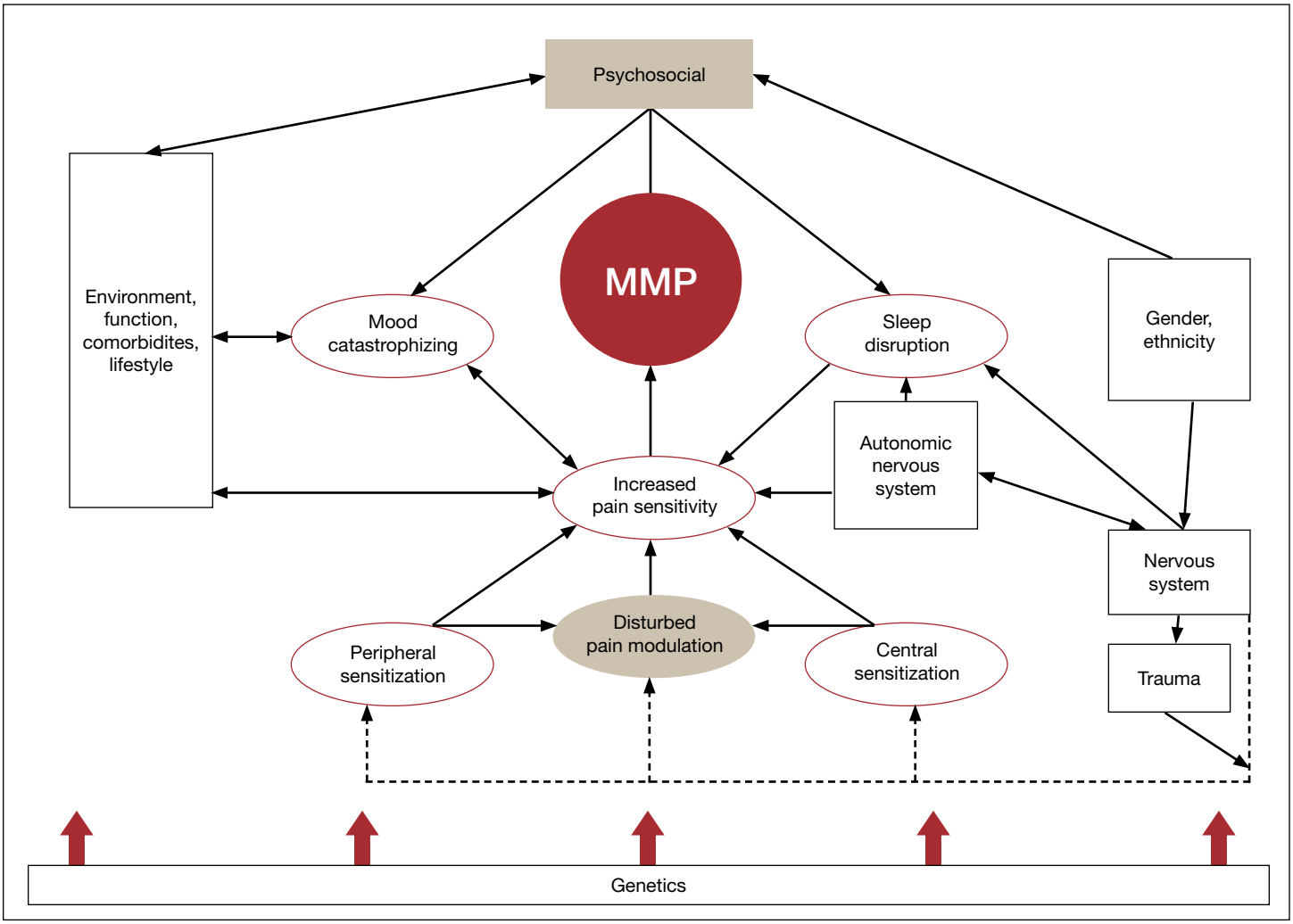

Fig 2-1 A complex disease model of MMP. Overall, it is reasonable to assume that MMP shares many of the features of other persistent pain conditions.[24] The pain in MMP occurs within a framework of nervous system changes initiated by external events and modified by various intrinsic factors (eg, mood, cognitive set, neurodegeneration).[24] It can also be viewed as a "gene by pain modulatory circuits by environment" interaction.[23] Multiple genes have been identified (eg, COMT, α-adrenoreceptor 2, glucocorticoid receptors, protein kinase, muscarinic receptors, transcription coregulators, and phosphorylators of G proteins[25–27]) that carry an increased risk for higher pain sensitivity. Environmental factors can increase the risk either through psychosocial mechanisms or physical factors such as trauma. The overall presentation of pain is determined by the interplay of several "brain" factors like context, cognition, mood, learning, memory, sleep, and neurodegeneration that affect inhibitory circuits.[23,24] Furthermore, biologic sex and ethnicity may influence the balance between factors.[23,24,28]

as genetics, proinflammatory states, cardiovascular and neuroendocrine function, trauma, and the social and environmental makeup of the individual[23] (Fig 2-1). Baseline data from the Orofacial Pain Prospective Evaluation and Risk Assessment (OPPERA) case-control study support the idea that TMDs are complex multifactorial conditions.[29] At this stage, the onset cases in the OPPERA study largely (85%) suffer from both MMP and TMJ disorders,[30,31] limiting the conclusions that can be drawn specifically about MMP pathophysiology.

Nervous System Alterations in MMP Patients

Pain modulation and MMP

Complex behavioral influences such as anxiety, depression, belief states, and cognition can separately influence pain perception and the pain experience. A key system that is able to

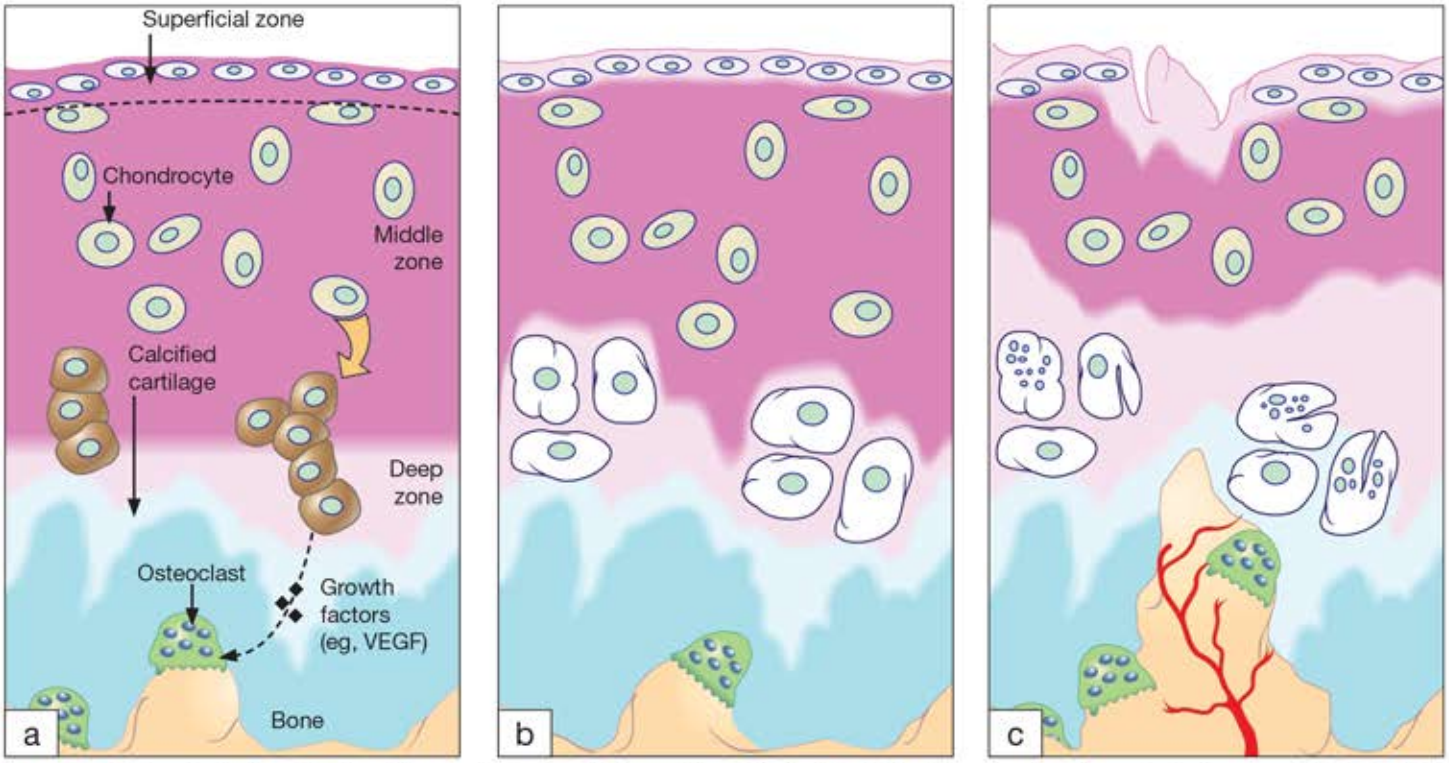

Fig 3-5 Hypothetical model of cartilage and subchondral bone interaction in OA. *(a)* Healthy chondrocytes suffering from a pathologic strain (due to instability of the joint or severly increased mobilization) start to become hypertrophic and produce growth factors (eg, VEGF) that diffuse toward the underlying bone marrow and stimulate osteoclastogenesis. *(b)* Persisting strain. Chondrocytes become more hypertrophic and produce less sulfated glycosaminoglycans (sGAG) to sustain the cartilage. Osteoclasts start to tunnel through the subchondral bone, inducing the first changes to the biomechanical properties of the tissue. *(c)* Progressive phase of OA. The tidemark between cartilage and bone shifts upward, reducing cartilage thickness. The remaining cartilage is strongly depleted of sGAG and becomes structurally deprived. Osteoclast activity extends into the calcified cartilage up to the border with the deep zone of the cartilage. There is vascular ingrowth into the cartilage via the pores. Later on, osteoblasts will infiltrate and start to deposit bone, resulting in end-stage sclerosis. (Reprinted from Weinans et al[42] with permission.)

and that the activated HIF-1 can induce osteoclastogenesis via repression of osteoprotegerin expression.

Subchondral bone

An intriguing aspect of OA is the increased turnover and subsequent changes in the subchondral bone. One of the few known molecules that could initiate this high turnover is VEGF. It has been observed that the deep articular chondrocytes show VEGF expression 2 weeks after OA induction by anterior cruciate ligament transection (ACLT) or a combination of ACLT and partial meniscectomy in the rat.[65] In vitro studies have shown that chondrocytes respond to mechanical overloading with the expression of HIF-1α and VEGF, subsequently leading to the induction of MMP-1, -3, and -13, which mediate a cartilage-destructive process.[61,66] VEGF has also been shown to promote angiogenesis and osteoclastogenesis as a consequence of overloading, which could potentially initiate a cascade leading to subchondral plate resorption and high subchondral bone turnover[67] (Fig 3-5).

An interesting molecule in this respect is sclerostin,[68] which was found to have greater expression in the chondrocytes in OA joints than in the chondrocytes in healthy joints.[69] Sclerostin inhibits the wingless/integrated (Wnt) signaling pathway, and Wnt signaling is known to be critically involved in the biology of the cartilage–subchondral bone unit.[70] An attempt to avoid an OA-related phenotype upregulation of sclerostin by chondrocytes could be the rescue response. In this way, cartilage degradation could be prevented while bone remodeling would be stimulated. This hypothesis has been supported by study findings in a rat model in which Wnt signaling inhibition indeed protected against the progression of OA.[71]

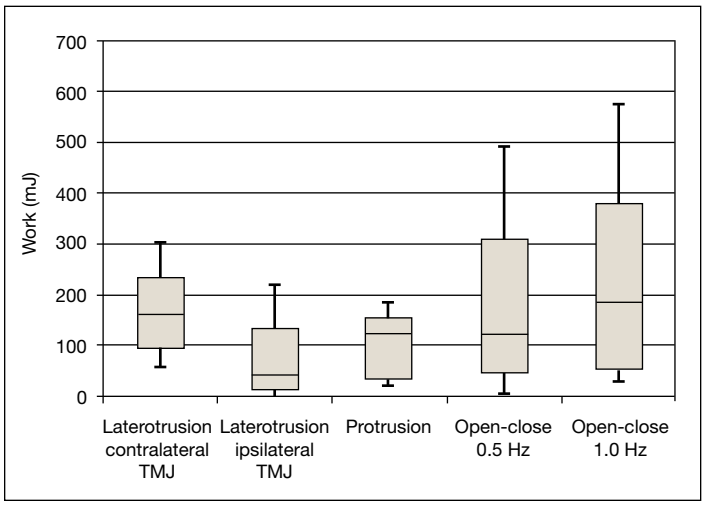

Fig 9-6 Box-and-whisker plots of the work done to the disc (in mJ) during different jaw movements (median, 25th, and 75th percentiles).

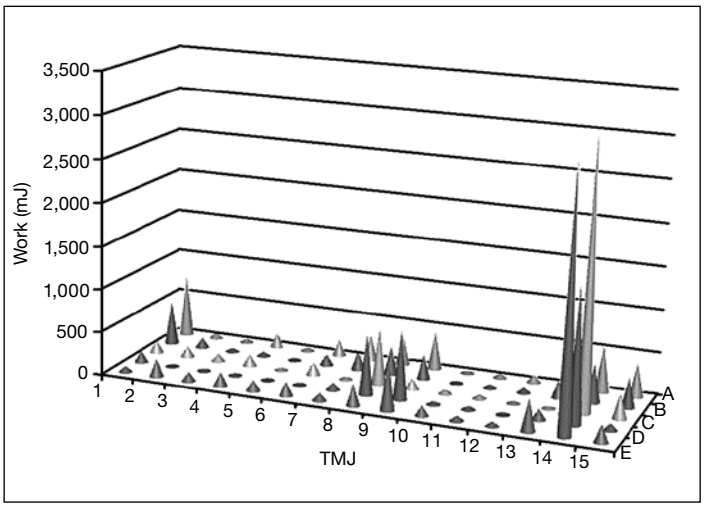

Fig 9-7 Mechanical work done to the disc (in mJ) for each TMJ during different jaw movements. Each number on the abscissa represents a TMJ. Notice that all movements lead to significantly larger mechanical work in numbers 8, 9, and 14 than in the others. A—open-close 1.0 Hz; B—open-close 0.5 Hz; C—protrusion; D—laterotrusion ipsilateral TMJ; E—laterotrusion contralateral TMJ.

Stress-Field Translation and Condyle Metabolism

Mechanical loading during movement is essential for maintenance of the articular tissues because, by regulating tissue remodeling, mechanical forces maintain healthy cartilage. However, not all loading conditions have a positive effect on cartilage metabolism. For instance, while cyclic loading or loading within a physiologic range increases proteoglycan synthesis, cartilage overloading, underloading, and static loading cause proteoglycan depletion.[62] Mechanical loading leads to compression of the articular cartilage and matrix deformation, stimulating the chondrocytes' metabolic activity. In particular, the mechanical loading leads to complex changes within the tissue that include matrix and cell deformation, hydrostatic pressure gradients, fluid flow, altered matrix water content and changes in osmotic pressure, and ion concentration. Chondrocyte mechanoreceptors such as mechanosensitive ion channels and integrins are involved in recognition of these mostly physical changes (mechanotransduction). For instance, activation of the mechanosensitive ion channels by the mechanical stimulation leads to ion influx, in particular calcium ions, and activates intracellular signaling pathways that modulate protein synthesis (see Ragan et al[10] for detailed information).

Chondrocytes respond to mechanical stimuli by activating anabolic or catabolic pathways. Changes from anabolic to catabolic signaling can lead to DJD. Consequently, cell-matrix interactions are essential for maintaining the integrity of the articular cartilage, and an intact matrix is essential for chondrocyte survival and transmission of mechanical signals.

The authors' pilot experiments showed that plowing can compromise cartilage integrity in a force-related manner by causing cell death at the cartilage surface. In addition, plowing alters chondrocyte metabolism by increasing the expression of the catabolic enzyme stromelysin-1 (matrix metalloproteinase 3 [MMP-3]), slightly decreasing that of aggrecan, and augmenting the degree of glycosaminoglycan (GAG) degradation (Figs 9-8 and 9-9). Plowing caused an increase in catabolic activities starting with a compression force of 25N and a decrease of the anabolic activity starting between 50 and 100 N. These results should be interpreted with caution and without inferring that this loading regimen definitely initiates a degenerative process, because the altered metabolism could simply represent remodeling activity.

Cartilage has a poor intrinsic healing capacity.[64] Nevertheless, after injury, the healthy chondrocytes promote a remodeling process involving the elimination of the damaged matrix and the building of new extracellular matrix (ECM). It is therefore possible that in the plowed cartilage the viable chondrocytes start remodeling the matrix by producing

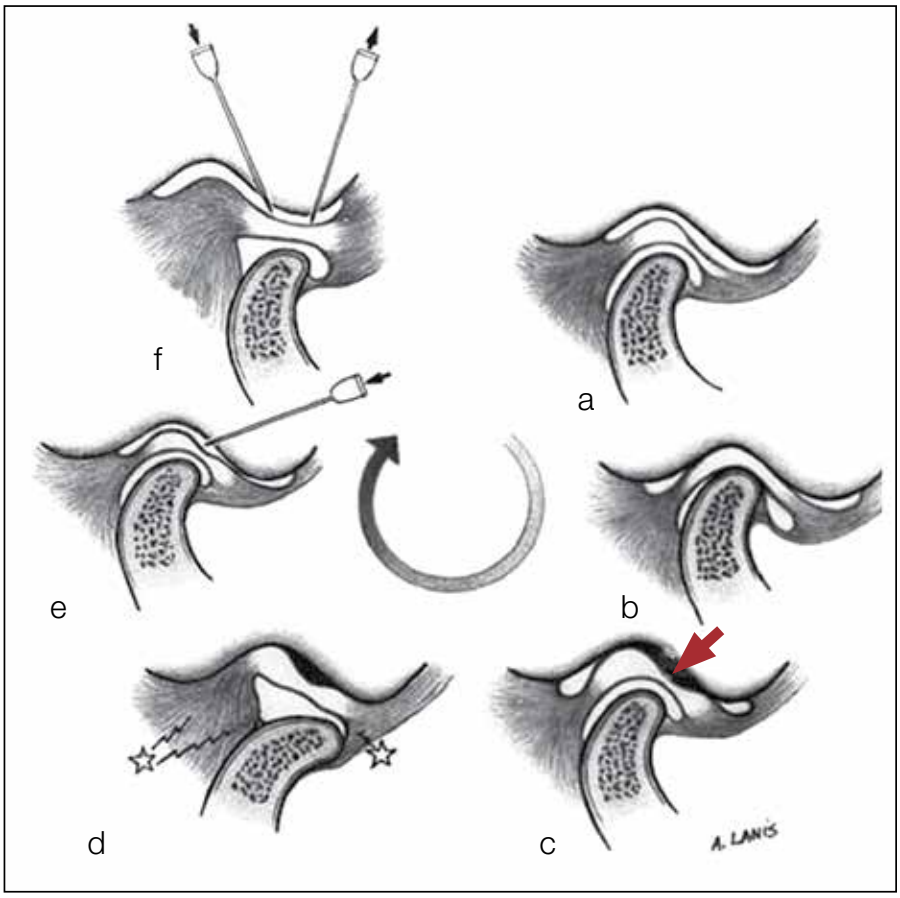

Fig 11-1 *(a)* Illustration of a normal TMJ. *(b to d)* Pressure in the TMJ upon tooth clenching (*b*) and the resulting stuck disc *(c and d)*. When the pressure on the disc ceases, its central area is separated from the bony surface, creating a vacuum that causes the periphery of the disc to adhere firmly to the surface of the eminence, thus preventing it from sliding *(red arrow)*. At this point, an attempt to open the mouth causes pain as the condyle is pulled forward, away from the adhered disc *(stars* indicate pain locations). *(e)* The disc is not released on the introduction of a needle. *(f)* The disc is released following lavage of the upper compartment of the joint. Adhesive forces, rather than only the vacuum effect, are responsible for the immobilization.

has been shown that degradation of HA by hyaluronidase does not detrimentally affect joint lubrication.[30] Interestingly, there is no significant difference in the molecular size of HA in the synovial fluid of patients with disc displacement and healthy individuals.[31] Thus, it was realized that HA is not a lubricant per se and that adding high–molecular weight HA to the synovial fluid does not affect the friction coefficient. However, a significant increase in the coefficient of friction was observed after the HA in the synovial fluid was changed to low–molecular weight HA,[32] thus supporting the possibility that HA has an indirect effect on joint lubrication. Hence, an array of other possible functions of HA in joint movement has been proposed, among which were the roles of a space filler, a wetting agent, a flow barrier within the synovium, and a protector of the cartilage surfaces.[33,34] Besides its mechanical role in joint function, HA has been found in vitro to support joint integrity biochemically by acting as a protector against the action of phospholipase, an inhibitor of phagocytosis and chemotaxis, and as an anti-inflammatory agent. It also prevents the formation of scar tissue and angiogenesis.[33]

According to Swann et al,[35] the main synovial lubricant is a large water-soluble proteoglycan, which they termed *lubricin* and which is also known as *superficial zone protein* and *proteoglycan 4*. The multifaceted lubricin, which is encoded by the PRG4 gene, has a molecular weight of 206 kDa and consists of approximately equal proportions of protein and glycosaminoglycans.[36] The latter contain negatively charged sugars, which possibly create the strong repulsive hydration forces that enable the molecule to act as a boundary lubricant. It is synthesized and selectively secreted by superficial chondrocytes in the articular cartilage (hence the term *superficial zone protein*) and by synovial lining fibroblast-like cells. The lubricin in the synovial fluid reduces the coefficient of friction of the articular cartilage surfaces,[37] and accordingly it prevents cartilage wear and synovial cell adhesion and proliferation. Several studies also imply that lubricin expression plays a role in condylar cartilage growth.[36]

It has been proposed that lubricin expression is regulated by mechanical stress; however, its influence regarding the TMJ remains unclear. Exposing synoviocytes, chondrocytes,

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