INSTRUCTIONAL COURSE LECTURES

Kenneth A. Egol, MD
Editor

Paul Tornetta III, MD
Assistant Editor

AAOS
AMERICAN ACADEMY OF ORTHOPAEDIC SURGEONS

DVD-VIDEO INSIDE
Applied Biomechanics in Articular Injuries: Perspectives in the Basic Investigation of Articular Injuries and Clinical Application

Steven A. Olson, MD, FACS
Thomas D. Brown, PhD
Kyriacos A. Athanasiou, PhD, PE
Roman M. Natoli, MD, PhD
Douglas R. Dirschl, MD

Abstract
Joint injury is an important cause of arthritis. Although the treatment of injury, in general, has been widely studied, the contribution of injury to the development of posttraumatic arthritis is still a relatively understudied area. One of the most perplexing aspects of investigating articular injuries is the complex nature of the injury itself and the multiple facets of the injury mechanism that can potentially lead to the development of arthritis.

A symposium by the Orthopaedic Research Society and the American Academy of Orthopaedic Surgeons was designed to examine the spectrum of basic science to clinical investigation in the role of biomechanics in the study of joint injury and subsequent posttraumatic arthritis. Four perspectives in the clinical aspects of managing articular injuries were investigated, including the clinical applications of basic science findings, the challenges and advancements in measuring and modeling articular fractures, the relationships of articular cartilage mechanical injuries and osteoarthritis, and the controlled creation of an intra-articular fracture to permit observations of the natural history of posttraumatic arthritis.

Instr Course Lect 2011;60:583-594.

The overall effect of the condition of the musculoskeletal system on health in the United States is increasing. Recently, a working group of the Bone and Joint Decade initiative has attempted to quantify the burden of musculoskeletal disease in the United States. Two of the major contributors to this burden of disease include arthritis and injuries. In adults, arthritis is the most common cause of disability in the United States and is among the leading conditions causing work limitations. From 2003 to 2005, arthritis was diagnosed in approximately 21% or slightly more than 46 million patients in the United States. By the year 2030, it is projected that 25% of the US adult population will have physician-diagnosed arthritis. Injuries to the musculoskeletal system account for another large portion of overall disease in the United States. In 2004, approximately 57 million musculoskeletal injury episodes were treated in physician offices, emergency departments, clinics, and other medical insti-
tutions. More than 33% of all injuries were reported as strains and sprains. Fractures represented nearly 25% of all reported musculoskeletal injuries.1

The subgroup of patients with injuries to the musculoskeletal system (particularly major joint injuries) in whom arthritis develops is less well defined. This population of patients with posttraumatic arthritis is a distinct group of patients contributing to the overall burden of musculoskeletal disease.2 As a disease entity, posttraumatic arthritis is relatively unstudied. Although arthritis can develop after any injury to a major joint, it most predictably and rapidly develops after intra-articular fractures.3 The traditional view of the development of arthritis after an articular fracture has been one of focal stress elevation related to articular malreduction following surgical or nonsurgical treatment of the injury.4 More recent studies suggest that elements of posttraumatic arthritis serve as components of the overall mechanism of disease and may alter chondrocyte viability, incite an acute inflammatory response, and contribute to altered mechanical wear.5,6

Many factors contribute to the relative lack of knowledge concerning posttraumatic arthritis.3 From a research perspective, posttraumatic arthritis is a difficult topic to study. The overall spectrum of disease that can lead to clinical arthritis after injury is extensive, ranging from articular fractures to injuries with ligamentous disruption to joint contusion without fracture.7,8 Articular fractures are examples of worst-case scenarios, with physical disruption of the articular surface, blunt impaction of the articular surface, and local hemorrhrosis; these fractures are often associated with a systemic inflammatory response. Each of these aspects of injury represents a unique physiologic and biomechanical mechanism that can contribute to the overall outcome of the patient. Traditional investigative techniques that study isolated mechanisms of disease have been applied to these mechanisms.5,7,9,10 Although these investigations provide new information, they do not replicate the complex conditions of an articular fracture, making clinical translation less certain.

Perhaps one of the most perplexing aspects of investigating articular fractures is the complex nature of the injury and the effects of the treatments designed to restore the displaced articular surface. Clinicians have inadequate tools to accurately and reliably assess the effects of the various aspects of injury on the ultimate clinical outcome.11 The physical disruption of the joint, the physiologic response to injury, and impaction of the articular surface are all inseparably related. For example, how can posttraumatic arthritis be prevented in a patient with a comminuted articular fracture? Should prevention efforts be focused on restoring articular reduction, mitigating the effects of impaction injury to the cartilage, enhancing a combination of local and systemic physiologic response to the injury, or should all of these areas be addressed? To improve patient functioning following a displaced articular injury, it is critical to develop research strategies to investigate the role of injury mechanisms that will allow the development of new therapies to limit or prevent posttraumatic osteoarthritis (OA).

The material presented in this chapter is based on a combined Orthopaedic Research Society and American Academy of Orthopaedic Surgeons (AAOS) symposium designed to examine the spectrum of basic science to clinical investigation in the role of biomechanics in the study of joint injury and subsequent posttraumatic arthritis.

Clinical Applications of Basic Science Findings

Like much of orthopaedic practice, fracture surgery is ruled by tenets. Common sense, the desire to serve patients, and the substantial influence of the AO group and its educational network have resulted in ideas that have become "fracture dogma." Two of the most closely and passionately guarded tenets in managing articular fractures are as follows: the objective of treatment is precise reconstruction of the articular surface, and patient outcomes will vary based on the accuracy of articular reduction.

A review of the published literature shows that the necessary precision recommended for articular reconstruction has changed over time. In the tibial plateau, for example, the "necessary" threshold for articular congruity has decreased over the past 20 years from 8 mm to 2 mm.12-16 Outcomes following care, however, appear to be largely unchanged.12-16 It appears that the threshold for acceptable reduction has more closely followed improvements in the technical abilities of surgeons rather than improvements in outcomes. Another important factor is that a surgeon's ability to reliably measure articular incongruity (even at a flat surface like the tibial plateau) is rather poor, with a 95% confidence interval of ±12 mm for quantifying articular step-off.31

In numerous instances, a perfect reduction in a simple, low-energy fracture will result in significant pain and extremely poor function. In contrast, there are other cases in which a poor reduction in a highly comminuted fracture results in little pain and good function. Despite the desire to follow established fracture tenets and principles, observations indicate that the relationship between articular reduction and outcome is neither as direct nor as simple as it appears.
The simple but nonintuitive truth is that articular congruity is not the only factor that influences outcomes after fracture. An array of confounding variables, many of which are poorly understood, have a profound impact on the patient's outcome following an articular injury. Some of these factors include the magnitude and type of articular injury, the magnitude of the soft-tissue injury, the patient's response to the injury, morphologic and mechanical differences between joints, subtle but pronounced effects of joint kinematics and dynamic instability, cartilage biology and its response to injury, the patient's age and its effect on injury response, and the effects of load distribution that is not restored with the restoration of articular congruity.

Current research is helping clinicians understand these factors. Appreciating the value of this new research and incorporating it into clinical practice requires that clinicians challenge their traditional thinking about articular fractures. For example, articular congruity; injury to the articular cartilage; and often factors such as limb alignment, joint stability, and kinematics can independently and in combination have an impact on patient outcomes. Most orthopaedic fracture surgeons focus on the primacy of articular reduction in improving outcomes. This approach is overly simplistic and does not take into account other factors that have a profound impact on outcomes. To overcome this bias, it is important to recognize several truths. (1) All of the factors affecting outcomes are intricately linked; there is no rational or realistic way to separate the effects of one from the others. (2) There is much evidence (new and old) in the literature to indicate that articular reduction may not be the most important factor in determining outcomes. (3) The appropriate weight of various factors is not yet known. If these truths are accepted, the clinician can acknowledge factors other than articular reduction as critically important to patient outcomes and can begin to incorporate these factors in the clinical care of patients with fractures.

In science, only what can be measured can be known. As medical scientists, orthopaedic fracture surgeons should embrace work that tries to improve methods to measurably characterize articular injury; the body's response to it; and the mechanical, kinematic, and biologic effects of treatment. Research currently in progress includes finite element modeling of injured and reconstructed joints, methods for quantifying injury severity, methods for measuring cartilage health and response to injury, methods for measuring dynamic mechanical stresses, methods for correlating measurements with outcomes, and methods for predicting outcomes and guiding treatment. The goals of these and other research studies should be to better determine the relationships between articular cartilage injury, articular reduction, other mechanical factors, and patient outcomes. The support of orthopaedic clinicians is needed to continue this type of research.

In daily interactions with colleagues, staff, and patients, surgeons should indicate that they understand that factors other than articular alignment are important to patient outcomes. Surgeons should be willing to recommend treatment other than open reduction and internal fixation when it is not clear that articular reduction will change the patient's outcome. Cartilage biology, joint and limb mechanics, and articular congruity should be considered when making treatment decisions and counseling patients.

Challenges and Advancements in Measuring and Modeling Articular Fractures

Despite the need to objectively characterize articular injury, quantify injury response at the tissue and whole-joint level, and measure the mechanical and biologic effects of treatment, there are few appropriate techniques to achieve these goals. Developing or refining assessment tools to yield reliable mechanical data on joint injuries poses substantial biomechanical technical challenges. Although joint injuries are "global" events, the resulting pathophysiology originates locally at the tissue and cell level; the efficacy of therapeutic interventions (surgical and nonsurgical) depends on achieving favorable local effects.

One of the classic challenges has been to measure chronic cartilage insult caused by residual incongruities following imprecise reduction of intra-articular fractures. Empirical clinical experience has shown that different joints and different specific fractures of these joints produce different tolerance levels for articular incongruity. Trying to reach agreement on specific acceptable tolerance levels has often resulted in controversy among leading surgeons. Corresponding aberrations of cartilage stress, either quasi-static stress concentrations locally near sites of surface irregularity or abrupt transients of cartilage stress associated with joint instability events, probably constitute much of the unifying explanation of why different joints behave or respond so differently.

Two distinct measurement methodologies using Fuji film (Sensor Products, Madison, NJ) or Tekscan pressure mapping (Tekscan, South Boston, MA) have been developed for measuring cartilage contact stress. The Fuji film method involves a mechanochemical transduction
process based on pressure-dependent rupture of populations of microcapsules (containing a photoactive liquid) deposited on the surface of paperlike acetate sheets. The sheets can be easily cut by hand to fit the articular anatomy of interest. The higher the contact pressure, the greater the fraction of microcapsules that rupture and the more intense the resulting (red) stain. The intensity of the Fuji staining is normally quantified using laser scanning and digital image analysis. Accuracies in the range of 10% to 15% are the generally accepted norm. Because of the size scale of the microcapsules, for practical purposes the resulting stain patterns are essentially continuous, thus providing excellent spatial resolution for assessing local details of pressure aberrations into the submillimeter range. The primary limitation of this method is that the data captures are necessarily static, reflecting the high-water mark of pressure experienced at any given site on the film. Despite this limitation, the Fuji film method has been useful in answering many pragmatic surgical questions concerning alternative fracture reconstruction techniques and dose-response relationships between incongruity and the resulting pressure abnormality at various anatomic sites.

The Tekscan transduction modality uses an entirely different methodology. It involves pressure-dependent changes in the electrical resistance between large numbers of intersection sites between rows and columns of conductors, separated by a thin layer of piezoresistive elastomer. This system enables transient recordings, although the spatial resolution of such recordings is limited by the row-column density of the conductor grid. Because trimming the sensors would destroy the electrical circuitry, the Tekscan system lacks the versatility of Fuji film to be easily cut to fit the anatomy of interest. Past biomechanical applications have usually involved general purpose sensor geometries designed for industrial purposes; therefore, this system may provide suboptimal coverage of an anatomic joint surface, or it may be difficult to accommodate the necessary (fragile) connecting cables. Recently, there have been several varieties of custom biomechanical sensors developed for specific anatomic locations (the knee, the ankle, and the hip), providing for well-conforming articular surface coverage and anatomically cognizant cable protection. Currently, maximum data capture rates exceed 100 frames per second, and available spatial resolutions are on the order of 0.5 mm² per sampling site. A major advantage of transient data collection is that a loaded joint can be studied throughout its range of motion, thereby providing information about habitual cartilage loading, rather than just snapshot information at specific instants that may not be representative of the duty cycle and may not identify worst-case situations. Recent Tekscan measurements focusing on tibial plafond fractures have identified incongruity-dependent abnormalities of local contact stress magnitude and contact stress rates of change, shifts of global load transmission patterns, and the occurrence of seemingly dramatically deleterious fluctuations of loading under conditions of joint instability.

Computational advancements in articular joint contact mechanics have greatly reduced the need for dependence on physical experimentation. Finite element techniques have spearheaded those developments. Previous limitations, which have recently been overcome, are the ability to simulate cartilage contact under physiologically realistic joint-loading magnitudes and the rates of change of joint-loading magnitudes in the presence of local incongruities. Another important development has been the use of numerical techniques to study the interaction of solid and fluid components of cartilage matrix for situations involving articular surface contact. This is an important consideration in evaluating local incongruities because of the heightened ease for fluid egress from ruptured cartilage surfaces. Another class of developments has been the ability to realistically simulate cartilage impaction events, both for impulsive loadings between native joint surfaces and for laboratory impaction events involving plates on exposed joint surfaces or of specialty osteochondral explant preparations. Probably the most important current improvement in articular contact finite element analysis has been the development of novel meshing techniques to accommodate arbitrary derangements of joint surface geometry. These improvements have allowed the study of actual clinically occurring fractures rather than geometrically idealized situations, such as straight-edged step-offs. These meshing techniques can be applied to prospective clinical studies to quantify risk factors for degenerative change.

Assessing injury severity has been another fertile area for computational innovation. It was intuitively accepted that joint fractures resulting from high-energy mechanisms had a greater risk for posttraumatic OA than low-energy fractures; however, a method to directly quantify the involved energy did not exist. A fundamental tenet of engineering fracture mechanics of brittle solids holds that the kinetic energy absorbed during the fracture event is transformed into free-surface energy of the resulting fragment fracture surfaces. In human clinical fractures, information on fragment free-surface energy is available post facto from CT images of the fracture bed and is based
on segmentation (edge delineation) of all individual fragments, a process that is well suited to automated computational analysis. This has allowed “backing out” a measure of the mechanical energy absorbed in bone fracture events. A series of laboratory computational/experimental studies has documented the quantitative accuracy of the essential concept. After several computational developments to streamline and expedite the analysis, it has now been applied to human prospective studies, allowing objective identification of the relative risk of posttraumatic OA to individual patients.

Another new area of computational development is the identification of anatomically correct reconstructions of displaced comminuted articular fractures. Surgical reduction of such fractures must be done piece by piece, with limited visibility, and with no way of knowing in advance if the reassembled fragments will result in gaps (especially perarticularly) because of missing or compacted fragments. An analogous process of three-dimensional puzzle solving performed computationally provides advanced information about appropriate geometric reassembly of individual fragments and identifies any region(s) of void that will necessarily result. To implement this process, the puzzle-solving algorithm begins with automated segmentations of the bony fragments, with their respective surface facets identified as being native periosteal surface, native subchondral plate, or de novo fracture surface. Native fragment surface facets are computationally matched to geometrically corresponding sectors on a surface template that is defined by mirror imaging of the intact contralateral limb. Successive fragment facets are then computationally “locked into place” using an iterative closest point algorithm in a manner that minimizes their topographic disparity with corresponding sectors on the template surface. Homogeneous surrogates with biofidelity, which were fractured under controlled laboratory conditions, were initially used to tune the puzzle solver to achieve fragment reassembly accuracy in the range of a few tenths of 1 mm. After porting this computational procedure (with appropriate modifications) to cadaver material, submillimeter accuracies in fitting the template surfaces were maintained. Facilitated by new computational procedures to expedite fragment segmentation and an advanced surgeon-friendly graphic interface to manipulate fragments, the procedure has been applied to “puzzlesolve” a clinical case series of comminuted tibial plafond fractures, to compare geometrically ideal versus surgically obtained reconstructions, and to help understand the practical difficulties in obtaining fully anatomic reconstructions (especially of the articular surface) on a case-by-case basis.

A large-animal survival model of intra-articular fracture that allows orthopaedic interventions analogous to those for human clinical cases is also being developed. This model complements the capabilities of a recently developed mouse model, whose primary strengths were the ability to understand the pathophysiology and natural history of intra-articular fractures, especially in concert with genetic-level assessments and interventions. The large-animal model involves evaluating the hock joint of the adult Yucatan minipig after fractures with controlled morphology (for example, replicable fracture line location on the articular surface) are achieved by a specially developed offset impaction technique. The investigator has knowledge and control of the delivery energy and impaction force. At the whole-joint level, the fracture patterns closely resemble those of human tibial pilon fractures.

At the cellular and tissue levels, the patterns of matrix damage and cell death (and its temporal and spatial progression after impaction) closely resemble those seen for impaction fractures of fully viable normal human ankle specimens obtained from above-knee tumor amputation patients. Minipigs are clinically tolerant of both plate and screw internal fixation and spanning external fixation of the hock joint; the pigs shortly resume non-weight-bearing protected limb usage. This model offers exciting promise for evaluating the efficacy of novel therapeutic interventions screened in vitro and in small-animal (nonreconstructible) fracture models and is a key laboratory testing step before translation to human clinical trials.

Articular Cartilage
Mechanical Injuries and OA

Mechanical injuries of articular cartilage can result from events such as motor vehicle crashes, falls, and sports injuries. Such injuries can lead to posttraumatic OA, although the pathophysiologic processes are not fully understood. Articular cartilage responds to injury by two separate processes that are linked to each other through mechanotransduction. During the injurious event, the tissue responds mechanically by deforming according to the applied load. Subsequently, the biologic response starts when the mechanical forces applied to the tissue activate intracellular signaling.

OA can be thought of as a condition that develops as a result of the overloading of healthy tissue (acute trauma) or from normal loading of abnormal tissue. Overloading of healthy cartilage can immediately cause surface fissuring, cell death, and damage to the extracellular matrix from which the tissue cannot recover. Alternatively, overloading of normal cartilage may cause
subcritical damage that leads to less robust tissue. Subsequent loading of this abnormal cartilage, even at physiologic levels, can result in chronic injury and damage accumulation that eventually manifest as OA. Articular cartilage does not heal well. Attempted self-repair results in the formation of mechanically inferior fibrocartilage-like tissue, which has more collagen type I and contains less glycosaminoglycan than normal articular cartilage. These biochemical changes lead to changes in the tissue's mechanical properties, preventing normal function.

Changes in the physical properties of articular cartilage contribute significantly to the development of OA. Because of damage and loss of extracellular matrix, the compressive and tensile stiffness decreases and permeability increases. Cartilage from osteoarthritic joints is thinner and more hydrated than healthy tissue. For example, a review by Knecht et al. reported that the compressive stiffness of articular cartilage decreases by 20% in early stages of the disease, a change that probably would be undetected by current clinical assessment methods. The decrease in compressive stiffness correlates with increased scores on the Mankin histologic scoring system for articular cartilage, increased tissue hydration, and decreased sulfated glycosaminoglycan content. The fact that changes in tissue occur so early suggests that timely intervention is needed to alter the course of OA.

Mechanical Considerations for In Vitro Studies of Cartilage Injury
Because the first response of articular cartilage to injury is mechanical, it is essential to understand the intrinsic mechanical characteristics of the tissue and the mechanical features of the external system causing injury. The mechanical properties of articular cartilage are the macroscopic result of its underlying organization and biochemical content. The collagen network of the tissue governs tensile behavior, whereas proteoglycans are necessary for resisting compression. The tensile stiffness of articular cartilage positively correlates tissue collagen content and collagen cross-linking. Within cartilage, collagen is arranged in a depth-dependent manner. Collagen is parallel to the articular surface in the superficial zone, oriented randomly in the middle zone, and perpendicular in the deep zone as it anchors into the calcified cartilage layer. In the superficial zone, collagen also follows preferred directions known as split lines. The tissue is stiffer when pulled in the direction of split lines when compared with off-axis pulling. The proteoglycan content of the tissue gives articular cartilage its ability to resist compressive loads because of the electrostatic repulsion of the negatively charged glycosaminoglycans when forced into close proximity. Injuries to articular cartilage that affect collagen or proteoglycans alter the biomechanical behavior of the tissue.

The mechanical features of the external system used for in vitro study of cartilage mechanical injury are also important because the type of loading, boundary conditions, and preinjury tissue processing all affect experimental outcome. Loading regimens have varied and include injurious compression, single impacts, and cyclical loads. Different load magnitudes and rates have been used with each of these regimens. Experimental setup (boundary conditions) must also be considered. Different setups with respect to the presence or absence of underlying bone and loading methods have been used. The loading methods include confined compression, unconfined compression, and indentation. Each method radially constrains surrounding tissue differently. Some studies have included preinjury tissue processing steps, including the use of full-thickness cartilage versus cartilage with the superficial zone removed, and equilibrating tissue in a culture medium before loading. These factors must be considered when comparing studies.

Early Postinjury Biology and Treatment
Following the mechanical response of cartilage to injury, a biologic response occurs. Within the tissue, mechanical loading generates streaming potentials, stress-strain fields, and hydrostatic pressure. The biologic response starts when chondrocytes experience the mechanical forces applied to the tissue and intracellular signaling cascades are activated through stretch activated channels and integrins located in the cell membrane. Following this mechanotransduction, the biologic response to injury evolves over time. Time-points for investigation after an in vitro mechanical injury have ranged from 3 hours to 2 weeks. Several cell matrix adhesion molecules have shown decreased expression as early as 3 hours after injury. With the exception of SOX9, a transcription factor promoting collagen type II, there is generally upregulation of gene expression from 4 to 24 hours after injury. Examples of upregulated genes include matrix metalloproteinases (MMPs), aggrecanases, and inhibitors of MMPs. These enzymes break down type II collagen and aggrecan. Further study has suggested these changes in gene expression normalize by 2 weeks after injury, and MMP-3 expression switches from increased to decreased expression, suggesting that MMP-3 could be a marker for time after injury.

Articular cartilage degradation is mediated by several factors, such as cell...
death, matrix degrading enzymes, and inflammation. In attempts to mitigate some of these changes, the poloxamer P188 has been used to decrease cell death. P188 is an 8.4 kDa nonionic surfactant triblock copolymer of polyoxethylene and polyoxypropylene that inserts into lipid membranes. Postinjury, promising results have been reported with P188 in both in vitro and in vivo rabbit models. In a study by Phillips and Haut, P188 (8 mg/mL) was delivered in the culture medium following a 25-MPa load to cartilage explants. With P188 treatment, there were more viable cells in the superficial zone at 1 hour and in all zones at 24 hours but only if the explants were manually compressed. Compression presumably aided P188 entry into the tissue. In a 4-day in vivo study, a one-time intra-articular injection of P188 was effective at reducing cell death in impacted retropatellar cartilage. A more recent study reported that P188 reduced cell death in tibiofemoral cartilage 6 weeks after injury. Natoli and Athanasiou evaluated P188 (8 mg/mL) following two levels of impact loading (1.1 and 2.8 J) using continuous treatment. They reported a 75% decrease in cell death at 1 week following the 1.1 J impact. In contrast to the study by Phillips and Haut, no compression protocol was needed to achieve this benefit, perhaps because of the adoption of a continuous treatment regimen compared with a one-time treatment. A recent 2009 study showed that P188 treatment was more effective at decreasing cell death in human ankle cartilage after impact than inhibition of caspase 3 or 9 (two enzymes that drive apoptosis). Future research should investigate combining treatments for apoptotic and necrotic cell death to further chondrocyte preservation after injury.

Osteoarthritic chondrocytes do not behave like native, healthy chondrocytes. Because traumatic injury may shift the phenotype of chondrocytes remaining in the tissue toward catabolic processes, the previously described studies of treatment to decrease cell death should be interpreted cautiously. The catabolic nature of these cells (for example, the production of matrix-degrading enzymes and inflammatory signals) is evident based on the continued degradation of articular cartilage after the inciting event. Although chondrocyte survival postinjury is necessary for tissue healing, it may not be sufficient. Future research must also address the behavior of viable chondrocytes after injury and should include measurements of tissue mechanical properties to assess tissue functionality. Researchers should also seek interventions that promote a healing response. In addition to preventing cell death, research has been directed at decreasing extracellular matrix degradation and inflammation after mechanical injury with methods such as pharmaceutical therapy.

Controlled Creation of an Intra-Articular Fracture: Observations on the Natural History of Posttraumatic Arthritis

The mechanisms leading to the progression of posttraumatic arthritis following articular fracture are not well understood. After injury, several factors may affect the development of posttraumatic arthritis, including disruption of the articular surface, variable amounts of impaction of the articular cartilage, residual displacement of the articular surfaces, and exposure of blood and marrow products to the articular surface and synovium. Because these predisposing factors are inseparably clinically linked with the injury, investigations of traumatic joint injury that focus on a single aspect of the acute injury, such as blunt trauma to the articular surface, are too limited. Traditional models of investigating a single aspect of injury trade simplicity for the complexity of a more realistic injury model system.

To gain a broader perspective on the effects of intra-articular fracture, it is necessary to understand the natural history of the development, over time, of posttraumatic arthritis in a displaced articular injury. A model was developed to create a closed joint injury in a relatively reproducible fashion that was usable in a survival animal model. Furman et al described work to prove the concept that established the ability to create a closed fracture of the tibial plateau with varying degrees of severity. A single hind limb fracture was created in strain C57/BL6 mice. The fracture was allowed to heal without attempts at fracture reduction or fixation, thus allowing the natural history of posttraumatic arthritis to be studied; the contralateral limb served as an internal control. Faxitron imaging, micro-CT at the time of limb harvest, and histologic analysis were used to assess the joints of both extremities from each specimen. In the C57/BL6 mice, this injury reliably resulted in the development of a tricompartmental arthritis at 4 and 8 weeks after injury, with complete loss of articular cartilage by 50 weeks after injury. Application of this method to the MRL/MpJ strain of mice proved enlightening. Clark et al was the first to describe the unique healing characteristics of MRL/MpJ mice. Because these mice were able to spontaneously regenerate tissue in ear punch holes without scarring, the strain was called the "super-healer." The creation of similar types of closed tibial plateau fractures in the MRL/MpJ mice did not result in the development of articular degeneration, despite articular fracture and displacement. The observation that a displaced fracture results in ar-

© 2011 AAOS Instructional Course Lectures, Volume 60
Figure 1 Graph illustrating the relationship between applied load (as represented by indenter displacement) and energy of fracture in the creation of a closed articular fracture in a murine model. (Reproduced with permission from Furman BD, Strand J, Hembree WC, Ward BD, Guilak F, Olson SA. Joint degeneration following closed intraarticular fracture in the mouse knee: A model of posttraumatic arthritis. J Orthop Res 2007;25(5):578-592.)

...in one strain but not in the other suggests altering physiologic response to injury is a potential intervention strategy.

Assessing the severity of injury is challenging. Three methods of injury severity assessment were applied in this model. (1) A modification of the AO/OTA classification for clinical fractures was applied to data from faxitron imaging and microCT. The basis for a classification system is, in part, to stratify discrete events into varying categories of severity. (2) The applied energy and the energy of injury at time of fracture are both known. A plot showing the relationship between applied energy and the energy of fracture is shown in Figure 1. This relationship allows the energy of fracture to be controlled. (3) Micro-CT from both control and experimental limbs were used to determine the liberated fracture surface as a third severity measure. Authors have described the assessment of liberated fracture as a means of assessing injury severity. In the murine model of tibial plateau fracture, the energy of fracture has an excellent correlation with the liberated fracture area.

Interest in the physiologic response following articular fracture in the C57/BL6 and the MRL/MpJ mice strains stimulated the development of novel techniques of assessing the response. Standard serum analysis of cytokines and biomarkers is a valuable technique. However, serum levels alone reflect incomplete information about physiologic response to injury. A novel technique was developed for quantitatively assessing cytokines and biomarkers in synovial fluid of the knee of mice following injury. Using small amounts of a calcium alginate compound to absorb synovial fluid with controlled lyse digestion allows a quantitative analysis. Gene activation following injury can be assessed from synovial tissue. The small amount of synovial tissue available from this technique in mice typically requires pooling of specimens to obtain adequate amounts of DNA to generate reliable data. Histologic analysis allows assessment of proteoglycan staining of cartilage and synovial cellular response to fracture. Determining the cellular viability and immunohistochemistry of the joints allows assessment of the variation of response, over time, following articular fracture.

The initial focus of research has been on understanding the initial events in the development of tricompartmental arthritis after fracture in the C57/BL6 mouse strain. Early effects of injury in the C57/BL6 strain show that the loss of cellular viability of chondrocytes parallels the structural damage of the articular surface as determined by the modified Mankin histologic scoring system for articular cartilage. Additionally, changes in the synovium with increasing cellularity are proportional to the increasing energy of fracture.

Preliminary results of comparisons of early events following articular fracture in the C57/BL6 and MRL/MpJ strains indicate important differences. The severity of injury and the basic fracture characteristics are similar between mice strains, as is the initial increase in the cellularity of the synovial layer; however, local gene activation, synovial fluid levels, and serum levels of cytokines differ between strains.

In the C57/BL6 strain there is a significantly more robust inflammatory response to injury compared with the MRL/MpJ strain. One example of the effect of this response is a markedly increased presence of activated macrophages in the synovial lining of the C57/BL6 mice that persists weeks after injury, whereas a transient blush of activated macrophages occurs initially in the synovium and then returns to levels of the control limb in the MRL/MpJ mice.

This simple observation provides the basis for new hypotheses regarding...
mechanisms beyond the traditional view of residual displacement of the articular surface as the cause of arthritis following fracture. Recent work in immunology suggests that, in the presence of necrotic material, macrophages become activated or primed to produce more inflammatory cytokines.\textsuperscript{89,90} Disruption of the articular surface inherently produces necrotic chondrocytes and other cell types. Is this a signal that can result in activation of synovial macrophages? The question suggests a shift in perspective from posttraumatic arthritis as a consequence of injury to the articular surface to that of an organ-level response to injury in which there is physiologic signaling between articular cartilage and other tissues within the joint. New methods of investigating the effects of injury that consider the organ level response of the joint may offer new insights into this important area.

Summary
Injury to the articular surface contributes to the development of the clinical condition recognized as posttraumatic arthritis in a large number of patients each year. The basic mechanisms by which articular injury contributes to the development of joint degeneration remain incompletely characterized. Currently, the clinical treatment of the fracture itself is the primary form of intervention in attempting to prevent the development of posttraumatic arthritis. There are no pharmacologic interventions or other therapies available that can prevent or delay the onset of posttraumatic arthritis. Several lines of ongoing research discussed in this chapter have the potential to add to the knowledge of posttraumatic arthritis, with the potential to identify future targets for intervention.

Although patients with articular injury generally have an increased risk for the development of joint degeneration, an improved ability to predict what injury patterns and patient characteristics are at a true high risk for joint degeneration is needed to study interventions as they become available. The need for prospective registries with longitudinal follow-up is important to identify these at-risk patient populations. Approaching posttraumatic arthritis from these varied perspectives will contribute to a better understanding of how articular injury contributes to this condition and will improve patient care.

Acknowledgments
The authors wish to acknowledge the contributions of Farshid Guilak, PhD, and Bridgette Furman, BA, to this chapter.

References


