Review

Current Concepts in the Treatment of Articular Cartilage Defects

Tom Minas, MD, FRCS(C), MS*
Stefan Nehrer, MD†

ABSTRACT

Over time, articular cartilage loses the capacity to regenerate itself, making repair of articular surfaces difficult. Lavage and debridement may offer temporary relief of pain for up to 4.5 years, but offer no prospect of long-term cure. Likewise, marrow-stimulation techniques such as drilling, microfracture, or abrasion arthroplasty fail to yield long-term solutions because they typically promote the development of fibrocartilage. Fibrocartilage lacks the durability and many of the mechanical properties of the hyaline cartilage that normally covers articular surfaces. Repair tissue resembling hyaline cartilage can be induced to fill in articular defects by using perichondrial and periosteal grafts. However, these techniques are limited by the amount of tissue available for grafting and the tendency toward ossification of the repair tissue.

Autogenous osteochondral arthroscopically implanted grafts (mosaicplasty), or open implantation of lateral patellar facet (Outerbridge technique), requires violation of subchondral bone. Osteochondral allografts risk viral transmission of disease and low chondrocyte viability, in addition to removal of host bone for implantation. Autologous chondrocyte implantation offers the opportunity to achieve biologic repair, enabling the surgeon to repair the joint surface with autologous articular cartilage. With this technique, care must be taken to ensure the safety, viability, and microbial integrity of the autologous cells while they are expanded in culture over a 4- to 5-week period prior to implantation. Surgical implantation requires equal attention to meticulous technique.

In the future, physiologic repair also may become possible using mesenchymal stem cells or chondrocytes delivered surgically in an ex vivo-derived matrix. This would allow in vitro manipulation of cells with growth factors, mechanical stimuli, and matrix sizing to allow implantation of mature biosynthetic grafts which would allow treatment of larger defects with decreased rehabilitation and morbidity.

Functional articular cartilage is critical to proper joint function. Unfortunately, articular cartilage frequently proves vulnerable to traumatic injury or degenerative conditions that may eventually lead to osteoarthritis (OA). This is particularly true in a large weight-bearing joint such as the knee. The problem is that the body has limited means by which it can repair or regenerate damaged articular cartilage—a fact that has been known for some time, probably even before it was first noted in 18th century medical literature.1

Although a variety of surgical procedures has been developed in an attempt to overcome this treatment challenge, none has been successful in achieving regeneration of normal articular cartilage. It is important to note that articular cartilage is the term used to describe normal joint cartilage, macroscopically and microscopically. Hyaline cartilage, on the other hand, is the term applied to the gross morpho-

From the *Department of Orthopedics, Brigham and Women’s Hospital, Harvard Medical School, Boston, Mass. and the †Department of Orthopedic Surgery, University of Vienna, Austria.

Reprint requests: Tom Minas, MD, FRCS (C), MS, Dept of Orthopedics, Brigham and Women’s Hospital, 75 Francis St, Boston, MA 02115.
logic appearance of articular cartilage ("glass-like"), often interchanged with the "ground-glass" appearance of the matrix on histologic specimens. The techniques used to date have been only partially successful in that they may reduce pain and increase mobility, but often only to a limited extent and over a short-term period. Some of these techniques stimulate the growth of fibrocartilage as a substitute repair tissue. However, fibrocartilage lacks the durability and many of the mechanical properties of normal joint cartilage which lines articular surfaces. Typically, fibrocartilage degenerates over time, resulting in the return of clinically significant symptoms. As a result, severely symptomatic patients with cartilage defects often require further reconstructive knee surgery, and eventually an artificial prosthesis.

A recent clinical report on the effectiveness of autologous chondrocyte implantation for the treatment of full thickness cartilage defects of the knee has renewed interest in cartilage repair. This article delineate the challenges encountered when attempting to achieve effective durable repair with hyaline cartilage. The various techniques that have been developed to treat clinically significant cartilage defects of the knee are reviewed.

**Obstacles to Physiologic Articular Cartilage Repair**

Much of the difficulty encountered when trying to bring about true repair of articular cartilage stems from the physiologic characteristics of the tissue itself. Viewed arthroscopically, normal articular cartilage appears as a homogeneous, slick, white surface, possessing no vasculature or innervation. Its surfaces are so slick as to be compared to surfaces with less friction than ice on ice. Its gross appearance suggests a primitive type of tissue. Yet despite its primitive appearance, articular cartilage is actually a complex tissue that serves to minimize stress on subchondral bone during peak loading and to reduce friction on the bearing surfaces of synovial joints. Articular cartilage is composed of a hydrated gel matrix that contains type II collagen fibers and sulfated mucopolysaccharides (Fig 1A). The matrix macromolecules are synthesized by chondrocytes. Collagen fibrils, principally type II, and crosslinked with type IX, provide the framework that lends cartilage its tensile strength and structure. The specific deep, crescentic arcades of collagen and superficial tangential arrangement are key to the mechanical integrity and function of normal articular cartilage. Articular cartilage specifically lacks types I and X collagen, which are often a precursor to endochondral ossification and are normally found in the hypertrophic chondrocytes of the growth plate in skeletally immature bones.

Articular cartilage has a highly organized tissue structure (Fig 1B). It is arranged in layers of differing morphology and biochemical composition, with mechanical properties varying according to the distance of the layer from the joint surface. The first layer, the superficial zone, is a thin, gliding surface with a high collagen and low proteoglycan content. The second, transitional zone, contains larger collagen fibrils
and has a higher proteoglycan content. The deep zone has the highest proteoglycan content and the lowest water concentration. The fourth zone consists of calcified cartilage formed from mineralized matrix, which delineates the separation of articular cartilage from the subchondral bone.

Once articular cartilage has matured, chondrocytes rarely divide, and their density declines with age. The complexity of the tissue, combined with the age-related decline in density and regenerative capacity, all may contribute to the observed difficulties encountered when trying to repair cartilage.

Cartilage injuries that do not extend to the subchondral bone and its vasculature, and thus cannot mount an inflammatory response, have the lowest self-healing capacity. Full-thickness cartilage injuries can undergo some degree of repair resulting from hematoma formation, stem-cell migration, and vascular ingrowth. The repair tissue initially consists predominantly of type I collagen, typical of fibrocartilage.

The amount of type II collagen associated with repair cartilage may increase, and the repair tissue may become increasingly hyaline for up to 24 months. However, after about 24 months, the repair surface typically splits and fibrillates, presenting changes similar to those seen in OA (Figs 2A-B).

The continuing presence of type I collagen suggests that normal hyaline cartilage never develops at these repair sites. Over time, this fibrocartilaginous repair tissue tends to deteriorate; hence, the frequent failures when repair is by means of fibrocartilage rather than hyaline cartilage.

**Natural History of Articular Cartilage Injuries**

*Acute Trauma, Focal Degenerative*
Lesions, Site, and Size. Much remains to be learned about the natural history and progression of cartilage lesions. Although there is little in the literature on the relationship between focal cartilage damage and OA, most researchers have assumed that unrepaired full thickness focal cartilage damage eventually progresses to OA by causing friction and overload to the opposing articular surface (Figs 3A-C).

Lesions in which subchondral bone plate is not well “shouldered” by a peripheral cartilage border are often symptomatic. Subchondral reactive vascular congestion and pain develop. Although location is a key factor, size is also important. Lesions $\leq 2\text{ cm}^2$, although symptomatic, may take time to develop OA. Of the lesions treated by Homminga et al\(^5\) and Brittrek et al\(^5\) some 3 years after onset of symptoms, the tibial articular surface did not demonstrate degenerative changes despite lesions of $2\text{ cm}^2$ to $3\text{ cm}^2$ on average.

Family history of OA, obesity, and limb malalignment may hasten the development of OA by increasing loading stress, particularly in patients who have already sustained some cartilage damage.

An animal study by Grande et al\(^6\) suggested that even articular cartilage defects that do not penetrate the subchondral bone may progress to OA. This contradicted earlier findings showing that isolated cartilage defects were unlikely to progress to OA.

A recently presented human study of type II or geographic bone bruises detected by magnetic resonance imaging (MRI) associated with anterior cruciate ligament (ACL) ruptures has provided useful information on cartilage injury.\(^7\) Bone bruises were assessed by arthroscopy and biopsy. These occult osteochondral injuries revealed severe early cartilage damage to cartilage overlying the bone bruise. Whether these injuries progress to OA will depend on further follow up. As MRI bone bruises are documented in up to 80% of acute ACL ruptures, this patient population may be at high risk of future degenerative changes.

Clinical evidence that some of these injuries progress to degenerative changes exists. By searching a 9-year data registry of 2266 arthroscopies in 1850 patients, 516 cases of ACL injury (23%) were found (Lanny Johnson, MD, personal communication). Of these ACL-injured knees, there were 10 cases (7 femoral, 3 tibial) of acute traumatic, full thickness cartilage injuries (1.9%). However, there were 98 cases (19%) of traumatic and degenerative focal lesions associated with ACL-deficient knees. This may suggest that a proportion of MRI-proven osteochondral “bone bruises” associated with ACL injury would progress to degenerative changes locally.

**Classification of Articular Defects**

Before repair is attempted, the extent of injury must be assessed. Two major systems have been used to classify and report the severity of articular injuries by arthroscopic appearance. The Outerbridge classification system (Fig 4) was developed for assessing chondromalacia of the patella and is often used to classify cartilage injuries of other articular surfaces of the knee.\(^8\) It documents the progression of cartilaginous defects, primarily according to their depth. Grade 0 represents normal articular cartilage.
With grade I defects, there is softening and swelling of the cartilage. A grade II defect is partial thickness; it demonstrates early fissuring on the surface, but it does not reach the subchondral bone, nor does its size exceed 0.5 in. With grade III defects, there is fissuring to the level of the subchondral bone in an area with a diameter >0.5 in. Bone is not visibly exposed. In grade IV injuries, the subchondral bone is exposed. Clinically, this classification is widely employed specifying defect size separately.

In an alternative system, Bauer and Jackson\(^9\) classify lesions of the articular surface according to cartilage fracture patterns, as shown in Table 1.

The Bauer and Jackson classification is useful in a descriptive sense as to the initial chondral lesion and its potential cause. For instance, grades I through IV are usually associated with recent trauma; grades V and VI are usually older injuries that may have progressed from an earlier grade, or may represent early degenerative joint disease. The Outerbridge classification of chondromalacia primarily addresses a degenerative process. In dealing with cartilage repair, however, the authors believe that the Outerbridge classification may be more useful. One may delineate a symptomatic focal area suitable for repair (Outerbridge III/IV defect(s) and size), and yet grade the remainder of the knee anatomically by degree of degeneration. This is important in comparing clinical results to knees of equal health or degeneration that are similarly treated by other surgeons/techniques (see proposed classification system explained in the treatment approach section).

### CURRENT TREATMENT OPTIONS AND OUTCOMES

The goal of articular cartilage repair is to restore the integrity of the joint surface and to provide full range of pain-free motion, preventing further tissue deterioration. A variety of treatment techniques have evolved in pursuit of this outcome. Treatment options can be categorized as treating the symptoms or effecting repair. Joint pain has contributions from osseous pain, intracapsular pain (synovitis), and extracapsular pain (inflammation and distension of the capsule).\(^10\) With cartilage loss, and loss of cushioning function, the subchondral bone layer is more exposed to pressure. Pain receptors of the periartrial nerve fibers of this layer are stimulated. The tissue reacts with increased venous blood flow and subchondral cancellous bone congestion with periartrial nerve stimulation. Parallel to these reactions, enzymatic metabolites from cartilage degradation cause a painful synovitis followed by inflammatory swelling of the fibrous capsule. Treatments resulting in symptomatic improvement may address one or all of these mechanisms of pain relief.

From the outset it should be noted, in reviewing current treatment modalities, that case series do not report on uniform indications. Rather than discussing focal femoral condyle Outerbridge grade III/IV traumatic/degenerative lesions, case series report on a mixed variety of indications, from the focal chondral femoral defect to mild to severe arthritis, as defined by bipolar disease. Clearly, future reports must separate “the apples from the oranges” before evaluating a new modality/technology and reporting its functional outcome.

**Lavage.** One of the most basic traditional techniques is lavage. The utility of arthroscopic lavage, though limited, was a serendipitous discovery by Jackson,\(^11\) the pioneer of arthroscopy in North America. In the course of performing diagnostic arthroscopies on patients with intra-articular knee problems, he observed that patients had significant pain relief following joint lavage. Joint lavage rinses the knee of loose articular debris and inflammatory mediators known to be generated by the synovial lining of damaged joints.\(^11\)

In Jackson's study, lavage resulted in symptomatic improvement at 3.5 years in 45% of the patients; 20% felt no improvement. When mechanical debridement was added to the lavage, results were somewhat better. In a follow-up study of 137 cases, 88% experienced improvement, and 68% had continued improvement at 3 years.\(^12\) A recent, randomized prospective study by Chang et al\(^13\) demonstrated similar pain relief at 1 year with both arthroscopic lavage with debridement of loose bodies and closed-needle joint lavage in patients with non-end stage OA of the knee.\(^13\) Lavage may provide some patients temporary pain relief for which may last as long as 3 years. However, the clinical results obtainable with lavage are generally insufficient for athletic or active young patients, providing only short-term symptomatic relief without correction of the underlying pathology.

Hubbard\(^14\) clarified the benefit of arthroscopic lavage versus debridement in a randomized, prospective study of 76 knees, assessing lesions of unipolar Outerbridge grade 3 or 4 medial femoral condyles in a radiographically normal knee. In an average follow up of 4.5 years, debridement was clearly superior. Using a modified Lysholm score, a mean improvement for the debridement group was 28 at 1 year and 21 at 5 years, and in the washout group it was 5 at 1 year and 4 at 5 years. Washout helps early on with tenderness and night pain, but debridement may provide measurable functional improvement for up to 5 years. Defect sizes were not described, nor were follow-up radiographs, to demonstrate progression to joint space narrowing.

Mesner and Maltei\(^15\) recently reported on the long-term prognosis for chondral injuries >1 cm\(^2\). A 14-year follow up of 28 patients with 25 grade
III and grade IV injuries was performed. Functionally, 21 patients were able to return to sports, and 22 patients had good or excellent Lysholm knee scores. Despite initial injuries during adolescence, when articular cartilage may still have intrinsic repair, 12 patients demonstrated >50% joint space narrowing of the injured compartment. Debridement alone may not be sufficient to protect from progression of disease.

Marrow-Stimulation Techniques. Several techniques aimed at stimulating cartilage repair can be classified under the rubric of marrow-stimulation techniques. These treatments attempt to utilize primitive stem cells, which are capable of differentiating into bone and cartilage under the influence of biological and mechanical factors associated with the knee. In each of the techniques, the subchondral bone is penetrated to reach a zone of vascularization, stimulating the formation of a fibrin clot containing the desired pluripotent stem cells. This clot then differentiates and remodels, resulting in a fibrocartilaginous repair tissue. Due to the fragility of this repair tissue, further surgical intervention designed to protect the affected area from excessive weight bearing, such as unloading osteotomy, is often concurrently pursued.

Abrasion Arthroplasty. Abrasion arthroplasty involves debriding the articular defect to a normal tissue edge so that fresh collagen capable of binding to a fibrin clot is exposed. The surface of the subchondral bone is then exposed and superficially penetrated. The previously applied tourniquet is released, causing a sudden perfusion of the subchondral bone extending through to the surface. This results in formation of a blood clot on the surface of the exposed bone. In a study by Johnson, 399 patients underwent arthroscopic debridement with abrasion arthroplasty; the average patient age was 60 years. Only 12% had no complaints postoperatively; 66% had pain; 44% used pain medications; 24% suffered loss of mobility; and 99% had some restriction of activity. In these patients, the repair tissue was initially shown to be fibrous. However, by 4 to 6 months, it had become fibrocartilage, with collagen typing in a few patients demonstrating increasing amounts of type II collagen and hyaline cartilage in the repair tissue up to 2 years postoperatively.

Friedman et al similarly noted that in patients age 54 years on average followed 12 months postoperatively, 53% had improved, 37% were unchanged, and 10% were made worse. In patients younger than 40 years old, there was an 86% improvement.

Subchondral Drilling. Another variant of the marrow-stimulation technique is subchondral drilling. The area of the defect is drilled through in pinpoint fashion to penetrate the vascularization of the subchondral bone, resulting in fibrin clot formation. The repair cartilage later filling the drill holes has been shown to include both hyaline and fibrocartilage. In a series by Tippett, at 62 months of follow up, 70.8% of the patients judged their knees to be excellent, 15.4% good, and 6.9% each fair and poor. These results were in combination with high tibial valgus osteotomy and reported results superior to that of osteotomy alone.

Microfracture. A similar marrow-stimulation technique is microfracture, in which the subchondral bone is exposed, gently abraded, but left intact, while adjacent cartilage is debrided to healthy cartilage. The subchondral bone surface is then broached using small picks so that it communicates with the marrow, and clot formation is stimulated.

Rodrigo et al demonstrated the usefulness of continuous passive motion (CPM) after microfracture. This paper did not evaluate the functional outcome of patients nor the histological biopsy appearance of treated defects. The paper evaluated the arthroscopic “second-look” appearance of treated focal full-thickness defects when treated by microfracture under the influence of CPM postoperatively. When CPM was used daily for 6 hours for 8 weeks, a clear statistical difference was noted independent of location. A total of 77 patients were followed. Only 15% of the CPM-treated group showed no improvement, whereas 45% of the non-CPM group was the same. The mean improvement in repair tissue grade was statistically significant (P=0.003) for the CPM-treated group versus the non-CPM group. It is unknown whether this difference was functionally or clinically significant. This paper is useful in advocating postoperative CPM for patients who have cartilage repair procedures to enhance “fill” of the defect. Experimentally, CPM has also improved the quality of the repair tissue.

Following these procedures, most rehabilitation programs combine the use of protective weight bearing and CPM to stimulate differentiation of the repair tissue into cartilage. There is some controversy as to the nature of the clot produced by all these marrow-stimulation procedures. Proponents argue that in addition to the marrow-derived stem cells, which produce fibrocartilage, pluripotent synovium-derived stem cells capable of differentiating into articular cartilage are also contained in the clot. However, some argue that the clot forms immediately after the tourniquet is released, suggesting that the majoritiy of stem cells present in the clot are marrow-derived.

High Tibial Osteotomy/Distal Femoral Osteotomy—Correction of Pre-disposing Factors. Since limb malalignment is a significant predisposing factor for focal degenerative lesions of the articular surface, correction of pre-existing varus or valgus deformities via unloading osteotomy is often pursued.

This intervention, in conjunction with marrow-stimulation techniques, reduces the weight stress on the area of cartilage repair and redistributes weight bearing to other, less fragile tissue.

Osteotomy with subchondral drilling yields results improved over osteotomy alone when compared to other series. The results reported are for unicompartamental (bipolar) OA, not focal chondral
injuries. Insall and Rosenberg\textsuperscript{22} reported on the long-term follow up of high tibial osteotomy for varus gonarthrosis. By 2 years after surgery 97\% and by 5 years 85\% of knees had a good or excellent result. However, only 63\% had a good or excellent result by 8.9 years and 23\% had been revised to a total knee. Only 37\% of the knees were pain free after 9 years.

Distal femoral varus osteotomy for valgus deformity of the knee yields similar results. McDermott et al\textsuperscript{23} reported 92\% good or excellent results at 4-year follow up using the Hospital for Special Surgery (HSS) rating score with an average score improvement of 28 points.

These studies emphasize the importance of correction of malalignment. Unless malalignment is recognized and treated along with a chondral injury, results may be jeopardized.

**Biologic Repair: Treatment With Autologous Tissue**

Perichondrial and Periosteal Grafting. In the continuing search for techniques that result in articular surface repair with hyaline cartilage, other possible means of obtaining viable cartilage are grafting with perichondrial and periosteal tissue. It has already been demonstrated by several investigators (eg. Homminga et al\textsuperscript{1}, Ritsilä et al\textsuperscript{24}) that perichondrium taken from the cartilaginous covering of a rib could be placed in a joint, where it would develop into hyaline cartilage. Similar procedures using rib perichondrium to reconstruct smaller joints such as the metacarpal and metapatellar joints have already been employed successfully by Skoog and Johansson\textsuperscript{25} in the plastic surgery setting. However, larger joints such as the knee present the additional technical challenge of graft fixation.

Animal studies conducted by several groups showed that neochondrogenesis of hyaline cartilage is also possible using autologous periosteal or perichondrial grafts sutured or glued with the cambium layer facing into the joint.\textsuperscript{1,20} In another examination of this technique, Rubak et al\textsuperscript{26} studied chondrogenesis in rabbits receiving tibial periosteal grafts to fill defects in the femoral articular cartilage. They were able to trace the origin of the cells proliferating in the healing defect and found that they originated from the graft rather than from subchondral bone.

A further contribution to the biology of neoochondrogenesis came from a group from Finland studying the chondrogenic potential of periosteal and perichondrial grafts.\textsuperscript{24} They found that the direction of differentiation, whether into bone or articular tissue, may be largely determined by the environment rather than by the phenotype of the transplanted cells. For instance, mesenchymal stem cells may be regulated in part by oxygen tension, with low oxygen tension favoring the development of cartilage tissue and high oxygen tension favoring differentiation into bone. This discovery, combined with the knowledge that hyaline cartilage can be derived from perichondrial and periosteal tissue sources, suggested the possibility that cartilage repair could be achieved with grafts of these tissues.

However, in vitro de/redifferentiation manipulation of these tissues, because of the expression of type X collagen, largely favors eventual formation into bone. Autologous chondrocytes alone do not produce type X collagen in a three-dimensional system.

Clinical Experience With Perichondrial Grafting. The first clinical study of perichondrial grafting for cartilage lesions of the human knee was performed by Homminga et al.\textsuperscript{5} In this study, 25 patients with 30 symptomatic chondral lesions received autogenous perichondrial grafts taken from the costal arch. The majority of the lesions were Outerbridge grade III/IV, and half were located on the medial femoral condyle. The opposing articulating surface had no greater than Outerbridge grade II changes.

The surgery was performed under general anesthesia. After exsanguination of the affected leg, the chondral lesion was debrided to the level of subchondral bone and extended into normal-appearing adjacent cartilage, creating a sharp border. A piece of perichondrium was dissected, with its chondrogenic layer, from the cartilaginous portion of one of the lower ribs and cut to match the size of the defect. Depending on the size of the defect, two pieces of perichondrium were sometimes used. A human fibrin glue was applied to the defect, and the graft was placed with the cambium layer facing into the joint. CPM was started 2 weeks after surgery, and non-weight-bearing mobilization using crutches was begun at 4 weeks. Weight bearing was permitted at 3 months after the operation.

Arthroscopy was performed on all 25 knees at an average of 10 months after implantation. Of the 30 grafted defects, 27 had completely filled with tissue resembling cartilage. In two cases, the defect was unchanged, and in one case, a patellar graft was covered with white tissue with a surface that appeared fibrillated. Three biopsy specimens were taken at 1 year after surgery. Microscopically, there appeared to be disruption of the cartilage and bone junction in two cases and uninterrupted contact in one. Visually, the regenerated cells appeared to be chondrocytes, and there were no signs of ossification present in that layer.

The mean preoperative HSS knee score was 73; at 1 year postoperatively, it was 90. One year after surgery, 18 of the 25 patients were completely symptom-free and had resumed previous occupational and athletic activities.

The first 14 patients in this series were assessed at a mean of 23.5 months (range, 17 to 32 months), at which time their mean knee score increased slightly from 85 to 87. Postoperative radiography at 1 year revealed no increase in joint space narrowing, number of osteophytes, cysts, or subchondral bone density. However, at this 1-year examination, increased density was visible in the region of the graft in 20 knees, suggesting increased calcium uptake into the basal layer of cartilage. At 5 to 7 years postoperatively, 20 of
the 30 grafts in this series developed endochondral ossification, with pain and graft degeneration. At this later follow up, 60% of the patients in this series had graft failure as a result of endochondral ossification (SK Bulstra, personal communication).

Limitations to Perichondrial Grafts. Although autologous periosteal and perichondral grafts appear to be quite effective in stimulating repair with hyaline cartilage, this approach has a number of shortcomings. One of the most significant is the fact that perichondrium is found largely on the cartilage borders of the rib cage adjacent to the sternum. The graft size is therefore limited by rib size, and several ribs often must be used to obtain sufficient perichondrium to graft multiple or large defects. In addition, endochondral ossification and delamination of the cartilage from the subchondral bone plate are potentially significant limitations to the long-term efficacy of this repair technique.

An example of failure due to endochondral ossification of a perichondrial graft 54 months after implantation in this author’s series (TM, unpublished data) is demonstrated in Figure 5.

Clinical Experience With Periosteal Grafts. Clinical experience with periosteum is limited. Lorentzon reported on 18 consecutive patients treated with drilling and periosteal grafting of the patella. The lesions ranged in size from 0.75 to 16.0 cm². Careful rehabilitation with CPM and protected motion were considered crucial to a successful outcome. At 27 months follow up, 14 were considered excellent and 4 good. Biopsies from 5 randomly selected patients were considered normal hyaline cartilage.

O’Driscoll reported on 23 patients age 14 to 25 years. A survey of 15 patients revealed nine satisfactory results and six unsatisfactory due to graft failure. Publications to include biopsy data and clinical outcomes are awaited.

Autologous Chondrocyte Implantation. As a consequence of the aforementioned limitations, alternative sources of biologic materials have been pursued. One possibility was the use of autologous chondrocytes with a population expanded in vitro and then implanted into the defect. In originally studying this possibility, Grande et al. found that 82% of cartilage was reconstituted in rabbits that had received transplants of autologous chondrocytes grown in vitro. This compared with a defect fill of only 18% in ungrafted controls. Autoradiography on reconstituted cartilage showed that there were labeled cells incorporated into the repair matrix. Hence, the implanted cells were partly or fully responsible for the repair tissue. This study also introduced a technical advance over earlier studies using autologous cultured chondrocytes in that a sutured periosteal flap was used for graft fixation. The histologic tissue at sacrifice was superior in its hyaline qualities with the implanted autologous cell model.

Based on the successful results obtained with this and other animal studies, Britberg et al. in Sweden decided to attempt the same technique in patients with cartilage defects of the knee. The initial 23 patients ranged in age from 14 to 48 years. All had symptomatic cartilage defects, ranging in size from 1.6 to 6.5 cm². Thirteen patients had femoral condylar defects due to trauma, and three had localized osteochondral lesions due to osteo-
chondritis dissecans. Seven patients suffered debilitating defects of the patella; six had chondromalacia; and one had a trauma-related defect. Of the 23 patients, 10 had previously been treated with shaving and debridement of unstable cartilage.

**Harvesting and Implantation.** Figure 6 illustrates the actual chondrocyte harvesting and implantation procedure used by Britberg et al. Chondrocytes were harvested through an arthroscopy from a minor load-bearing area on the upper medial femoral condyle of the affected knee. After enzymatic digestion using clostridial collagenase, chondrocytes were filtered and resuspended in a culture medium supplemented with the patient's serum. Following technique-sensitive culturing, propagated cells were available for reimplantation 14 to 21 days later (Fig 7).

At the time of implantation, the chondral lesion was excised to the level of normal-appearing surrounding cartilage to the subchondral bone plate. The defect was covered with a periosteal patch obtained from the proximal medial tibia and sutured to the rim of the debrided defect. The cultured chondrocytes were then injected beneath the patch. The joint capsule, retinaculum layer, and skin were sutured in separate layers. Active movement without weight bearing was initiated within 2 to 3 days following the procedure. Gradual introduction of weight bearing and isometric quadriceps training were begun during the first 8 weeks.

**Results.** In the Swedish study, the 23 patients were evaluated every 8 to 12 weeks, with arthroscopy performed first at 3 months postoperatively and repeated 12 to 46 months postoperatively. Graft hardness was tested with a probing hook, and the extent of the repair documented videographically. At the second arthroscopy, biopsy specimens extending to the subchondral bone were taken from the center of the graft.

Pain and crepitus were considerably reduced following the surgery, and knee-locking or catching ceased completely during the 16- to 60-month follow up (mean, 39 months). At initial arthroscopy, regenerated areas of cartilage with borders level with the surrounding articular surface were visible. The arthroscopic appearance of the transplanted areas was similar to that of the surrounding healthy cartilage (Fig 8).

A soft area in the center of the grafts that did not reach the subchondral bone was felt on early postoperative probing. In most cases, early probing of the grafts resulted in a wave-like motion, which suggested a loose attachment to the subchondral bone in this central portion of the graft. At the second arthroscopy, most of the transplants had a biologically acceptable macroscopic appearance, but were firmer when probed, with the wave-like motion no longer noted.

Two years postoperatively, 14 of 16 patients with femoral condylar transplants had good to excellent results (Table 2). Two patients followed for the longest period maintained excellent results at 55 and 59 months postoperatively. The two patients with poor results suffered severe central wear in their grafts with locking and pain 11 and 14 months after the procedure.

Among patients who had received patellar grafts, 2 of 7 had results graded excellent or good, while 3 patients had fair results, and 2 had poor results. The 2 patients with poor results had severe chondromalacia and underwent a second operation for debridement and resection of the failed graft and subchondral bone.

**Confirmation of Hyaline Cartilage.** At the time of biopsy, the remnants of the periosteal flaps were visible close to the articular surface. Eleven of the 15 biopsy specimens revealed an intact articular surface with a hyaline appearance; chondrocytes were present in lacunae, and metachromatic staining
was comparable to that of surrounding cartilage (Fig 8B). Immunohistochemical staining for type II collagen was positive for 5 of the femoral transplant biopsy specimens tested. These findings indicate that near-normal hyaline cartilage had regenerated in the defect. Only 1 of the 7 patients with patellar transplants revealed an intact articular surface and a hyaline appearance. The other 6 biopsy specimens revealed central areas of fibrous tissue surrounded by more hyaline tissue. The authors of the study hypothesize that the poorer results obtained in patients with patellar defects could be attributed to patellar maltracking. The authors suggest that the results obtained in this subset of patients could be further improved by correcting these abnormalities concurrently with the implantation.

In summary, this initial series of 23 patients yielded highly promising results. Further follow up reveals the results of femoral condyle grafts remain as stated. The patients with patellar grafts have improved further. The good result improved to excellent. Two fair results are now considered good.

Since the publication of the New England Journal of Medicine article, there have been over 251 patients treated with autologous chondrocyte implantation (ACI) in Sweden, as reported by Lars Peterson, at the American Academy of Orthopaedic Surgeons (AAOS) Annual Meeting (unpublished data, February 1996). There were 246 patients treated with knee injuries, 2 patients with ankle injuries, and 3 patients with shoulder defects. There were 308 treatment defects (locations) involving the medial femoral condyle in 131, lateral femoral condyle in 45, trochlea in 51, medial tibial plateau in 4, lateral tibial plateau in 9, patella in 61, and other in 7. Retrospective review of the medical records for 153 patients followed up to 57 months has been completed by Britterberg et al.2

Using the Britterberg score for evaluation, the improved outcomes of patients with greater than 2-year follow up were included in this presentation (Table 3). More than 80% of patients have noted improvement after 2 years of follow up. There were no serious unanticipated related adverse events and no significant post-implantation infections in this series of patients.

Occasionally, patients with hypertrophic graft edges may present with symptomatic “catching” requiring arthroscopic trimming of the edges flush to surrounding native cartilage. This does not adversely affect graft outcome, and is considered part of the treatment.

In the author’s (TM) experience with 50 patients undergoing ACI, a patient-reported improvement over time is noted. Patients report that by 4 to 6 months, 50% of pain has improved; by 7 to 9 months patients report 70% to 80% improvement; by 12 months 90% improvement, and by 18 months there is near complete resolution of pre-treatment pain. This timetable reflects repair-tissue maturation over time as noted arthroscopically. By 3 months, probing demonstrates “wave-like” motion of grafts without firm anchorage to underlying bone; by 6 months “rubber-like indentability” is present, and firm, non-indentable, porcelain-like surfaces are present by 18 months. This parallels the Swedish experience discussed by Peterson.

At this time, the longest clinical follow up is 9 years. There are no grafts undergoing ossification nor degeneration with recurrent symptoms.

**Table 2**

<table>
<thead>
<tr>
<th>Clinical Grade</th>
<th>Femoral Condyle (n=16)</th>
<th>Patella (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent</td>
<td>24 months</td>
<td>36 months</td>
</tr>
<tr>
<td>Good</td>
<td>6 patients</td>
<td>1 patient</td>
</tr>
<tr>
<td>Fair</td>
<td>8 patients</td>
<td>1 patient</td>
</tr>
<tr>
<td>Poor</td>
<td>2 patients</td>
<td>3 patients</td>
</tr>
</tbody>
</table>

Excellent: No pain, swelling, or locking with strenuous activity
Good: Mild aching with strenuous activity, but no swelling or locking
Fair: Moderate pain with strenuous activity, occasional swelling but no locking
Poor: Pain at rest, swelling, and locking

Physiology of Autologous Cell
Implantation Repair. The authors offered three hypotheses regarding the physiologic nature of the repair process. One is that the implanted chondrocytes re-populate the area of the defect and produce new cartilage matrix. The periosteal patch functions solely as a watertight seal, which isolates the chondrocytes and permits them to incubate, differentiate, and fill the cartilage defect. The second possible explanation is that growth factors in the periosteum are able to stimulate the cultured chondrocytes to divide. The third is that the implant and periosteal patch stimulate chondrocytes in adjacent cartilage, in the subchondral bone, or in the periosteum, to enter the defect and repair it. Additionally, the periosteal patch may act as a protective semipermeable membrane that allows nutrients from the synovial fluid to nourish the implanted chondrocytes.

Patient Selection Criteria for Autologous Chondrocyte Implantation. It is important to note that while this technique is proving to be effective, the safe cultivation of autologous cells is a demanding process. When culturing other tissues for use in cell-based therapies, some academic centers have reported infection rates of 25% to 68%.

Accordingly, cell processing must be pursued through use of a standardized system that will ensure safe, viable cells for implantation. Strict sterile technique in an undeviating aseptic environment for up to 4 or 5 weeks of cell processing is mandatory.

Autologous chondrocyte implantation is particularly advantageous for healthy, young, and active patients with clinically significant injuries (>2 to 3 cm²) to articular cartilage. Symptomatic patients previously treated for articular injury and those suffering focal degenerative lesions not due to acute trauma are also likely to benefit from this articular repair method.

Standing radiographs and arthroscopic evaluation are necessary to identify patients who have moderate to severe OA (ie, bipolar lesions) and thus are not currently candidates for ACI. Arthroscopy is the gold standard for diagnosis in this setting and yields more valuable information than MRI. Visualization under careful arthroscopic probing is essential to demonstrate the true extent of the cartilage damage as well as the health of the adjacent cartilage.

Incidence studies to determine the frequency of suitable lesions for ACI are unknown. However, data from a recent analysis of 855 arthroscopic abrasion arthroplasties over 15 years revealed only 197 patients between the ages of 15 and 50 years (Lanny Johnson, MD, personal communication). Of this group of 197 patients, only 38 (19.3%) would be considered suitable for ACI. The criteria are an otherwise healthy joint, with focal unipolar Outerbridge grade IV femoral defect with tibial chondromalacia of Outerbridge grades 0, I, or II changes only. Outcome data were not available at the time this article was published for the results of arthroscopic abrasion arthroplasty for these focal injuries.

Osteochondral Autografts/Allografts. Chondral injuries treated by these techniques represent an invasion of the subchondral bone. Lateral patellar facet autografts for repair of large osteochondral defects was first described by Outerbridge. Ten patients were followed for an average of 6½ years with excellent relief of symptoms and minimal donor site morbidity.

Multiple osteochondral arthroscopic transplantation (mosaicplasty) was first reported by Matsusue. Using osteochondral plugs derived from the lateral intercondylar notch during ACL reconstruction, chondral defects were repaired. Second-look arthroscopy demonstrated excellent fill with good clinical outcome. Bobic reported on 12 cases of arthroscopic mosaicplasty of lesions 10 to 22 mm in diameter. Ten of 12 patients had excellent results at 2 years follow up.

Success rates of greater than 80% have been reported in wafer allografts by Zukor and Gross osteochondral plugs by Garrett and shell allografts by Convey. Unloading osteotomies are often needed to prevent collapse and failure of grafts. meticulous attention to matching size and inlay fixation are critical to success. Fresh grafts pose logistical issues with management and viral transmission of disease; frozen grafts do not ensure chondrocyte viability.

TREATMENT APPROACH
When faced with a symptomatic unipolar full thickness chondral lesion, what treatment should be offered? Many factors contribute to selection by surgeon and patient. A careful evaluation for predisposing factors, or concomitant injuries, must be undertaken to prevent recurrent chondral injury. Tibiofemoral or patellofemoral malalignment and ligamentous (ACL) or bone insufficiency (osteocondritis dissecans, avascular necrosis, or osteochondral fracture), must be managed prior to, or concurrently managed with, the chondral injury. Other issues to be dealt with include the lesion size, type of repair tissue desired, patient expectations with regard to expected level of activity (ie, high demand sports or activities of daily living [ADLS]), surgical invasiveness, compliance with rehabilitation, and procedural costs.
TABLE 4

ACI Injury classification

<table>
<thead>
<tr>
<th>SIMPLE</th>
<th>Unipolar grade III/IV chondral lesion femur, tibial surface or patella no worse than grade II, no generalized chondromalacia</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMPLEX</td>
<td>Multifocal unipolar grade III/IV chondral lesions, femur Unipolar lesion patella/tibia Treating marginal uncontained chondral injuries Osteochondritis dissecans Concomitant correction of tibiofemoral/patellofemoral Malalignment use of femoral periosteum</td>
</tr>
<tr>
<td>SALVAGE RECONSTRUCTION</td>
<td>Bipolar focal chondral lesions Presence of osteophytes or radiographic joint space narrowing Generalized chondromalacia grade II or greater</td>
</tr>
</tbody>
</table>

Small focal defects (<2 cm²) in the short term (3 to 5 years) when treated with debridement or narrow stimulation techniques have not been shown to progress to degenerative joint disease (DJD) as likely the chondral border effectively shouler the exposed bone from damaging the opposing articular surface (Fig 3A, left).

The authors propose for a low demand patient with a small focal defect, arthroscopic debridement offers symptomatic relief for up to 5 years in 50% of the patients; alternatively, a fibrocartilage repair may be provided in a rehabilitation-compliant patient who requires a more active lifestyle with a 50% success returning to sports and 75% success of being comfortable with activities of daily living. These options offer a minimally invasive, low cost treatment.

If this should fail, then ACI has been shown to be 90% successful in a revision chondral surgery situation to returning a patient to a high level activity, albeit a staged procedure, which is invasive, costly, and requires a compliant patient for effective rehabilitation.

Mosaicplasty also may be offered as a revision chondral surgery for the small lesion, although it converts a chondral to an osteochondral injury. It offers a minimally invasive, low cost option. However, studies are limited to small repairs.

When chondral injuries are large, (≥2 cm²) the repair tissue must prevent the subchondral bone from bottoming out (Fig 3A, right) so that secondary articular damage does not occur to the opposing articular surface, leading to DJD. Arthroscopic debridement will not prevent eventual DJD, although symptoms may be temporarily improved, high level durable improvement is unlikely and this treatment is not recommended.

The success rate of narrow stimulation techniques in producing durable fibrocartilage repair for these large injuries is unknown. If patients prefer a less invasive repair procedure, these techniques may be pursued. Failure will not preclude successful ACI as a revision chondral repair technique.

For the high level activity patient, the authors recommend ACI as the first line treatment for lesions ≥2 cm², as this produces a durable repair tissue with >90% success.

If ACI fails, the cause should be sought before repeat attempts (which can also be successful). Large osteochondral allografts would be used to salvage a failed revision ACI; subchondral bone would then be sacrificed. Allograft failure would then require prosthetic arthroplasty.

When treating chondral injuries, treatment groups should be compared to aid in determining treatment effectiveness. Table 4 presents a classification proposed in ACI.

The classification proposed was devised by assessing clinical results reported by Britberg et al. those presented in Table 3, and the author’s personal experience (TM) with ACI. Intraoperative technical and rehabilitative problems as well as clinical results were used to create a classification of progressive advancement of severity of disease and prognostic clinical outcome.

The simple category involves a healthy knee with a unipolar femoral condyle weight-bearing lesion, known to provide an excellent clinical result >90% of the time within 12 to 18 months of surgery with patients returning to sports.

The complex category addresses other factors that may contribute to a lesser clinical result or involve adjuvant procedures that may affect the outcome. However, this is in a knee free of generalized chondromalacia, except for unipolar chondral lesions. Multiple unipolar lesions on the femur will yield highly successful results; however failure of even one graft may compromise the overall clinical result.

Initial patellar resurfacings have not fared well, however, concomitant realignment procedures are improving results for the patella. Similarly, unipolar tibial repairs have done well in the author’s series (TM) up to 2 years.

Uncontained lesions requiring suturing to the synovium or bone anchors pose technical challenges, and harvesting of femoral periosteum may promote intra-articular adhesions or quadricsceps heterotopic ossification.

Osteochondritis dissecans seems to be an ideal indication for ACI; however, due to the depth of the repair required, it may take up to 18 to 30 months to obtain excellent clinical improvement.

The salvage category attempts to provide repair to severely injured knees or degenerative knees. Bipolar “kissing” lesions, or those joints with evidence of DJD (ie, generalized chondromalacia, mild radiographic joint space narrowing, or osteophyte formation), obviously have differing clinical expectations and prognosis.

This classification is based on preliminary results and technical aspects in an attempt to group different disease states so that results may be compared similarly. It also may provide categories for clinical outcome and prognosis. Long-term results will help to clarify these categories further.

CONTINUING TECHNICAL REFINEMENTS: THE FUTURE

At present, several alternative cell
delivery approaches are being tested in animals. Of most interest is arthroscopic delivery of phenotypically normal autologous chondrocytes in a variety of carrier matrices.

Also in the early research stage is the use of mesenchymal stem cells, derived from the periosteum or bone marrow, which possess a capability of differentiating into bone or cartilage. In a recent study, these pluripotent cells were embedded in a type I collagen gel and then implanted into large, full-thickness defects in rabbit knees. As early as 2 weeks after the procedure, the mesenchymal stem cells had differentiated into chondrocytes and the deeper area of the full-thickness defect had filled in with vascularized bone up to the bone cartilage junction. A normal calcified zone of cartilage and tidemark did not develop.

This study demonstrated significant limitations, including the thinning and fibrillation of the repair tissue by 24 weeks post-implantation, incomplete integration with the host cartilage at some locations, and a tendency of the repair tissue to ossify over time with possible DJD as has occurred clinically with endochondral ossification in perichondrial grafts.

Another study using mesenchymal stem cells derived from skeletal muscle used a polyglycolic acid polymer matrix for implantation. Cartilage and bone formation were demonstrated with the development of a tidemark in a rabbit model.

Evaluation of type I and type II collagen sponge carrier matrices seeded with articular chondrocytes in our facility demonstrated that the chondrocytic phenotype was maintained in the type II collagen sponge. This was demonstrated in vitro as well as in a canine model (Fig 9).

**CONCLUSION**

The inability of articular cartilage to repair itself has been known for at least 200 years. Medical science has developed a number of treatments to manage the symptoms of articular cartilage damage, most being notably ineffective at providing a long-term treatment solution. The earliest attempts using marrow-stimulation techniques such as abrasion and drilling result in some degree of tissue repair. However, the repair tissue generated by these procedures is fibrocartilage rather than articular cartilage. As such, it lacks the mechanical, structural, and physiologic characteristics of healthy, durable articular cartilage.

Later studies demonstrated that periosteum or perichondrium could be used to treat defects, resulting initially in a hyaline repair. The techniques of autologous perichondrial or perioseal grafting are, however, limited by poor graft integration and the strong likelihood of eventual endochondral ossification of the grafted tissue.

Osteochondral autografts and allografts may have a role in the treatment of osteochondral injuries; however, they are aggressive options for chondral injuries.

Autologous chondrocyte implantation offers a durable hyaline repair in appropriate focal unipolar chondral disease. Patients with 9-year follow up to 9 years in Sweden function well without pain.

Future research into combining cells, matrices, and growth factors will allow implantation of larger grafts at a more advanced stage of differentiation. This will enhance patient selection and rehabilitation.

**REFERENCES**


538