Articular cartilage has a poor intrinsic capacity for healing. The goal of surgical techniques to repair articular cartilage injuries is to achieve the regeneration of organized hyaline cartilage.

Microfracture and other bone marrow stimulation techniques involve penetration of the subchondral plate in order to recruit mesenchymal stem cells into the chondral defect. The formation of a stable clot that fills the lesion is of paramount importance to achieve a successful outcome.

Mosaicplasty is a viable option with which to address osteochondral lesions of the knee and offers the advantage of transplanting hyaline cartilage. However, limited graft availability and donor site morbidity are concerns.

Transplantation of an osteochondral allograft consisting of intact, viable articular cartilage and its underlying subchondral bone offers the ability to address large osteochondral defects of the knee, including those involving an entire compartment.

The primary theoretical advantage of autologous chondrocyte implantation is the development of hyaline-like cartilage rather than fibrocartilage in the defect, which presumably leads to better long-term outcomes and longevity of the healing tissue.

Use of synthetic scaffolds is a potentially attractive alternative to traditional cartilage procedures as they are readily available and, unlike allogeneic tissue transplants, are associated with no risk of disease transmission. Their efficacy, however, has not been proven clinically.

Bone Marrow Stimulation: Microfracture

Bone marrow stimulation is the most frequently used technique for treating small symptomatic lesions of the articular cartilage in the knee. These procedures are technically straightforward, and the costs are low compared with those of other treatment modalities. Bone marrow stimulation techniques involve perforation of the subchondral plate in order to recruit mesenchymal stem cells from the bone marrow space into the lesion. The mesenchymal stem cells are able to differentiate into fibrochondrocytes, which contribute to fibrocartilage repair of the lesion. However, the overall concentration of the mesenchymal stem cells is quite low and declines with age. The formation of a stable blood clot that maximally fills the chondral defect is important, and it has been correlated with the success of bone marrow stimulation procedures. Unstable
Clots that are only partially adherent to or fill only a portion of the defect will result in suboptimal repair. Reparative fibrocartilage consists of type-I, type-II, and type-III collagen in varying amounts. The fibrocartilage does not resemble the surrounding hyaline cartilage and has less type-II collagen. Unlike other cartilage restoration techniques, bone marrow stimulation does not involve transfer of chondrocytes into the lesion.

Creating a contained lesion is critical to achieving a stable base for filling the defect with a clot and adhesion of the clot. If the lesion is not shouldered by a stable rim of healthy cartilage, achieving a stable clot may be more difficult. The calcified cartilage layer at the base of the lesion must be removed as well (Figs. 1-A through 1-D). Removal of this layer is important for clot adhesion and the ultimate success of the microfracture technique. The prepared channels must be of sufficient depth to ensure penetration of the subchondral plate and communication with the marrow. Fatty droplets should be seen to emanate from the channel apertures to confirm that adequate depth has been achieved.

The postoperative regimen after bone marrow stimulation procedures is demanding and has been reported to be a critical aspect of the ultimate efficacy. Patients with a femoral condylar lesion are initially treated with continuous passive motion with a 0° to 60° range of motion for six weeks postoperatively. Studies have shown that continuous passive motion improves cartilage nutrition and stimulates mesenchymal stem-cell differentiation. The patient typically remains non-weight-bearing with the use of crutches for six weeks. Patients who have undergone microfracture of a patellar or trochlear defect are allowed to bear weight as tolerated postoperatively, but knee motion is restricted from 0° to 40° in a brace. Continuous passive motion is initiated immediately and used, within this arc of motion, for approximately six to eight hours daily. At two months, unrestricted motion is typically allowed and closed-chain exercises are initiated. Short-arc closed-chain concentric and eccentric muscle strengthening is effective and protects the patellofemoral articulation. Typically, a return to full activities is permitted at three months after a full, painless range of motion is achieved.

Outcomes (See Appendix)

Steadman et al. reported what we believe to be the first long-term follow-up study of microfracture, in which seventy-one knees were followed for an average of eleven years. The patients all had a traumatic full-thickness chondral defect, had no meniscal or ligamentous injury, and were less than forty-five years of age. At the time of final follow-up, the patients had significant improvement in multiple clinical outcome measures (p < 0.02). The authors found that age was an independent predictor of functional improvement. Mithoefer et al. performed a prospective study of forty-eight patients (mean age, forty-two years) a mean of 3.6 years following the operation. Most of the lesions (52%) were between 1 and 4 cm². Overall, knee function was good to excellent in thirty-two (67%) of the forty-eight patients, fair in twelve (25%), and poor in four (8%). The authors found that a lower body mass index correlated with better outcomes. Magnetic resonance imaging showed that 54% of the patients had good fill with repair tissue, 29% had moderate fill, and 17% had poor fill. The grade of fill on magnetic resonance imaging correlated with better clinical outcomes.

Microfracture has been compared with other cartilage restoration procedures in multiple well-designed, randomized studies. Knutsen et al. compared autologous chondrocyte implantation with microfracture in eighty patients with an average age of 32.2 years. The average lesion size was 4.8 cm². After two years of follow-up, both groups had significant clinical improvement (p < 0.05). The Short Form-36 (SF-36) score, however, was significantly better in the microfracture group (p = 0.004). Histological assessment demonstrated hyaline-like or mixed hyaline/fibrocartilage-like tissue in 29% of the patients in the microfracture group and 50% of those in the group treated with autologous chondrocyte implantation. There was, however, a 23% failure rate with both procedures.

Gudas et al. compared the outcomes of osteochondral autologous transplantation with those of microfracture in young athletes in a randomized, controlled study. Fifty-seven patients (twenty-eight treated with osteochondral autologous transplantation and twenty-nine treated with microfracture) were available at the time of final follow-up. The average age was 24.3 years, and the average lesion size was 2.8 cm² (range, 1 to 4 cm²). At a mean of thirty-seven months postoperatively, both groups had substantial clinical improvement. However, on the basis of Hospital for Special Surgery (HSS) and International Cartilage Repair Society (ICRS) scores, 96% had a good-to-excellent result after the osteochondral autologous transplantation compared with 52% after the microfracture procedure. Biopsy specimens were obtained from 58% of the patients and histological evaluation of repair showed better ICRS scores for the group treated with osteochondral autologous transplantation. In addition, subjective evaluation of lesion fill, osseous incorporation, and surface congruency with magnetic resonance imaging showed good-to-excellent repair in 94% of the patients treated with osteochondral autologous transplantation compared with only 49% of those treated with microfracture. Twenty-six (93%) of the patients treated with osteochondral autologous transplantation and fifteen (52%) of those treated with microfracture returned to sports activities at their preinjury level at an average of 6.5 months. The authors concluded that osteochondral autologous transplantation was clinically superior to microfracture for the treatment of cartilage lesions in patients under the age of forty years.

Several recent studies have focused on the outcomes of microfracture in high-level athletes. Steadman et al. reviewed the outcomes of twenty-five active National Football League (NFL) players at an average 4.5 years after they underwent microfracture to treat a full-thickness chondral lesion. Nineteen players (76%) returned to football the season following the microfracture. The athletes who returned to football played an average 4.6 seasons (range, one to thirteen seasons) and fifty-six games (range, two to 183 games) after the
procedure. Gobbi et al.\textsuperscript{25} reviewed the results in fifty-three athletes (twenty-six professional and twenty-seven recreational) with a mean age of thirty-eight years and a mean lesion size of 4 cm\textsuperscript{2}. At six years following the microfracture surgery, the International Knee Documentation Committee (IKDC) score\textsuperscript{26} was normal or nearly normal in 70\% of the patients and the Tegner score\textsuperscript{27,28} had increased from 3.2 to 5.0 points. The authors found that an age of less than forty years, lesions of <2 cm\textsuperscript{2}, preoperative symptoms of less than twelve months' duration, and no prior operative intervention were associated with a better return to high-impact sports. Cerynik et al.\textsuperscript{29} reported on changes in efficiency ratings for twenty-four professional basketball players who had undergone microfracture surgery. The mean time until they returned to play was thirty weeks. Twenty-one percent were unable to return to competition. Similarly, Namdari et al. reported the outcomes for twenty-four professional basketball players who had undergone microfracture for the treatment of a chondral lesion of the knee\textsuperscript{30}. Eight of these athletes were unable to return to competition, and those who did return to competition had a significant reduction in the number of points scored (p = 0.008) and minutes played (p = 0.045) postoperatively, although the authors found no difference in performance variables that had been averaged over forty minutes of play.
Proper patient selection and meticulous attention to technical detail are critical to achieving a successful outcome following microfracture. Several studies have documented better outcomes in younger patients. Kreuz et al. compared the results of microfracture in eighty-five consecutive patients and found that patients less than forty years of age had significantly better results than those over forty (p < 0.01). Older patients had evidence of deterioration of the healing cartilage on magnetic resonance imaging as early as eighteen months after the operation. Osseous overgrowth has been found to occur after errant removal of the subchondral bone during the microfracture procedure. Osseous overgrowth is common, occurring in 25% to 49% of patients, and can lead to adverse biological and biomechanical outcomes.

Even with meticulous operative technique and proper patient selection, the results of microfracture appear to deteriorate over time. Mithoefer et al. found that, despite the initial improvement in clinical outcomes, the results deteriorated over time in 47% of elite athletes. Similar results have been found in other studies as well. Thus, although microfracture is a straightforward technique that is commonly employed as a first-line treatment for small cartilage lesions, the results are not as good in older patients and tend to deteriorate over time.

### Adjuvants to Bone Marrow Stimulation

Adjuvants to improve the stability of the clot and the lesion fill with marrow stimulation procedures have been described. Hoemann et al. demonstrated that stabilization of the blood clot through the addition of chitosan, a thrombogenic and adhesive polymer, resulted in improved lesion fill, cellular organization, and biochemical composition of healing tissue compared with those variables after microfracture alone in an ovine model. Growth factors used as biological augments to in vivo cartilage repair have been studied as well. Insulin-like growth factor placed into fibrin clots in an equine chondral defect model improved both the quantity and the quality of cartilage repair tissue and reduced the severity of postoperative inflammation. Platelet-derived growth factor is another potent mitogen for mesenchymal cells, and preliminary studies have demonstrated promising results with respect to its ability to stimulate hyaline cartilage formation and chondrocyte proliferation.

Hyaluronic acid viscosupplementation has also recently been evaluated as an adjunct to microfracture for chondral lesions of the knee. Strauss et al. evaluated the results of microfracture of focal medial femoral condylar defects with and without viscosupplementation in a New Zealand White rabbit model. At three months postoperatively, gross and histological examination of the repair tissue revealed better fill and more hyaline-like tissue compared with controls. In addition, at the final, six-month follow-up evaluation, the knees that had received viscosupplementation were observed to have less degenerative change than controls. However, adjuvants to bone marrow stimulation have not been tested in clinical trials of patients, and therefore their clinical efficacy remains unproven at this time.

### Platelet-Rich Plasma

There has been a remarkable increase in the use of platelet-rich plasma to facilitate healing in a variety of pathological musculoskeletal conditions. The theoretical advantage of this autologous blood product rests in the concentrated platelets and associated quantity of platelet-derived growth factor and other mitogenic factors that may promote the healing of chondral injuries. Sun et al. compared the efficacy of platelet-rich plasma delivered in a poly-lactic-co-glycolic acid (PLGA) scaffold with that of the scaffold alone in a rabbit osteochondral defect model and noted improved bone formation and histological characteristics of the cartilage repair tissue in the platelet-rich plasma-treated specimens. Furthermore, Mishra et al. demonstrated, in a clinical study, that platelet-rich plasma increases mesenchymal stem cell proliferation and chondrogenic differentiation. Akeda et al. similarly demonstrated increased cell proliferation and proteoglycan and collagen production by adult porcine chondrocytes cultured in platelet-rich plasma-augmented media. Despite these encouraging preliminary results, however, no clinical studies have proven the efficacy of platelet-rich plasma injection for focal chondral injuries of the knee, to our knowledge.

### Whole-Tissue Transplantation

#### Autologous Osteochondral Transplantation

Autologous osteochondral mosaicplasty, sometimes referred to as OATS (osteartoicular transfer system), is an effective method for resurfacing osteochondral defects of the knee. The technique involves transplantation of multiple small cylindrical autogenous osteochondral plugs harvested from the less weight-bearing periphery of the articular surface of the femoral condyle and transferred to create a congruent and durable resurfaced area in the defect (Figs. 2-A, 2-B, and 2-C). The procedure offers several advantages over other repair techniques, including transplantation of viable hyaline cartilage, a relatively brief rehabilitation period, and the ability to perform the procedure in a single operation.

The limitations of autologous osteochondral mosaicplasty include donor site morbidity and a limited availability of graft that can be harvested from the patellofemoral joint or the zone adjacent to the intercondylar notch. Other potential limitations include differences in orientation, thickness, and mechanical properties between donor and recipient cartilage as well as graft subsidence at the surface with postoperative weight-bearing. In addition, absence of fill and the potential dead space between cylindrical grafts may limit the quality and integrity of the repair. Lane et al. transplanted autologous osteochondral grafts into the knee joints of goats and found a lack of integration of the cartilage, resulting in the persistence of full-thickness gaps in all specimens. A magnetic resonance imaging analysis in a clinical setting similarly demonstrated a failure of chondral integration, although there was good osseous integration of the subchondral bone.

Donor site healing by natural processes results in filling of the defects with cancellous bone and an overlying fibrocartilage-
like cap. However, larger grafts are associated with greater donor site morbidity. It has been suggested that, when grafts with a diameter of >8 mm are harvested, filling of the defect with biocompatible material may help to prevent morbidity at the donor site. Feczkó et al. evaluated healing of donor site defects treated with hydroxyapatite, carbon fiber, polyglyconate B, compressed collagen, and two versions of polycaprolactones in a canine model. While all of these substitutes demonstrated good integration with the surrounding cancellous bone, only limited repair-tissue formation was evident even at thirty weeks postoperatively. Compressed collagen, however, yielded the most favorable fibrocartilage covering as seen on second-look arthroscopy and histological evaluation.

The effect of surface plug incongruity on articular surface contact pressures has been evaluated. Koh et al. assessed contact pressures with controlled axial loads on swine knees with variable plug positions. The study demonstrated that flush or slightly sunk grafts could restore contact pressures to nearly normal levels, but that elevated angled grafts adversely increased contact pressures. The authors also demonstrated that grafts seated 0.5 to 1 mm proud relative to the adjacent surface resulted in a 50% increase in mean contact pressures.

The biomechanical stability of the plug after autologous osteochondral transplantation is important and is affected by several technical factors. In experimental models, osseous in-
Integration of the graft and recipient has been observed at four weeks. Prior to this healing, the press-fit mechanism is critical for maintaining a stable graft position. Plugs of a matched depth (i.e., with the donor plug length and recipient defect length matched) are more stable than short plugs (i.e., with a cavity left at the bottom of the defect), which rely exclusively on circumferential frictional forces for stability. This stability of short plugs is further compromised in multiple plug configurations in which gaps between the round plugs and surrounding bone reduce frictional forces.

The effect of impact loading of the hyaline cartilage during delivery of the osteochondral plug has been evaluated. Chondrocyte viability is critical, as each cell maintains a discrete maximum volume of robust matrix around it. Whiteside et al. demonstrated that the percentage of chondrocyte death was predicted more strongly by the mean force of impact than by the number of impacts required during placement of the graft. Huntley et al. identified a marked marginal zone of cell death with a thickness of ~400 μm at the plug periphery within two hours after harvesting. Using a planar model for mosaicplasty, they demonstrated that approximately one-third of the mosaicplasty surface was nonviable (secondary to the 24% rate of marginal zone cell death and 9% rate of interposed dead space between grafts). Gulotta et al. recently corroborated these findings of chondrocyte necrosis, apoptosis, and matrix degradation after press-fit osteochondral autograft implantation in a rabbit model.

**Outcomes (See Appendix)**

The outcomes of autologous mosaicplasty for symptomatic chondral defects have been encouraging, and the procedure has been used with success. Hangody and Füles evaluated the largest series of mosaicplasties (831) performed for localized Outerbridge grade-III or IV chondral lesions and reported good-to-excellent results for 92% of femoral lesions, 87% of tibial lesions, and 79% of patellofemoral lesions. The rate of donor site morbidity, as assessed with the Bandi score, was 3%. Eighty percent of the second-look arthroscopic procedures performed in eighty-five patients demonstrated congruent gliding surfaces and histological evidence of transplanted hyaline cartilage. Oztürk et al. reported on the clinical and radiographic outcomes of nineteen patients with a grade-IV chondral lesion treated with mosaicplasty. The mean Lysholm score improved from 46 points preoperatively to 88 points postoperatively, with an 85% rate of good-to-excellent results after a mean duration of follow-up of thirty-two months. Magnetic resonance imaging revealed excellent fill and congruency of <1 mm without fissuring or delamination in 84% of the cases.

Authors of recent studies have also reported on the successful use of autologous osteochondral grafts for the stabilization and healing of unstable osteochondritis dissecans lesions. Twenty patients were assessed arthroscopically, and the lesions were fixed in situ with use of multiple 4.5-mm osteochondral dowel grafts. All knees were scored as clinically normal by eighteen months, and serial magnetic resonance images demonstrated healing of the osseous lesion in all cases by six months and with a continuous articular cartilage surface by nine months.

The use of autologous osteochondral transplantation for the treatment of symptomatic, isolated patellar chondral lesions has recently been evaluated. Nho et al. retrospectively evaluated twenty-two patients (mean age, thirty years) followed for a mean of twenty-five months after plug transplantation. Nine patients underwent a concomitant distal patellar realignment procedure for the treatment of associated instability. The mean defect size was 1.66 cm², and the mean donor plug size was 9.7 mm in diameter. An average of 1.8 plugs were placed in each defect. The mean IKDC score improved from 47.2 points preoperatively to 74.4 points postoperatively. Magnetic resonance imaging performed at the time of final follow-up revealed nearly complete or complete fill in all plugs, with 71% being completely incorporated and flush with the adjacent hyaline cartilage.

The efficacy of mosaicplasty has been compared with that of autologous chondrocyte implantation in some series. Two randomized, prospective studies comparing mosaicplasty with autologous chondrocyte implantation demonstrated a 90% rate of good-to-excellent results in the autologous osteochondral transplantation group and more rapid improvement with osteochondral autologous transplantation than with autologous chondrocyte implantation. A small randomized controlled trial of forty-seven patients assigned to receive autologous chondrocyte implantation or mosaicplasty after an initial arthroscopic assessment and débridement of a focal chondral lesion was performed by Dozin et al. The study, which had limited power, demonstrated clinically equivalent outcomes in the two groups. Interestingly, one-third of the patients had spontaneous improvement after débridement alone, raising some concern regarding the efficacy of either intervention.

**Osteochondral Allograft Transplantation**

Osteochondral allograft transplantation is a cartilage resurfacing procedure that involves transplantation of a cadaver graft consisting of intact, viable articular cartilage and its underlying subchondral bone into the defect. The size, depth, and location of the defect are all critical factors in the tailoring of the donor graft. Advantages to the use of osteochondral allografts include the ability to achieve precise surface architecture, immediate transplantation of viable hyaline cartilage as a single-stage procedure, the potential to replace large defects or even hemicondyles, and no donor site morbidity. Use of a large dowel osteochondral transplant in this capacity (Figs. 3-A and 3-B) eliminates the dead space that is encountered between the smaller cylindrical grafts that are used with autologous mosaicplasty. Limitations of osteochondral allografting include limited graft availability, high cost, risk of immunological rejection, possible incomplete graft incorporation, potential for disease transmission, and the technically demanding aspects of machining and sizing of the allograft.
Fresh Allografts

Fresh osteochondral allografts are typically utilized, as freezing and cryopreservation have both been shown to decrease chondrocyte viability. Although the critical threshold of viable chondrocytes necessary to achieve clinical success remains unknown, chondrocyte function is critical to maintain the dynamic homeostasis of the extracellular matrix and is an important factor in ensuring long-term allograft survival in vivo. Traditionally, grafts have been harvested, stored in lactated Ringer solution at 4°C, and transplanted within one week. Recently, there has been a shift toward allograft storage in culture medium. At fourteen days, specimens stored in lactated Ringer solution demonstrated an 80% rate of chondrocyte viability compared with a 91% rate for those stored in culture medium. This is particularly important in the setting of modern tissue-banking procedures for microbiological screening and recipient matching, which have necessitated prolonged periods of storage prior to implantation.
The matrix properties and chondrocyte viability of stored fresh osteochondral allografts have been evaluated. Allen et al. demonstrated preserved biomechanical and matrix characteristics but decreased chondrocyte density and metabolic activity in specimens stored for twenty-one days before implantation. The superficial zone of cartilage was most severely affected. Pearsall et al. studied sixteen refrigerated allografts and reported progressively less matrix staining with prolonged refrigeration and a mean chondrocyte viability at one year in cryopreserved osteochondral specimens. Although the biomechanical properties and matrix integrity of hyaline cartilage are preserved for up to twenty-eight days, the number of viable chondrocytes has been shown to decrease progressively over that time. Nonetheless, the rate of chondrocyte viability was approximately 50% at sixty days, which may represent a potentially longer window for successful implantation.

A number of studies have confirmed the long-term survival of donor chondrocytes after transplantation. Hyaline cartilage is a relatively immunoprivileged tissue with an avascular matrix that shields donor chondrocytes from the host immune reaction. Williams et al. reported on twenty-six retrieved osteochondral allograft specimens after an average survival time of forty-two months. The rate of chondrocyte viability was 82%, and there was evidence of allograft bone incorporation in most specimens. The allograft bone is necrotic and is replaced by creeping substitution, but it provides a structural scaffold to support the articular surface during this gradual incorporation.

**Cryopreserved Allografts**

Cryopreservation involves rate-controlled freezing of specimens in a nutrient-rich, cryoprotectant medium (glycerol or dimethyl sulfoxide) to minimize cellular freezing and maintain cell viability. Recently, Gole et al. found a 77% rate of chondrocyte viability at one year in cryopreserved osteochondral allografts implanted into load-bearing sites in an animal model. However, another study demonstrated degenerative changes at the articular surface of cryopreserved allografts compared with fresh allografts at five years. A study of an ovine model by Schachar et al. demonstrated that membrane integrity of the allograft chondrocytes immediately following cryopreservation is the most reliable predictor of the long-term outcome of the graft. Use of cryopreserved allografts achieved an overall intermediate result compared with the results associated with the use of fresh autografts (the positive controls in the study).

**Fresh-Frozen Allografts**

Fresh-frozen preservation of allografts offers the advantages of reduced immunogenicity and decreased disease transmission at the expense of reduced chondrocyte viability. The process of deep freezing to \(-80^\circ\)C destroys the viability of all articular cartilage cells within the graft, and retrieval studies have demonstrated deterioration of cells and matrix over time.

**Outcomes (See Appendix)**

A number of retrospective studies have been performed to assess the outcomes of osteochondral allograft transplantation for the treatment of focal osteochondral defects of the knee, and they have demonstrated good-to-excellent results. Chu et al. reported on fifty-five knees at a mean of six years after transplantation of fresh osteochondral allografts. Eighty-four percent of the knees treated for an isolated focal defect were rated as having a good-to-excellent outcome with use of the Merle d’Aubigné and Postel scale, while similar success was achieved in only 50% of the knees that had undergone transplantation for the treatment of bipolar lesions (i.e., articular chondral defects on both the tibial and the femoral side). Ghazavi et al. reported the results at a mean of 7.5 years following 126 procedures for the transplantation of fresh osteochondral allografts for the treatment of posttraumatic condylar defects. While a good-to-excellent result was achieved in 85% of the knees, an increased rate of failure was seen in the setting of bipolar lesions and limb malalignment and in patients insured by Workers’ Compensation. Bugbee and Convery reported the outcomes at a mean of fifty months after the use of fresh osteochondral allografts in ninety-seven knees. An 86% success rate was achieved in the treatment of large unipolar defects (mean size, 8 cm²), whereas only a 54% success rate was seen after the management of bipolar lesions. Other factors contributing to failure in this series included diffuse arthritis, inflammatory conditions, and lower-extremity malalignment. Davidson et al. reported on sixty-seven patients who had received an osteochondral allograft for the treatment of a symptomatic femoral chondral lesion. At a mean of forty months postoperatively, significant improvements in both the IKDC and the SF-36 scores, as compared with the preoperative scores, were noted (p = 0.002). So-called second-look arthroscopy was performed in ten knees and revealed repair tissue that was grossly similar to native cartilage with a persistence of a small seam surrounding the cylindrical grafts. Chondrocyte viability and density in the repair tissue did not differ from those of native (control) cartilage retrieved with biopsy. Overall, these studies indicate that, while allograft transplantation is largely successful when done for appropriate indications, outcomes are less reliable and predictable in the settings of primary osteoarthritis, inflammatory arthropathy, limb malalignment, and bipolar lesions of the knee.

Favorable results have been reported after allograft transplantation for the treatment of osteochondritis dissecans lesions of the knee. In a study of sixty-three knees followed for a mean of 4.3 years, Bugbee et al. reported an 89% rate of good-to-excellent functional outcomes as rated with the modified Merle d’Aubigné and Postel scale. Emmerson et al. reported the outcomes at a mean of 7.7 years after osteochondral allograft transplantation for osteochondritis dissecans lesions. The mean allograft size was 7.5 cm², and either a dowel or shell technique was utilized on the basis of the lesion location and the surgeon’s preference. The authors reported a 72% rate of good-to-excellent outcomes as rated with the Merle d’Aubigné and Postel scale. The preliminary results of osteochondral al-
lograft transplantation for treatment of condylar osteonecrosis have also been encouraging. Görtz and Bugbee found that 88% of forty-three patients treated with allograft transplantation for osteonecrosis were satisfied with the result, and 82% thought that the condition of the knee was improved\(^8\). At a mean of 4.5 years, none of the patients had required conversion to a total knee arthroplasty.

The use of osteochondral allografts for the management of patellofemoral chondral lesions has yielded variable results. Chu et al. reported a good-to-excellent outcome in five patients at a mean of six years after they had undergone transplantation of a fresh osteochondral allograft into an isolated patellar defect\(^9\). Jamali et al., however, reported only a 60% rate of good-to-excellent results at a mean of 7.8 years after transplantation of a fresh osteochondral allograft into the patellofemoral joint of twenty knees\(^8\). Five knees in that series subsequently required salvage with revision allograft transplantation, patellectomy, arthrodesis, or total knee replacement.

Extended storage time for allografts enhances the effective use of these tissues by allowing improved identification of suitable recipients and more feasible scheduling of operative treatments. Williams et al. demonstrated no correlation between functional outcome scores and graft storage times of up to forty-two days\(^8\). Eighteen of nineteen patients demonstrated a normal appearance of the articular cartilage on magnetic resonance imaging at a mean of twenty-five months (Fig. 3-C). A similar study corroborated these results as it demonstrated no correlation between the duration of storage of fresh grafts before implantation and the cellular viability or density at a mean of forty months postoperatively\(^4\). McCulloch et al. reported that 84% of twenty-five patients were satisfied two years following allograft transplantation with use of a “prolonged fresh” graft that had been stored for a mean of twenty-four days (range, fifteen to forty-three days)\(^9\). LaPrade et al. reported on twenty consecutive patients who had undergone treatment of a focal chondral defect of the femoral condyle with a refrigerated osteochondral allograft stored for a mean of 20.3 days (range, fifteen to twenty-eight days)\(^6\). The mean IKDC score improved from 52 points at baseline to 68.5 points at the time of final follow-up (at three years), with good incorporation and a stable position in the host bone in twenty-two of the twenty-three cases.

Osteochondral allograft transplantation has also been investigated in survivorship studies. Gross et al. reported survival rates of 95% at five years, 85% at ten years, and 73% at fifteen years after osteochondral allograft transplantation for posttraumatic femoral condylar lesions\(^2\). Sixty-eight percent of the patients in their series had concomitant limb-realignment procedures, and they were not found to have any differences in outcomes or complications as compared with the patients who did not have such procedures. Histological characteristics favoring long-term survival included viable chondrocytes, functional preservation of the matrix, and complete replacement of the graft with host bone. The authors concluded that a high density of viable chondrocytes and mechanical stability of the allograft are crucial for long-term survival. In a series of ninety-two knees that underwent fresh allograft transplantation, Beaver et al. found survival rates of 75% at five years, 64% at ten years, and 63% at fourteen years\(^2\). Failure rates were higher in patients older than sixty years of age or in those with bipolar lesions.

**Autologous Chondrocyte Implantation**

Autologous chondrocyte implantation, originally described in 1994\(^9\), is an innovative, novel technique to restore cartilage cells into full-thickness chondral defects. The primary theoretical advantage of autologous chondrocyte implantation is the development of hyaline-like cartilage rather than fibrocartilage in the defect, presumably leading to better long-term outcomes and longevity of the healing tissue. However, the procedure is not without limitations. It involves a minimum of two operations, one for tissue harvest and the other for cell implantation. Furthermore, autologous chondrocyte implantation is technically demanding, and complications related to the periosteal graft have been reported\(^3\).\(^4\).

**Outcomes (See Appendix)**

The initial outcomes of autologous chondrocyte implantation were reported by Brittberg et al.\(^3\), in a study of twenty-three patients ranging in age from fourteen to forty-eight years and with lesions ranging in size from 1.6 to 6.5 cm\(^2\). The average duration of follow-up was forty-four months. Biopsies showed that eleven of fifteen femoral transplants and one of seven patellar transplants had the appearance of hyaline cartilage. Fourteen of the sixteen patients with a femoral condylar lesion had a good-to-excellent result. Zaslav et al. recently performed a prospective clinical study to determine the effectiveness of autologous chondrocyte implantation in patients with failed prior treatments for articular cartilage defects of the knee\(^6\). One hundred and twenty-six patients were followed for a mean of four years in this multicenter study. At the time of follow-up, 76% of the patients were deemed to have a good clinical result based on knee pain, quality of life, and overall health. The results did not differ if the patient had had a prior marrow stimulation procedure or débridement. The authors concluded that autologous chondrocyte implantation was effective in providing pain relief as well as an improved quality of life for patients who had undergone a previous operative procedure for the defect.

Many studies have compared autologous chondrocyte implantation with other cartilage restoration techniques. Anderson et al. compared autologous chondrocyte implantation with microfracture in a prospective study\(^7\). There were twenty-three patients in each group, and all lesions were \( > 2 \) cm\(^2\). There was a mean improvement in the overall condition score in both groups (1.3 points in the microfracture group and 3.1 points in the autologous chondrocyte implantation group, \( p < 0.05 \)). It should be noted, however, that the outcomes of microfracture reported in that series were considerably inferior to those reported by other authors\(^9\). Bentley et al. performed a prospective, randomized study comparing autologous chondrocyte implantation with mosaicplasty, with fifty patients in
each treatment group\textsuperscript{99}. The patients were young (average age, thirty-one years), and the lesion were an average of 4.7 cm\textsuperscript{2}. At an average of nineteen months postoperatively, 88\% of the patients treated with autologous chondrocyte implantation and 69\% of those treated with mosaicplasty had a good-to-excellent clinical result. Arthroscopy at one year demonstrated a good-to-excellent repair in 82\% of the patients after autologous chondrocyte implantation and in 34\% after mosaicplasty. The authors concluded that autologous chondrocyte implantation was better than mosaicplasty in terms of both clinical and biological outcomes.

Autologous chondrocyte implantation is not without limitations. Many patients are unwilling to undergo two procedures and the long recovery time that is necessary in order to allow the chondrocytes to mature. There is also a risk of donor site morbidity at the periosteal harvest site. Wood et al. reviewed the adverse outcomes of autologous chondrocyte implantation reported to the U.S. Food and Drug Administration from 1996 to 2003\textsuperscript{100}. During this time, there were 7500 lots of Carticel (Genzyme Tissue Repair, Cambridge, Massachusetts) distributed to physicians and 294 adverse-event reports. More than one adverse event was reported for 135 (46\%) of the 294 patients. The most common adverse event was graft failure, accounting for 24.8\% of all adverse events. Delamination accounted for 22.1\% of the adverse events, and tissue hypertrophy accounted for 17.7\%. Of the 294 patients who had an adverse event, 273 (93\%) required a total of 389 surgical revisions subsequent to implantation. Almost 25\% of the revisions were periarticular procedures such as lysis of adhesions, lateral release, or synovectomy. Eight patients underwent a total knee replacement. Furthermore, Peterson et al. reported fifty-two adverse events, including twenty-six instances of periosteal hypertrophy and seven graft failures, in 101 patients\textsuperscript{101}. Thus, although the overall complication rate appears to be relatively low, the adverse events that do occur following autologous chondrocyte implantation can be substantial and often result in subsequent operative intervention.

Cell-Based and Scaffold Treatment

Although cell-based therapies for inducing cartilage regeneration, such as autologous chondrocyte implantation, have demonstrated progress, the results have not been highly predictable or reproducible. In addition, limitations have included a requirement for a two-stage procedure and a technically demanding operation that fails to provide structural support for cells during the postoperative healing and incorporation phase.

So-called second-generation techniques in which harvested autologous chondrocytes are delivered on absorbable scaffolds that support the cells during the preimplantation culturing and postoperative healing phases have evolved. Essential properties of these scaffolds include biocompatibility and biodegradability through safe biomechanical pathways at suitable time intervals. In the matrix-associated chondrocyte implantation procedure, chondrocytes are incorporated into a porcine type-I/III collagen membrane. One surface has a relatively higher density of collagen fibers that creates a smooth low-friction surface, while the other has a rough appearance because of larger interstices between the collagen fibers to allow for seeding of chondrocytes. Hyaluronan-based scaffolds deliver the autologous chondrocytes in a scaffold of hyaluronan derivatives. Advantages of these procedures over autologous chondrocyte implantation include a more even cell distribution, avoidance of periosteal harvest and implantation, and increased technical ease without the need for suturing to adjacent articular cartilage.

Matrix-Associated Chondrocyte Implantation

Although chondrocytes are harvested in a fashion identical to that used for the autologous chondrocyte implantation procedure, matrix-associated chondrocyte implantation minimizes donor site morbidity by avoiding the harvest and implantation of a periosteal flap and prevents dedifferentiation of chondrocytes during the culturing process. In addition, matrix-associated chondrocyte implantation makes an arthroscopic implantation technique feasible for accessible lesions. In a multicenter study\textsuperscript{102} of the clinical outcomes after autologous chondrocyte implantation, 26\% of the procedure-related complications were associated with the open arthroscopy. Furthermore, periosteal hypertrophy occurs between three and seven months after surgery in 10\% to 25\% of cases and often requires revision surgery\textsuperscript{103,104}. Some authors have reported a substantial risk of arthrofibrosis as well\textsuperscript{104}. Marlows et al. demonstrated the efficacy of suture-free fixation of the cell-scaffold matrix-associated chondrocyte implantation construct with the use of fibrin glue only\textsuperscript{105}. In a pilot study of sixteen patients who had undergone matrix-associated chondrocyte implantation to treat a weight-bearing chondral defect of the femoral condyle, high-resolution magnetic resonance imaging was used to grade the quality of the attachment of the implant at a mean of thirty-five days postoperatively. A completely attached graft was observed in 88\% of the patients.

Jones et al. utilized an ovine model of articular cartilage injury repair to assess the efficacy of the matrix-associated chondrocyte implantation procedure\textsuperscript{106}. Six-millimeter defects were created on the trochlea and medial femoral condyle of twenty-one sheep that were randomized to treatment with matrix-associated chondrocyte implantation or unseeded, porcine-derived type-I/III collagen membrane alone. Arthroscopic assessment with ICRS scores\textsuperscript{107} at ten weeks postoperatively revealed superior fill, integration, and appearance of the matrix-associated chondrocyte implantation-treated trochlear and condylar lesions compared with the controls. Magnetic resonance imaging demonstrated that the results of matrix-associated chondrocyte implantation were superior to those in both the untreated control and the scaffold-only group at all time points. Overall, unseeded scaffolds were characterized by immature cartilage with poor architectural restoration and demonstrated no treatment effect compared with unfilled control lesions. Matrix-associated chondrocyte implantation demonstrated an improved treatment effect across time points in comparison with the use of a collagen scaffold only and...
unfilled controls for all parameters of assessment except histological findings\(^\text{108,109}\).

**Outcomes**

Zheng et al. examined the phenotype of chondrocytes seeded on a type-I/III collagen scaffold and performed progressive histological analyses of matrix-associated chondrocyte implants in a cohort of fifty-six patients over a period of six months postoperatively\(^\text{110}\). Chondrocytes in the delivery scaffold appeared spherical and appropriately integrated into the matrix, expressing aggregan, type-II collagen, and S-100. Histological analysis of biopsy specimens revealed 75% hyaline-like cartilage regeneration after six months. Behrens et al. reported on thirty-four patients with a localized cartilage defect who were treated with matrix-associated chondrocyte implantation\(^\text{111}\). The mean follow-up period was 34.5 months, and the mean lesion size was 4.1 cm\(^2\). The Meyer, Lysholm-Gillquist, and ICRS scores\(^\text{27,28,107}\) were all substantially improved in eleven patients at five years postoperatively.

In a similar study, Trattnig et al. serially monitored repair after matrix-associated autologous chondrocyte implantation in twenty patients using noninvasive cartilage-specific magnetic resonance imaging\(^\text{112}\). In ten of these patients, incomplete defect filling progressed to complete defect filling (six patients) or less incomplete defect filling (four patients). The signal intensity of the matrix-associated chondrocyte implants was the same as that of native cartilage in thirteen patients, and complete integration was achieved in ten cases.

Bartlett et al. presented the outcomes of a matrix-associated chondrocyte implantation “sandwich” technique for treatment of symptomatic chondral defects with a depth of >8 mm in five patients\(^\text{113}\). With this technique, two membranes are templated and cut to the size of the defect. The first membrane is secured with fibrin glue to the base of the prepared defect with its rough cell-loaded surface facing up. The second membrane is implanted on top of the first one with the cell surface down and is sealed with fibrin glue to the adjacent cartilage. Within six months after the surgery, all five patients had improved Cincinnati knee, Stanmore functional rating, and visual analogue pain scores\(^\text{27,28}\). Four patients had arthroscopy at one year postoperatively, and stable reparative tissue (ICRS grade II in two knees and grade III in two) was seen.

**Hyaluronan-Based Scaffolds**

Hyaluronan-based scaffolds are another approach to cartilage repair that employs a biodegradable, three-dimensional scat-

---

**Fig. 4**

A: To create tissue-engineered collagen scaffolds, harvested autologous chondrocytes are cultured in an acellular honeycomb collagen matrix for six weeks with mechanical loads applied to stimulate matrix production and mature organization. B: An arthroscopic photograph made three months after implantation of a tissue-engineered collagen scaffold (outlined by red dots) seeded with autologous chondrocytes for treatment of a focal femoral condyle chondral defect. Note the excellent incorporation, fill, and congruous margin with the adjacent native cartilage. C: Sagittal fast spin-echo magnetic resonance image of a focal medial femoral chondral defect (left) and T2-mapping sagittal images, made at one year (middle) and two years (right) postoperatively, demonstrating progressive maturation and stratification of repair tissue to approach the appearance of native articular cartilage (Images courtesy of Dr. Dennis Crawford, MD, Portland, Oregon).
fold for cell proliferation. A benzylic ester of hyaluronic acid is used to generate a scaffold with variably sized interstices between 20-μm-thick fibers. In addition to providing the structural support for cell contact and matrix deposition, the three-dimensional nonwoven scaffold prevents dedifferentiation of harvested autologous chondrocytes even after long periods of ex vivo culture expansion and promotes the expression of chondrocyte-specific markers. Gradual degradation occurs as the cells start secreting their own extracellular matrix to allow for an optimal transition between newly formed and existing tissue.

Outcomes
The results of implantation of hyaluronan-based scaffolds seeded with autologous chondrocytes to treat chondral defects have been encouraging. Histological analysis has shown hyaline-like cartilage in the lesion as soon as twelve months after implantation. Marcacci et al. reported the clinical outcomes in a prospective series of seventy patients with a hyaluronan-based scaffold in a lesion as soon as twelve months after implantation. Ninety-two percent of the patients had improvement in the IKDC score, and 96% had the involved knee rated as normal or nearly normal by the treating surgeon. Kon et al. compared the clinical outcomes, after five years of follow-up, of treatment with a cell-seeded hyaluronan-based scaffold and treatment with a microfracture repair technique in patients with a grade-III or IV chondral defect. Both groups showed significant improvement in IKDC scores, but better improvement in the IKDC objective and subjective scores was observed in the hyaluronan-based-scaffold group. The return to sports at two years was similar in the two groups; however, it remained stable after five years in the hyaluronan-based-scaffold group but not in the microfracture group.

Tissue-Engineered Collagen Matrices Seeded with Autologous Chondrocytes
Tissue-engineered collagen matrices seeded with autologous chondrocytes provide a promising new technology with which to address chondral lesions of the knee. This procedure involves harvesting of the autologous chondrocytes from non-weight-bearing aspects of the knee in a manner analogous to conventional autologous chondrocyte implantation. The cells are then loaded onto a type-I bovine collagen honeycomb matrix and are cultured ex vivo (Fig. 4). In distinction to second-generation techniques, however, the cell-scaffold construct is subsequently subjected to mechanical stimulation with use of a proprietary bioreactor that applies hydrostatic pressure to the chondrocytes for a minimum of seven days. A lack of mechanical stimulation may be responsible for chondrocyte dedifferentiation and inferior mechanical properties, and the application of mechanical load stimulates chondrocytes to produce increased amounts of type-II collagen, aggrecan, and other critical components of a hyaline extracellular matrix.

Use of tissue-engineered scaffolds with autologous chondrocytes requires a staged procedure that begins with an arthroscopic biopsy for chondrocyte harvest, which is followed by an arthrotomy for implantation. The harvested chondrocytes are cultured in the acellular honeycomb collagen matrix for six weeks. A mini-arthrotomy is then performed to provide direct access to the chondral lesion. The lesion is debrided to create stable vertical edges, and meticulous hemostasis is obtained. A template of the dimensions of the chondral defect is then obtained, typically with use of a malleable device that delineates its vertical margins. The collagen membrane is meticulously cut to match the shape of the lesion, but with approximately 10% greater dimensions in anticipation of slight shrinkage after implantation and fixation. The implant is fixed with use of a proprietary collagen bioadhesive, which is applied to the base of the defect and evenly coated over the implant and its seam to the adjacent native cartilage.

Outcomes
Given the relatively recent development of this technology, reports on the clinical outcomes associated with tissue-engineered collagen matrices seeded with autologous chondro...
drocytes are very limited. However, Crawford et al. recently reported the results of a phase-I clinical trial of eight patients with twenty-four months of follow-up. Outcomes were assessed with use of a visual analogue pain scale and the IKDC subjective score. Serial evaluations were performed at six, twelve, and twenty-four months. As a secondary outcome, cartilage repair quality was evaluated with magnetic resonance imaging at three, twelve, and twenty-four months (Fig. 4, C). No serious adverse events were identified. By twelve months, all patients had decreased pain scores (mean, 0.9 ± 1.5 points) compared with the baseline scores (mean, 3.3 ± 2.8 points). At twenty-four months, the pain scores remained significantly lower than the baseline scores, and the IKDC score had increased in seven of the eight patients, to a mean of 76 ± 17 points from a mean of 57 ± 25 points at baseline. Magnetic resonance imaging showed that seven of the eight patients had nearly complete or complete filling of the defect at one year, and six of the eight retained good filling at two years. Magnetic resonance imaging was performed to assess the collagen matrix content and organization. At twenty-four months, four of the eight patients had stratification of T2 values similar to that of the adjacent hyaline cartilage. These promising results prompted a prospective, randomized phase-II trial of thirty patients to compare this technique with microfracture; this trial is currently in progress.

Overview
In conclusion, the management of articular cartilage lesions of the knee is a challenging problem for orthopaedic surgeons. While a number of surgical approaches have been described, it remains difficult to compare the efficacy of these techniques because of a paucity of well-designed randomized controlled trials in the literature (Table I). The current evidence, based primarily on large case series, suggests that bone marrow stimulation procedures and whole-tissue transplantation of allografts or autografts can achieve favorable outcomes when used for the management of focal chondral defects of the knee. Cell-based techniques performed with or without a scaffold have demonstrated early promise in animal and basic-science models, but additional human trials must be completed in order to validate their efficacy in achieving successful clinical outcomes.

Appendix
Tables summarizing studies in the literature about the various techniques described in this review are available with the electronic version of this article on our web site at jbjs.org (go to the article citation and click on “Supporting Data”).

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marrow stimulation procedures</td>
<td>B</td>
</tr>
<tr>
<td>Adjuncts to marrow stimulation</td>
<td>I</td>
</tr>
<tr>
<td>Platelet-rich plasma</td>
<td>I</td>
</tr>
<tr>
<td>Autologous osteochondral transplantation</td>
<td>B</td>
</tr>
<tr>
<td>Osteochondral allograft transplantation</td>
<td>B</td>
</tr>
<tr>
<td>Autologous chondrocyte implantation</td>
<td>C</td>
</tr>
<tr>
<td>Hyaluronan-based scaffolds seeded with autologous chondrocytes</td>
<td>I</td>
</tr>
<tr>
<td>Tissue-engineered collagen matrices seeded with autologous chondrocytes</td>
<td>I</td>
</tr>
</tbody>
</table>

*A = good evidence (Level-I studies with consistent findings) for or against recommending intervention, B = fair evidence (Level-II or III studies with consistent findings) for or against recommending intervention, C = poor-quality evidence (Level-IV or V studies with consistent findings) for or against recommending intervention, and I = there is insufficient or conflicting evidence not allowing a recommendation for or against intervention.

Management of Articular Cartilage Defects of the Knee

References


76. Bugbee W, Emmerson BC, Jamali AA. Fresh osteochondral allografting in the treatment of osteochondritis dissecans of the femoral condyle. Read at the 70th Annual Meeting of the American Academy of Orthopaedic Surgeons; 2003 Feb 5-9; New Orleans, LA.


88. Anderson AF, Fu F, Mandelbaum B. A controlled study of autologous chondrocyte implantation vs microfracture for articular cartilage lesions of the femur. Read at the 69th Annual Meeting of the American Academy of Orthopaedic Surgeons; 2002 Feb 13-17; Dallas, TX.


121. Torzilli PA, Bhargava M, Park S, Chen CT. Mechanical load inhibits IL-1 induced matrix degradation in articular cartilage. Osteoarthritis Cartilage. 2009 Sep 1 [Epub ahead of print].


