
# Selected Instructional Course Lectures

## The American Academy of Orthopaedic Surgeons

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# AUTOLOGOUS CHONDROCYTE IMPLANTATION

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Injuries to joint surfaces can result from acute high-impact or repetitive shear and torsional loads to the superficial zone of the articular cartilage architecture. Direct arthroscopic visualization has suggested that the prevalence of isolated, focal articular cartilage defects is approximately 5%[1,2]. In a retrospective review of more than 31,000 arthroscopic procedures, Curl et al. found a 63% prevalence of chondral lesions with an average of 2.7 lesions per knee[1]. Older patients had more lesions. Curl et al. found grade-IV lesions (according to a modification of the Outerbridge classification system[3]) in 20% of the patients, but only 5% of the individuals who had such a lesion were less than forty years old. Three out of four of the patients had a solitary lesion. A prospective study demonstrated chondral or osteochondral lesions in 61% of the patients, whereas focal defects were found in 19%[2]; these percentages are similar to those found in the retrospective analysis[1]. In the prospective assessment, the mean defect size was 2.1 $cm^2$. A single, well-defined International Cartilage Repair Society (ICRS) grade-III or IV defect[4] (at least 1 $cm^2$) accounted for 5.3%, 6.1%, and 7.1% of the arthroscopic procedures in patients younger than forty, forty-five, and fifty years old, respectively[2]. The prevalence of articular lesions secondary to work-related and sports activities has been reported to be as high as 22% to 50% in other studies[5,6]. Such injuries alone or in combination with ligamentous instability, meniscal lesions, or mechanical malalignment can be debilitating.

Articular cartilage is an avascular, aneural tissue that has limited repair capabilities compared with other mesenchymal tissues. Chondrocytes also have limited migratory ability and, as a result, the surrounding normal cartilage cells do not fill the defect. Chondrocytes have a transient but insufficient response to injury[7]. They increase their mitotic activity as well as their production of glycosaminoglycan and collagen but only for a short period of time and to a limited degree. Normal articular cartilage has only a few cells, which exist in isolated cell lacunae within the extracellular matrix, further decreasing the healing potential of articular cartilage. These factors in combination with the continued use of the extremity by the individual, producing repetitive compressive and shear forces, create an extremely poor environment for spontaneous repair.

When the injury extends through the subchondral bone and causes bleeding, multipotential mesenchymal stem cells are allowed to fill the articular cartilage defect. Fibrocartilage is produced, but this tissue lacks the biomechanical properties required to protect the underlying subchondral bone, especially in a high-demand patient[8,9]. When the defect is large, the normal articular cartilage no longer protects the subchondral bone at the base of the lesion from direct injury (Fig. 1). Exposure of the subchondral bone to repetitive axial and shear forces leads to progressive pain and disability, especially in a high-demand patient.

Several techniques have been used to improve the repair potential of articular cartilage by implanting other cell or tissue phenotypes that have chondrogenic potential[10-14]. Grande et al. reported the successful repair of full-thickness cartilage defects following implantation of cultured articular chondrocytes in a rabbit model[15]. On the basis of these promising results, the technique was

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- **"Technical Aspects of Osteochondral Autograft Transplantation," by Anthony Miniaci, MD, FRCSC, and Paul A. Martineau, MD, FRCSC**

first used on humans in 1987 and was termed *autologous chondrocyte transplantation.* In the United States and most of Europe, implantation has been substituted for transplantation and the procedure is called *autologous chondrocyte implantation*.

## Indications

Autologous chondrocyte implantation is ideally suited for symptomatic ICRS grade-III and IV lesions along the femoral condyle or trochlear regions[16,17]. High-demand patients between fifteen and fifty-five years of age with excellent motivation and potential for compliance are the best candidates. Studies[18,19] have shown a mosaicplasty or microfracture to be an acceptable initial procedure for a lesion of <2 $cm^2$. However, autologous chondrocyte implantation is a viable option for a symptomatic patient with a lesion of >2 $cm^2$ but ≤12 $cm^2$ and for a patient who continues to have pain after a mosaicplasty or microfracture procedure. Bone involvement is not a contraindication, but staged or concomitant autologous bone-grafting should be undertaken when the bone involvement is deeper than 6 to 8 mm[20].

Although the senior one of us (L.P.) has had experience, and some success, with autologous chondrocyte implantation in some high-demand patients with reciprocal or "kissing" lesions, such lesions are currently considered a contraindication for the technique[21,22]. Surgeons are increasingly using autologous chondrocyte implantation to repair patellar lesions. While the initial results were not as successful in this region, the concomitant use of tibial tubercle osteotomy and anteromedialization has improved patient outcomes[23,24].

## Preoperative Assessment

To identify appropriate candidates for autologous chondrocyte implantation, all factors that could compromise successful healing of the implant should be recognized and corrected in a staged or concomitant manner. Key factors to consider while evaluating patients are physiologic age, desired postoperative activity level, etiology, potential for postoperative compliance, and social factors that can delay treatment and complicate postoperative physical therapy regimens such as strenuous postoperative work conditions and limitation of the time that the patient will be allowed off from work.

Physical examination should focus on gait status, knee alignment, and

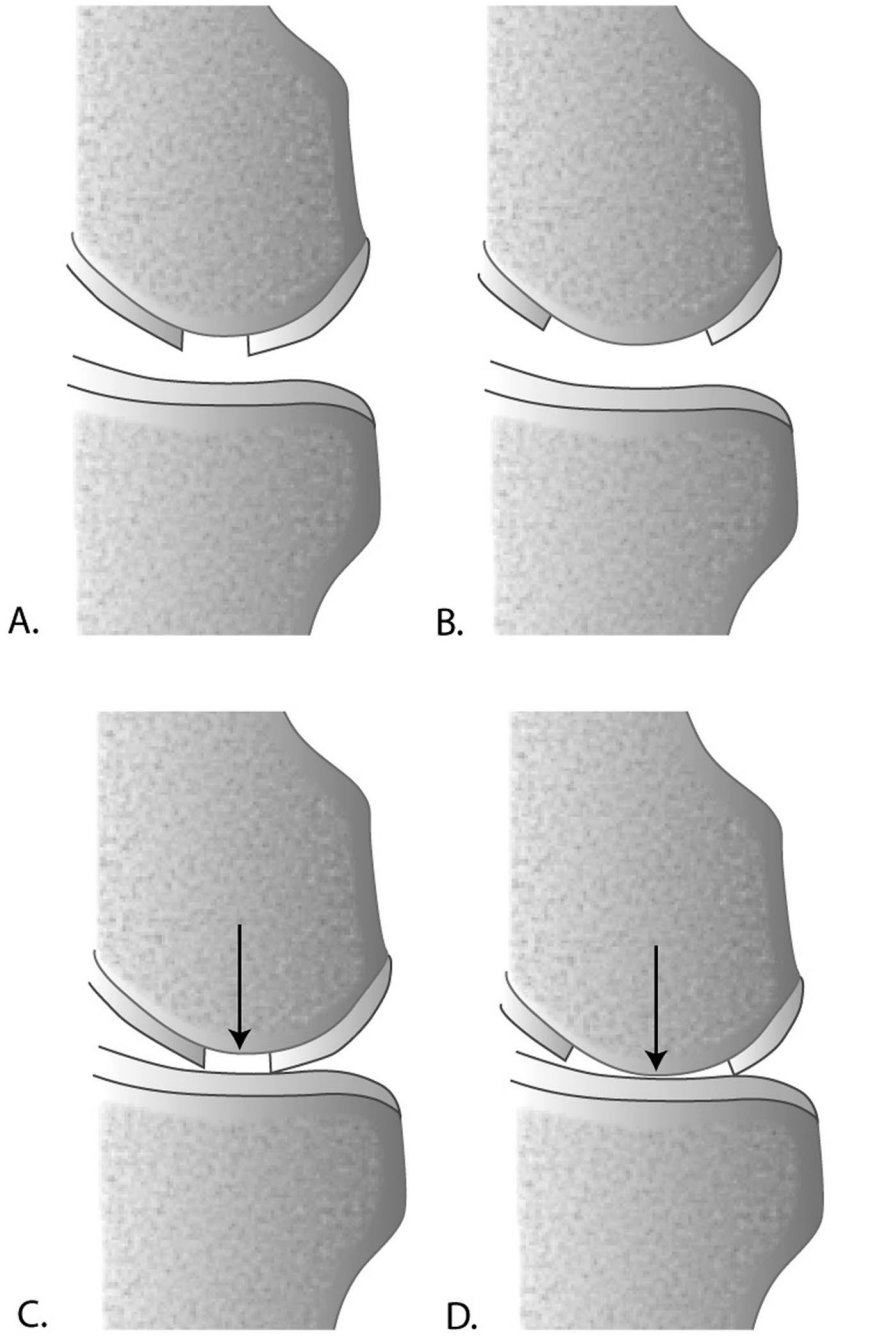


Fig. 1

Schematic representation of the loading of focal femoral condyle defects. Small lesions (A and C) are well contained and protect the tibial surface during activity and movement of the joint. Larger lesions (B and D) expose the subchondral bone and the margins of the lesion to the tibial articular surface, with a resulting increase in rates of cartilage wear as well as mechanical symptoms and pain.

body-mass index. Weight reduction should be an integral component of the preoperative program. A lower body-mass index has been correlated with higher scores for activities of daily living as well as better Short Form-36 Physical Component Summary scores following cartilage repair procedures[25]. No body-mass index represents an absolute contraindication to the performance of autologous chondrocyte implantation; however, the goal should be a body-mass index of <30 kg/m$^2$ prior to surgical intervention to ensure optimal results. The medial and lateral femoral condyles, trochlear groove, and patellar facets are palpated. Tender areas should be correlated with the symptoms. During chondrocyte implantation, it is not uncommon to find isolated regions of ICRS grade-II change along the articular surface; if these areas are not tender on examination they should be ignored. Patellofemoral crepitus should be assessed for location and quality (i.e., coarse or fine); furthermore, provocative maneuvers such as the patellar grind test should be performed and correlated with symptoms. Associated cruciate ligament insufficiencies should be recognized and further evaluated with magnetic resonance imaging. Clinically relevant complete or partial tears should be treated with staged or concomitant reconstruction[26]. Meniscal lesions have a well-defined association with chondromalacia and osteoarthritis[27]. Patients who have undergone a previous meniscectomy may require concomitant or staged meniscal transplantation.

*Radiographic Assessment*

The initial radiographic assessment should include a posteroanterior weight-bearing view as described by Rosenberg to assess for medial and/or lateral compartment narrowing and bilateral Merchant views to assess for patellar facet wear, subluxation, and tilt[28-31]. Finally, bilateral long-limb standing radiographs (hip to ankle) should be made to determine the mechanical axis and potential sites of increased load to the repair site[32]. A direct side-to-side comparison should be performed on all views to delineate subtle narrowing in comparison with the contralateral side. Asymmetries should not be ignored but should be addressed to unload the involved compartment in preparation for the sensitive chondrocytes that will be implanted.

*Magnetic Resonance Imaging*

Controversy remains regarding the sensitivity and specificity of magnetic resonance imaging in detecting isolated chondral injuries, but it is becoming a reliable, noninvasive method of diagnosing osteochondral injuries. In 1998, Potter et al. used cartilage-sensitive pulse sequencing to detect defects in the articular surface and reported high sensitivity and specificity for chondral lesions with minimal interobserver variability[33]. They concluded that magnetic resonance imaging was an accurate and reproducible imaging modality for the diagnosis of chondral lesions in the knee. Friemert et al. reported that magnetic resonance imaging had a sensitivity of 33% to 53% and a specificity of 98% to 99% for detecting advanced articular cartilage lesions when compared directly with diagnostic arthroscopy[34]. Palosaari et al. found an even higher sensitivity (80% to

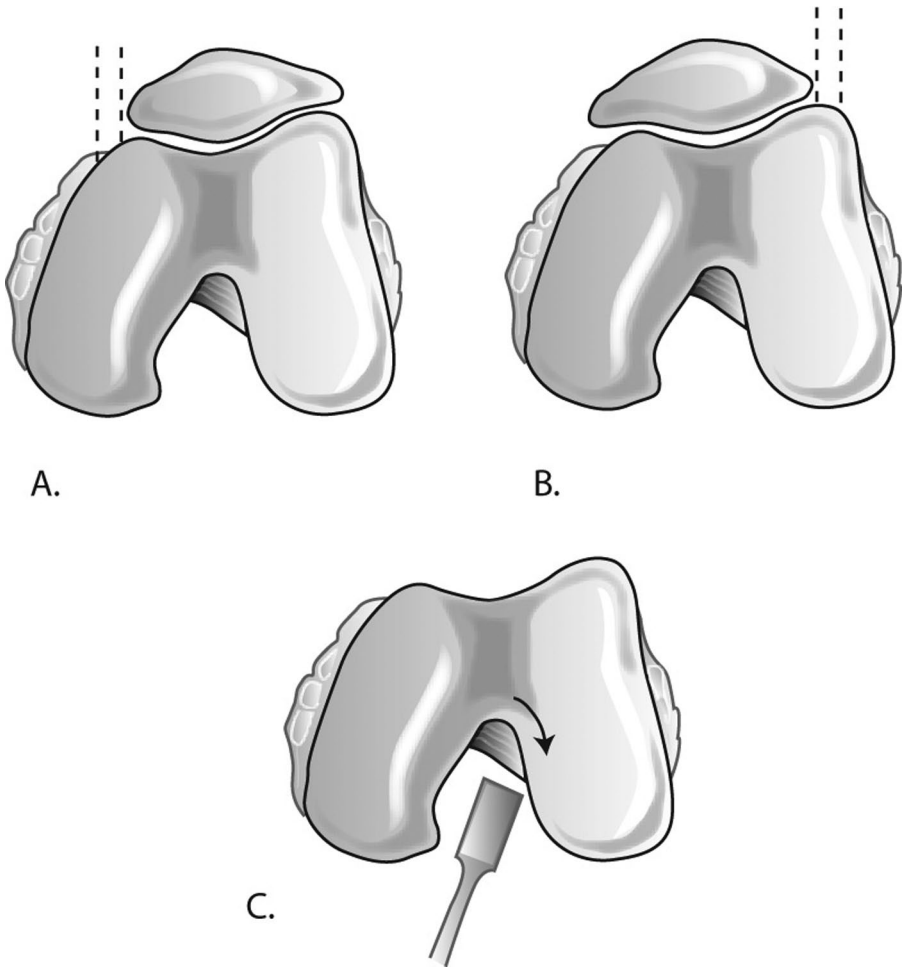


Fig. 2

Appropriate cartilage biopsy sites include the superomedial trochlear ridge (A), uncovered superolateral trochlear ridge (B), and lateral aspect of the intercondylar notch (C). All sites should be sharply incised prior to harvest to avoid gouge slippage. (Reprinted, with permission, from: Minas T, Peterson L. Advanced techniques in autologous chondrocyte transplantation. Clin Sports Med. 1999;18:13-44.)

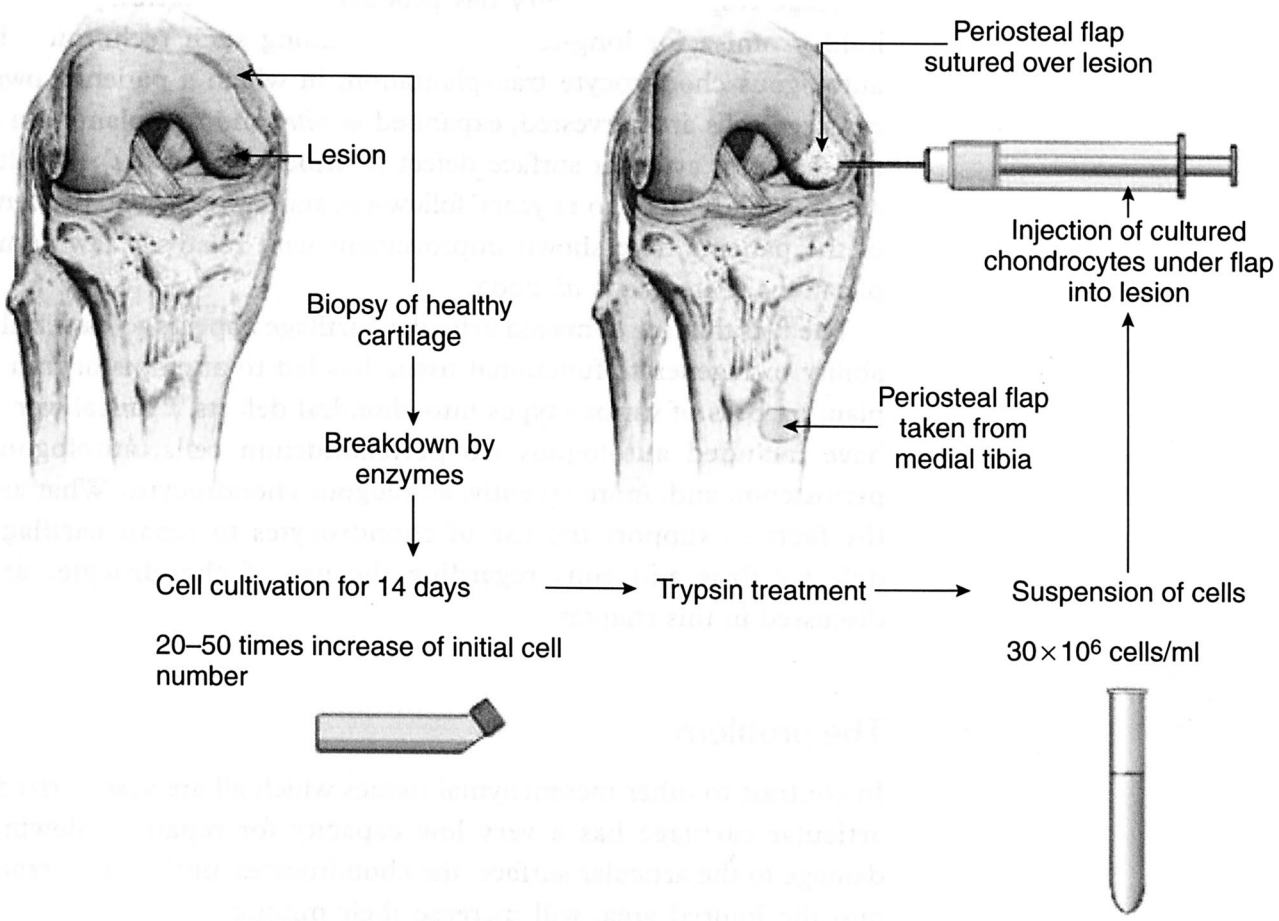


Fig. 3

Schematic drawing showing the cartilage biopsy preparation and autologous chondrocyte implantation. (Reprinted, with permission, from: Brittberg M, Peterson L. Autologous chondrocyte transplantation can effectively treat most articular cartilage lesions of the knee. In: Williams RJ, Johnson DP, editors. Controversies in knee surgery. Oxford: Oxford University Press; 2004. p 440.

96%) when diagnosing cartilaginous lesions with magnetic resonance imaging[35]. As is the case with cartilage defects detected with direct observation, lesions detected with magnetic resonance imaging should be correlated with clinical symptoms and treated only if they produce pain.

### *Arthroscopic Assessment and Biopsy*

Arthroscopic assessment is done after a careful physical examination and the radiographic studies just discussed. Areas of ICRS grade-III or IV change are noted and measured, and the reciprocal surface is evaluated for the degree of damage as well. If the patient is deemed an appropriate candidate for chondrocyte implantation, a biopsy is done. The biopsy specimen is best taken from the superomedial edge of the femoral trochlea, but if pathological involvement extends into this region or if there is concern about the patellofemoral articulation, the superolateral trochlear edge can be used. An additional site for biopsy is the lateral aspect of the intercondylar notch, the area typically used for notchplasty during anterior cruciate ligament surgery (Fig. 2). The total weight of the biopsy specimen should be 200 to 300 mg, and the specimen should include the entire cartilage surface along with a small portion of the underlying subchondral bone. This tissue should contain between 200,000 and 300,000 cells. Even though cartilage from femoral osteophytes and débrided cartilage have type-II collagen and molecular activity consistent with that of normal articular chondrocytes, the cells needed for implantation should not be obtained from these "abnormal" sources of cartilage[36,37]. The surgeon should also resist the temptation to use cartilage from a discarded osteochondritis dissecans fragment.

The harvested cells are maintained at 4°C until processing (Fig. 3). Isolated defects of up to 6 $cm^2$ can be treated with one vial. Each vial typically contains a cell pellet (~12 million cells per vial) and 0.3 to 0.4 mL of Ham F-12 medium with serum supplementation. The number of cells in a vial should allow full coverage of the defect base with a confluent cell population. If there are multiple lesions and areas of >6 $cm^2$, more than one vial will be re-

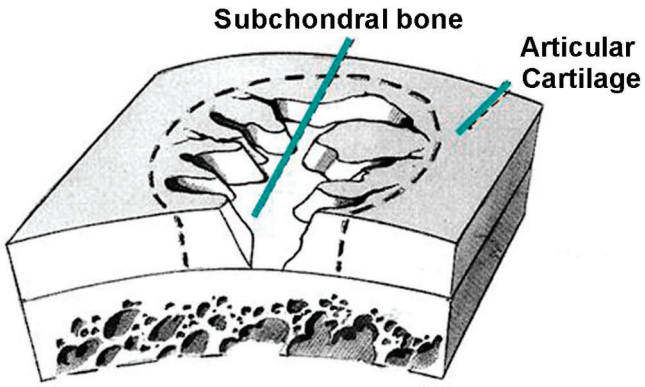


Fig. 4-A

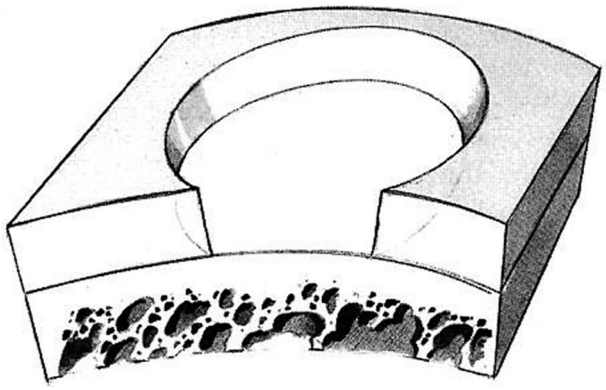

Fig. 4-B

**Figs. 4-A, 4-B, and 4-C** Preparation of the defect. **Fig. 4-A** A fibrillated cartilage lesion. **Fig. 4-B** Débridement to healthy cartilage margins, with smooth vertical borders created on completion.

quired; lesion size should be taken into account when ordering cells prior to implantation.

## Surgical Technique

### *Exposure*

A midline skin incision is used. Implantation can be done through a medially or laterally based mini-arthrotomy, to avoid the creation of quadriceps weakness and intra-articular adhesions postoperatively. Alternatively, a subvastus approach can be used, particularly for lesions of the medial femoral condyle. Damage to the anterior horns and central bodies of the menisci should be avoided when dissection is carried out along the anterior tibial surface. When a lesion of the tibial plateau is treated, the meniscus should be reflected by releasing the intermeniscal ligament and the anterior meniscal horn of the involved compartment as previously described[38]. When a concomitant tibial tubercle osteotomy is done, slight lateral placement of the incision avoids injury to the infrapatellar branch of the lesser saphenous nerve.

### *Preparation of the Defect*

The articular defect should be débrided back to normal vertical articular cartilage margins (Figs. 4-A, 4-B, and 4-C). All fibrillated and partially delaminated cartilage should be removed. The margins of the lesion are first demarcated with a number-15 blade, and the damaged cartilage is then removed, typically with a ring-shaped curet. One should avoid breaking through the subchondral bone plate to prevent bleeding into the defect.

Minimally chondromalacic (grade-I and early grade-II) areas along the border of the lesion are left alone when appropriate suture fixation is possible. When débridement necessitates extension into poorly contained regions, the bone edge should be prepared for later suture fixation of the periosteal graft. This can be performed with the use of a number-5 Keith needle acting as a drill bit creating a bone tunnel for later suture placement (Fig. 5-A). Small suture anchors are commercially available (Microfix; Mitek, Raynham, Massachusetts) and can be used. Prior to placement, the anchors must be reloaded with a 5-0 or 6-0 Vicryl (polyglactin) suture. These anchors are ideal for poorly contained regions such as the intercondylar notch or the peripheral aspect of the femoral condyle or areas such as the posterior edge of a lesion located in the 70° to 90° flexion zone, where it is difficult to place sutures appropriately (Figs. 5-B, 5-C, and 5-D). With extension into the intercondylar notch, interrupted and running suture techniques can be utilized to supplement graft fixation. Strong fixation of the periosteal graft to the defect is critical to prevent future delamination of the graft and to allow early motion of the joint.

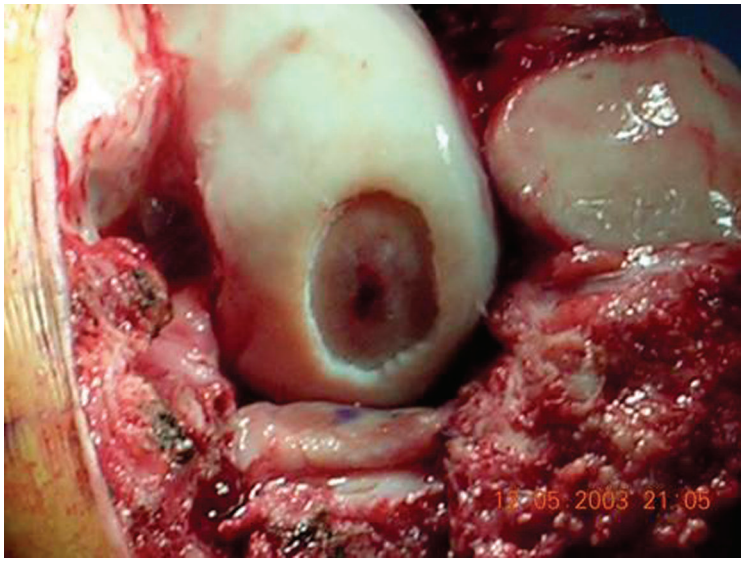

Fig. 4-C

Isolated cartilage lesion following débridement.

**TABLE I Normal Cartilage Maturation Process Following Autologous Chondrocyte Implantation**

| Stage | Time | Tissue |
|---|---|---|
| Proliferation | 0-6 wk | Soft, primitive repair tissue |
| Transition | 7 wk to 6 mo | Expansion of matrix into putty-like consistency |
| Remodeling | 6-18 mo (changes can occur up to 3 yr) | Matrix remodeling, tissue stiffens to normal hardness |

In many instances, intralesional osteophytes or sclerotic bone regions are encountered following removal of the calcified cartilage layer and/or fibrocartilage. While it is ideal to avoid exposure of the cancellous bone, a high-speed burr should be used to remove the protuberant bone region and sclerotic bone layer. If that procedure is carefully performed, a thin layer of subchondral bone should remain, serving as an appropriate viable bed for chondrocyte attachment. After débridement, the tourniquet, if used, should be deflated and complete hemostasis should be obtained. Initial attempts at hemostasis should involve the use of cotton pledgets soaked in a 1:1000 epinephrine-normal saline solution mixture. The pledget is applied, and pressure is maintained during harvest of the periosteal graft. We have found that thrombin spray has helped in cases of continued bleeding. Finally, if there are sites of excessive bleeding, particularly when previous bone procedures such as microfracture have been performed, a needle-tip Bovie cautery unit on a low setting (20 to 25 coagulation setting) should be used judiciously.

When the bone deficiency is deeper than 6 to 8 mm, such as can occur with an osteochondral fracture, osteochondritis dissecans, or a failed osteochondral grafting procedure, concomitant or staged bone-grafting should be performed[21]. If it is performed in a staged manner, bone graft should be placed up to the level of the subchondral bone plate. Prior to bone-grafting, it is important to remove all sclerotic bone; particularly in patients with osteochondritis dissecans, drilling through the bed following débridement allows appropriate blood flow into the defect, ensuring subsequent incorporation of the bone graft (Figs. 6-A through 6-D). Fibrin glue, sutures, or resorbable membranes such as the Restore patch (DePuy, Warsaw, Indiana) can be used to maintain the bone graft in place. Postoperative continuous passive motion with touch-down to 25% partial weight-bearing for four to six weeks is advised. The patient is then allowed to resume full weight-bearing, but chondrocyte implantation is not done for another five to eight months to allow reconstitution of a subchondral bone plate (Figs. 7-A and 7-B).

Alternatively, the "sandwich technique" can be used to treat a deep lesion[20]. With use of a high-speed burr, the sclerotic bone bed is removed down to bleeding cancellous bone and the base of the lesion is drilled as previously described. Following bone-grafting to the level of the subchondral bone plate, a periosteal flap the size of the osseous defect is harvested and is anchored in place with the cambium layer facing up into the defect and the fibrous layer facing the bone graft. Leaving a small ridge of healthy subchondral bone can help to stabilize the placement of this initial periosteal flap. One of us (D.G.J.) has successfully used Microfix anchors to help anchor this first periosteal flap (Figs. 8-A through 8-G). Fibrin glue can be placed around the base of the defect at the periosteal edge to obtain hemostasis. Additionally, or as an alternative, simple compression of the bone graft and periosteal construct for two to three minutes can help stop the bleeding. A second periosteal flap is then applied, as will be described.

*Harvest of Periosteal Graft*

The defect should be measured with a sterile ruler to determine the appropriate graft size. Alternatively, a paper template of the defect site can be created by placing paper directly over the site and tracing the defect on it with sequential dots with use of a surgical skin marker. One additional technique is to use a sterile knife-blade package as an aluminum template, pressing it directly into the defect to create an imprint of the lesion. The paper or aluminum template is created by cutting around the edge of the dots or imprint. The template should be 2 mm larger in diameter than the actual defect when the femoral condyle or tibial plateau surfaces are being treated. When the trochlear groove or patellar surfaces are being grafted, a template 3 mm larger in diameter than the actual lesion should be created to take into account the concave and convex surfaces, respectively[21].

Several sites are available for harvest of a periosteal graft. The first option should be the proximal-medial aspect of the tibia distal to the pes anserinus insertion or distal to the semitendinosus tendon insertion. This site typically has robust but thin enough periosteum, making it ideal for implantation. Normal periosteum is a thin membrane several cell layers' thick consisting of an outer fibrogenic layer and an inner osteogenic cambium layer. An incision is made over the proximal part of the tibia through the subcutaneous fat and the thin fascial layer. Care should be taken to remove all overlying fascial and fatty layers prior to removal of the periosteum. This is typically best performed with use of sharp scissor dissection, revealing an underlying white, shiny periosteum. Attempts at periosteal débridement following harvest can cause button-holing through the graft surface with resultant sites of cell leakage at the time of implantation. Electrocautery should not be used around the periosteum prior to harvest as it will damage the periosteum and can kill cells in the cambium layer. Sec-

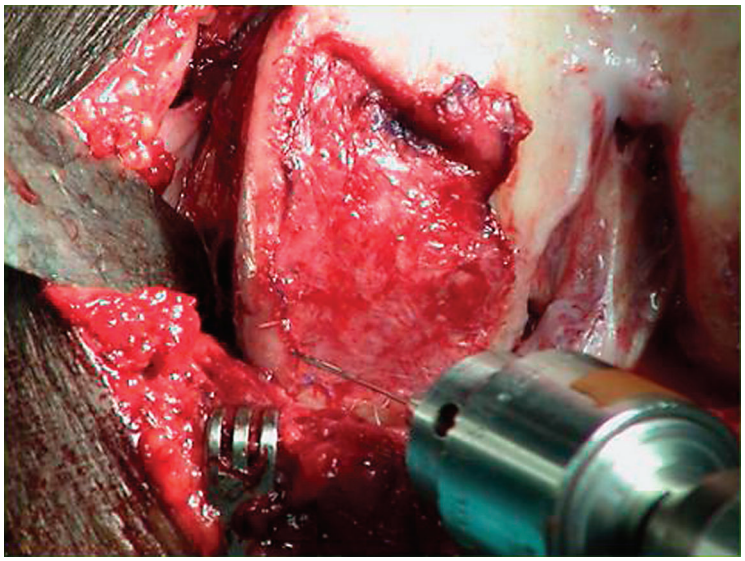

Fig. 5-A

A number-5 Keith needle used as a drill bit in a poorly contained lesion, creating an osseous tunnel for later suture placement.

ondary sites of graft harvest include the femoral metaphyseal-diaphyseal region, which can be exposed with retraction of the quadriceps musculature. Harvest of a periosteal graft from this location requires careful incision of the overlying synovium to expose the underlying periosteum. The synovium should be placed back into its normal anatomic location following graft harvest from the femur to prevent postoperative scarring. The femoral periosteum is typically thicker, and this theoretically may inhibit diffusion of synovial fluid and cell nutrition during the initial growth phase. Thicker periosteum may also predispose to increased rates of periosteal overgrowth. Finally, the required soft-tissue dissection in the suprapatellar region can lead to an increased prevalence of postoperative intra-articular adhesions. Therefore, femoral periosteum should be used only as a secondary source of periosteal graft during autologous chondrocyte implantation. After harvest, the periosteal graft should be kept moist. When multiple grafts are taken, each should be labeled to prevent confusion during implantation.

Resorbable membrane substitutes have become commercially available. Two examples are Chondrogide (Geistlich Biomaterials, Wolhusen, Switzerland) and Restore (DePuy, Warsaw, Indiana). Haddo et al. reported on thirty-one patients in whom Chondrogide had been used in place of periosteum[39]. They reported no evidence of hypertrophy of the periosteal grafts and satisfactory clinical outcomes at two years. One of us (D.G.J.) used the Restore patch as a substitute for periosteum in thirty patients as well as in patients requiring autologous bone-grafting. At the time of short-term follow-up (at one to two years), there were no adverse events or effects on clinical outcome. Bartlett et al. reported similar results[40]. The use of resorbable membranes as a defect cover, replacing the traditional autologous periosteum, has been termed *collagen-associated autologous chondrocyte implantation*[41].

### *Graft Fixation*

The periosteal graft is secured in place with 6-0 Vicryl suture with use of a P-1 cutting needle. Dyed suture is recommended as it is easy to see against the articular cartilage. Sterile mineral oil coating the suture helps to prevent binding between the suture and the periosteal graft. The needle is passed first through the superficial surface of the periosteum about 2 mm from the graft edge and then into the cartilage margin, entering the vertical border perpendicular to the inside wall of the defect. The needle should enter the cartilage approximately 2 mm from the surface and extend peripherally, exiting the defect 4 mm from the edge of the defect. A simple instrument-tying technique is used with each throw. This localizes the knot over the periosteum rather than placing it on the articular surface, where it

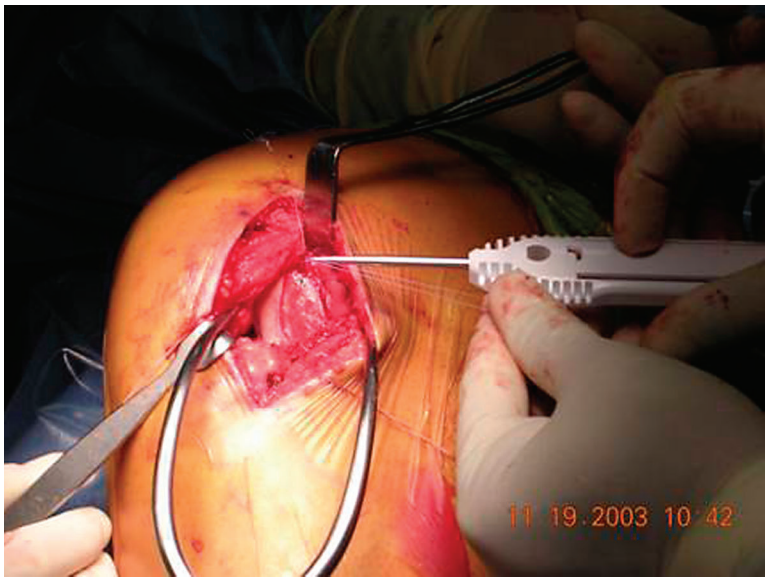


Fig. 5-B

Microfix anchor (Mitek, Raynham, Massachusetts).

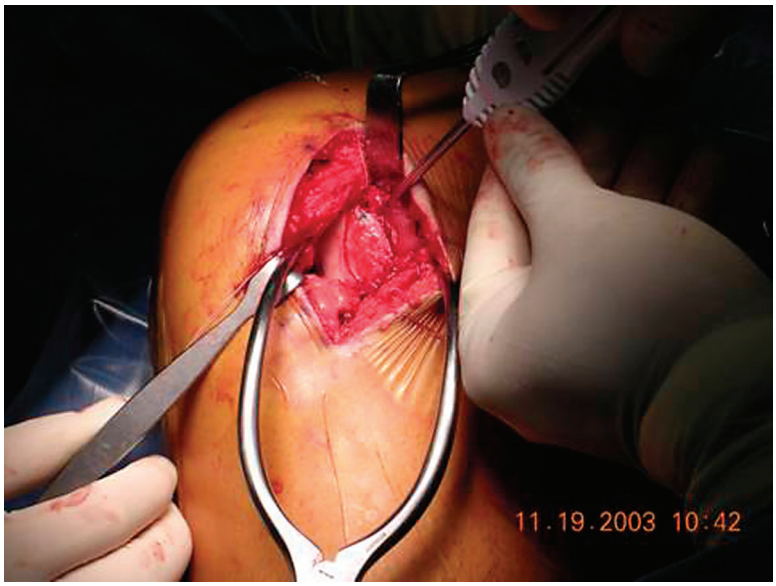


Fig. 5-C

Following use of the Microfix drill bit and replacement of the nonabsorbable suture with 5-0 Vicryl suture, the anchor is implanted.

could be exposed to shear forces damaging fixation. All four quadrants of the graft should be tied initially to stabilize the graft. Additional sutures are then placed at 3-mm increments around the lesion, producing a watertight seal. An alternative method of suture placement is used during trochlear autologous chondrocyte implantation. In this procedure, the sutures are first placed along the medial margin and are then sequentially placed from medial to lateral, producing a convex surface to allow appropriate patellar tracking (Fig. 9). Similarly, the contour of the graft should be considered when autologous chondrocyte implantation is performed in the patella, especially in a centrally based patellar lesion; the normal convexity of the patella should be considered as should the height of graft placement along the defect, as shear forces in this area can lead to catching at the leading and trailing edges of the defect with knee motion[21].

One region along the lesion should be left open to allow cell implantation. However, to prevent cell extrusion after implantation, the sutures are placed in the standard fashion but not tied immediately. Prior to cell implantation, the repair should be assessed to determine whether a watertight seal has been created. Normal saline solution without antibiotics should be placed into the planned area of cell implantation with use of a 1.5-in (3.8-cm) 18-gauge angiocatheter and tuberculin syringe. The intra-articular portion of the knee is dried, and sites of leakage are noted. Additional sutures are placed into any leakage site, and testing is performed again. Once a watertight seal has been created, the cells can be implanted.

Cells, provided by Genzyme Biosurgery (Cambridge, Massachusetts), arrive in a small vial and should be maintained at 4°C until they are implanted. The typical concentration is 12 million cells/0.4 mL of serum-supplemented culture medium as previously described. Once again, one vial should cover a lesion of ~6 $cm^2$. The cells have typically settled into a pellet at the bottom of the vial and must be gently resuspended into a solution form with use of an angiocatheter; cells are then injected into the defect. Sutures are tied over, and fibrin glue or Tisseel (as described below) is applied to the site of implantation. Only after a watertight seal has been verified should the wound edges be further sealed with fibrin glue.

Autologous fibrin glue is formed by taking the cryoprecipitate from 1 U of the patient's whole blood and combining it with a mixture of bovine thrombin and calcium chloride. An excellent alternative to this cumbersome technique is to use the commercially available fibrin glue called Tisseel (Baxter Healthcare, Glendale, California). It is important to limit the amount of Tisseel or fibrin glue placed into the joint as it has the potential to increase postoperative fibrous adhesions. Further-

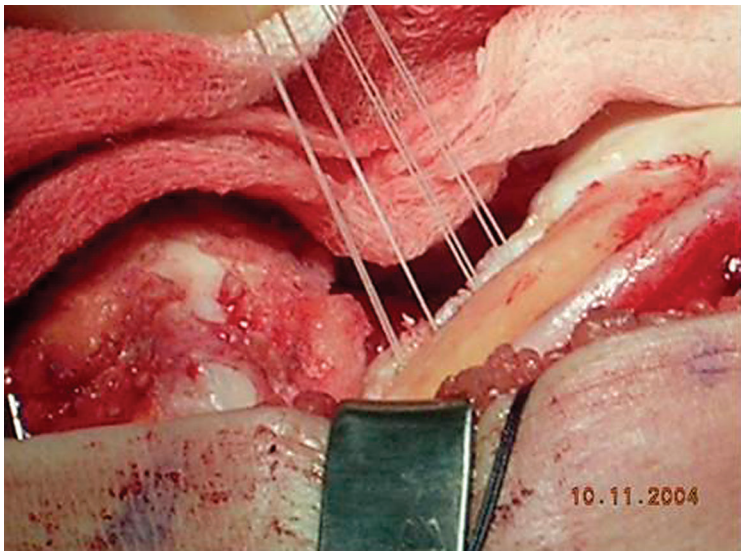


Fig. 5-D

Application of several anchors along the poorly contained border of the lesion.

more, Brittberg et al. demonstrated potential deleterious effects of Tisseel on chondrocyte migration and healing potential in an vivo rabbit model[42]. As a result, care should be taken to limit the amount of Tisseel applied and to avoid exposing it to the chondrocytes.

In large, particularly long defects, the contour of the femur may not allow placement of the angiocatheter utilized for cell implantation far enough into the defect. This can limit the ability to create an even cell suspension at the base of the lesion. In these cases, leaving a more posterior, distal second site of cell implantation is helpful. Cells are implanted in this site first, the sutures are tied, and then cells are implanted into the more anterior, proximal site secondarily.

## Postoperative Rehabilitation

Cartilage maturation occurs through several phases (Table I), and this process must be considered during the critical rehabilitation process after surgery. The first phase, termed the *proliferative phase,* occurs during the first six weeks. Cells should be allowed to adhere to the subchondral bone plate, a process that can take from twelve to eighteen hours. As a result, knee motion should be restricted for this period of time following implantation, to allow cell adherence and early proliferation to occur. Continuous passive motion is initiated after twelve to eighteen hours, to provide a chondrogenic stimulus as demonstrated by O'Driscoll and Salter[43]. The continuous passive motion machine should be used for six to eight hours a day for the first four weeks after the surgery. A soft, primitive repair tissue forms during this initial phase.

The second phase of cartilage maturation, termed the *transition phase,* occurs during the next four to six months. This phase is characterized by expansion of the matrix released by the chondrocytes into a putty-like consistency. Weight-bearing is begun after the first month. The size and location of the lesion influence the time at which to start weight-bearing. Patients with a well-contained lesion that is protected by the surrounding native cartilage can start bearing weight as early as four weeks postoperatively (Figs. 10-A and 10-B). Patients with a poorly contained lesion should not bear full weight until eight to twelve weeks after the surgery (Figs. 10-C and 10-D). Patients with multiple lesions should progress even more slowly. If there is varus or valgus knee malalignment of 3°, compared with the alignment on the contralateral side, in association with a medial or lateral-based lesion, respectively, an unloader brace should be used on initiation of weight-bearing. If there is knee malalignment of >3°, performance of a concomitant or staged osteotomy, which would avoid the need for prolonged postoperative use of the unloader brace, should be seriously considered.

Patellofemoral lesions are not subjected to forces when the patient bears weight with the knee in full extension. Use of a hinged immobilizer locked in extension during walking al-

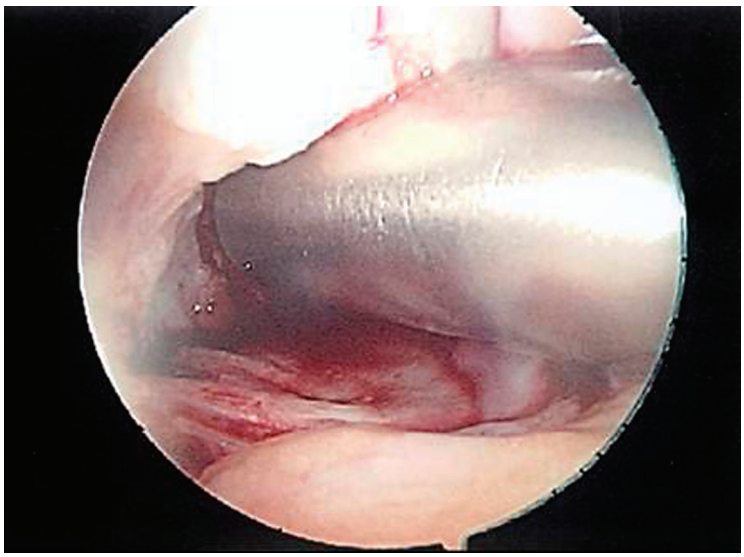

Fig. 6-A

**Figs. 6-A through 6-D** Bone-grafting. **Fig. 6-A** Débridement of an osteochondritis dissecans lesion to bleeding healthy bone.

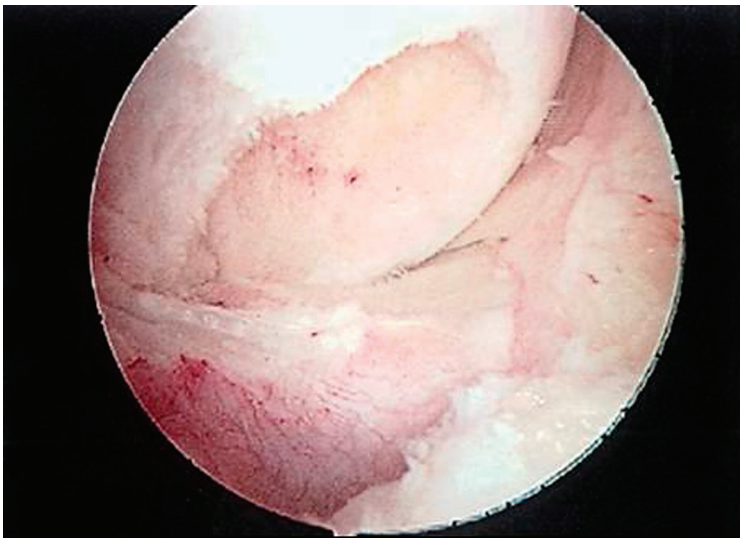

Fig. 6-B

The base of the lesion was drilled to create bleeding.

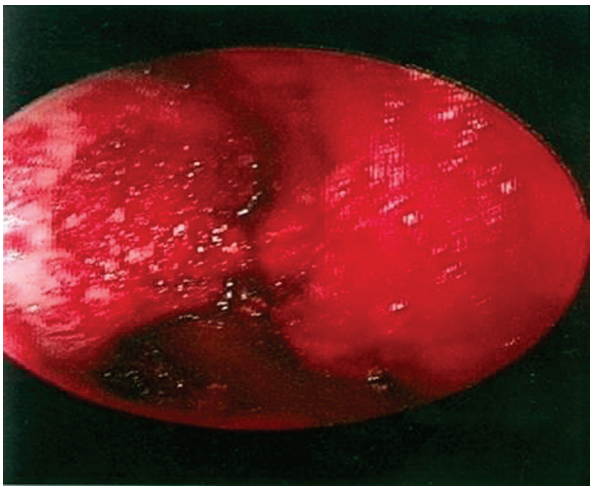

Fig. 6-C

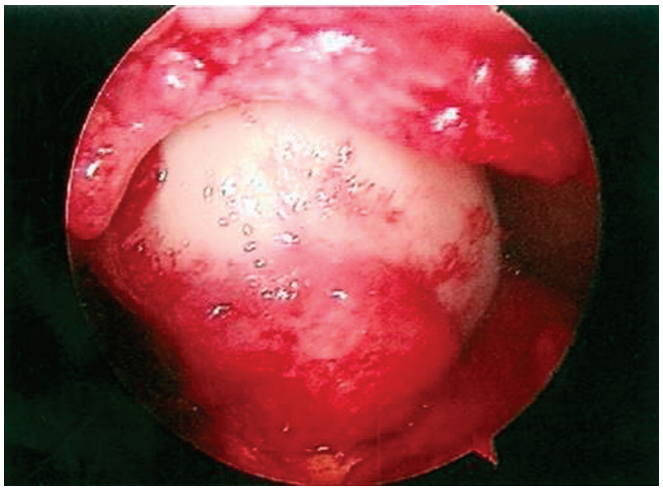

Fig. 6-D

**Fig. 6-C** Autologous bone graft was applied to the defect. **Fig. 6-D** Fibrin glue was applied over the defect to maintain the bone graft in place and to avoid extravasation into surrounding tissues.

lows such patients to bear weight during the initial six postoperative weeks. Open-chain exercises should be avoided during the first four to six months to reduce the shear forces that can occur across an implant on the patellofemoral articular surface. Continuous passive motion is initiated one month after surgery, but progression to >90° of flex-

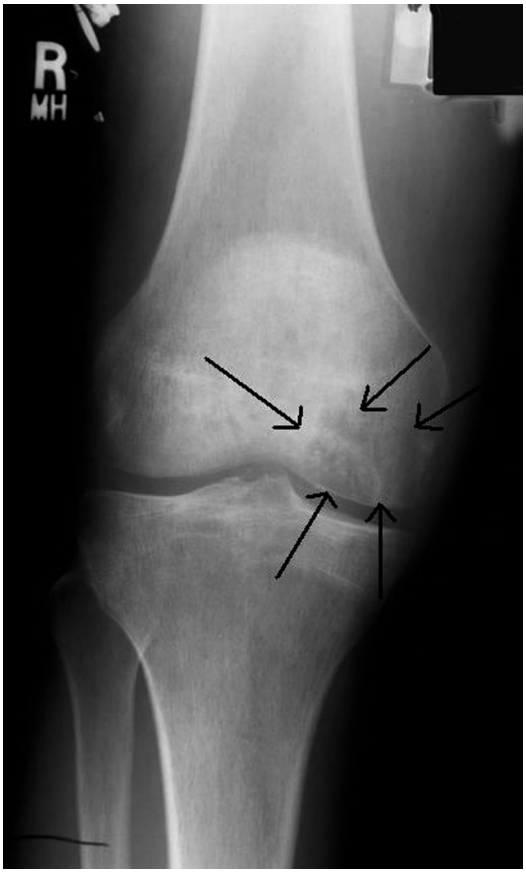


Fig. 7-A

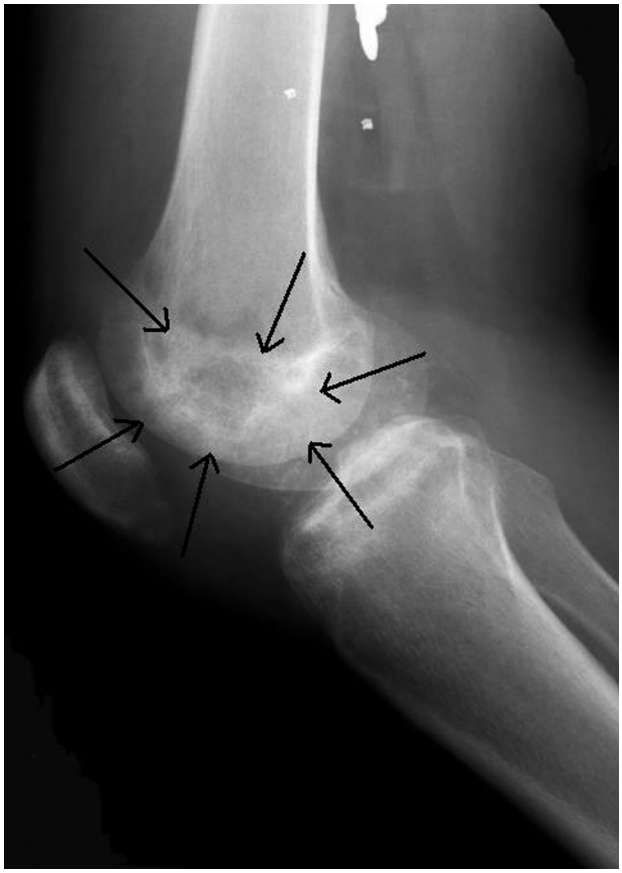

Fig. 7-B

**Fig. 7-A** Postoperative anteroposterior radiograph made four months following application of bone graft to the defect. The arrows show the reconstitution of the subchondral bone contour following treatment with a continuous passive motion machine and non-weight-bearing for four weeks. **Fig. 7-B** Lateral radiograph demonstrating the normal subchondral contour (arrows).

ion should occur more slowly than with a femoral lesion.

The final phase in cartilage maturation, termed the *matrix remodeling phase,* is characterized by progressive hardening of the cartilage tissue to the firm quality of the adjacent native cartilage. This process begins at about six months and continues over the ensuing six to twelve months. Although patients are allowed to resume regular activities at one year after the surgery, the graft continues to mature for up to three years. Factors that affect this process are lesion size and location as well as the patient's physiologic age and final desired activity level. Patients will continue to have some symptoms along the implant site as the activity level is increased during this period. However, as the graft matures, providing greater protection of the subchondral bone, preoperative symptoms should resolve slowly. Preoperative education of the patient regarding this biologic process and, in particular, the expected length of time until full recovery is critical. The informed patient is less likely to expose the graft to traumatic forces during the initial phases of cartilage maturation.

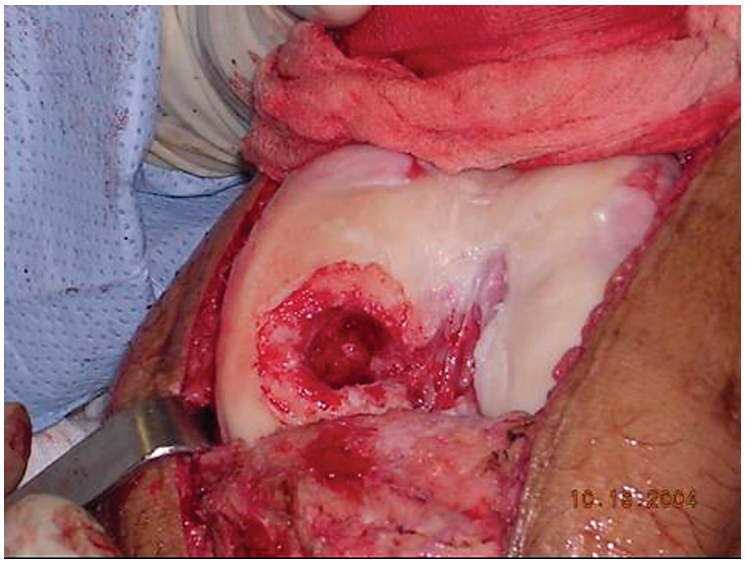

Fig. 8-A

Bone lesion following débridement of sclerotic bone and drilling of the base of the lesion. Note the shelf of normal subchondral bone around the osseous defect.

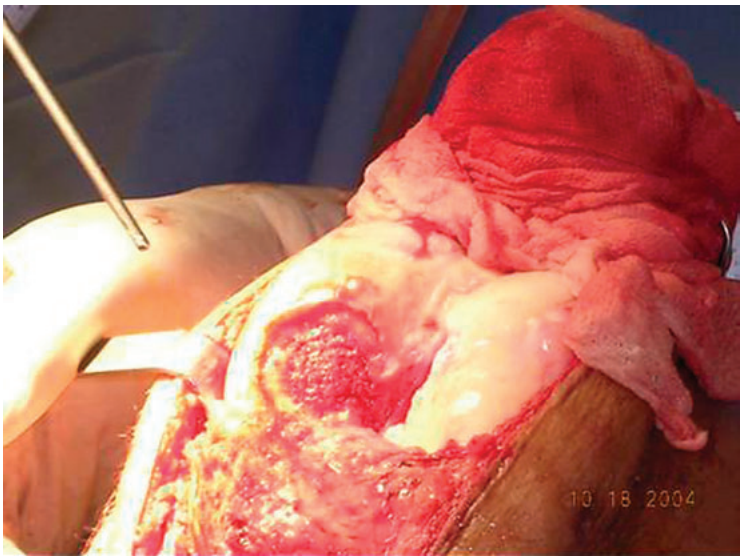


Fig. 8-B

Bone-graft application up to but not over the subchondral bone height.

## Discussion

Magnetic resonance imaging has become an increasingly important means of assessing articular cartilage and its repair[44]. It can be used to monitor the patient's progress after a biologic reconstructive procedure[45,46]. Henderson et al. reviewed the results in fifty-three patients (seventy-two lesions) for up to two years with clinical evaluation, magnetic resonance imaging, second-look arthroscopy, and biopsy[45]. Magnetic resonance imaging demonstrated that 75% of the defects had at least a 50% defect fill, 46% had a nearly normal signal, 68% had mild-to-no effusion, and 67% had mild-to-no underlying bone marrow edema at three months. These values improved to 94%, 87%, 91%, and 88%, respectively, at twelve months. At twenty-four months, there were additional improvements to 97%, 97%, 96%, and 93%, respectively. Improvement in clinical outcome correlated well with the information obtained from second-look arthroscopy and the core biopsies when that information was assessed along with the magnetic resonance imaging findings at twelve months[47]. Brown et al. evaluated the findings of 180 magnetic resonance imaging examinations of 112 patients performed just over a year after cartilage-resurfacing procedures, including eighty-six microfractures and thirty-five autologous chondrocyte implantation procedures[48]. The defects that had been treated with autologous chondrocyte implantation had, at all times, consistently better fill than the defects treated with the microfracture, but there was graft hypertrophy in 63% of the cases treated with autologous chondrocyte implantation. In contrast, the repair cartilage over the microfracture was depressed with respect to the level of the native cartilage and had a propensity for bone development and

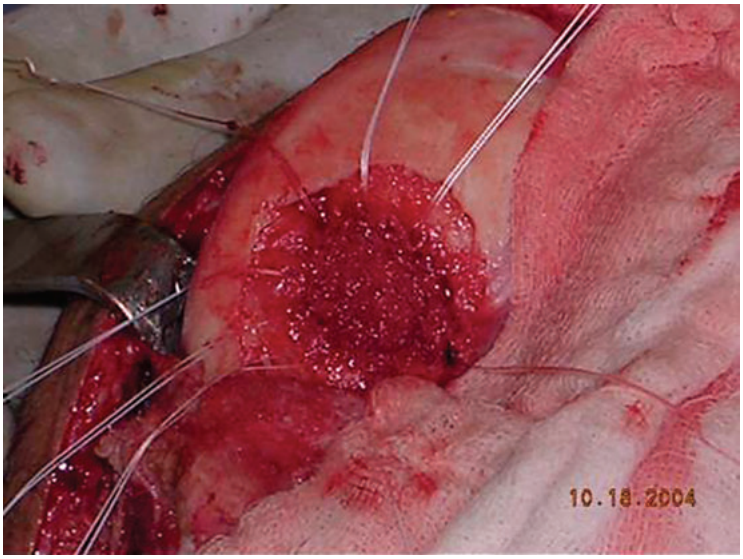


Fig. 8-C
Application of Microfix anchors (Mitek) around the periphery of the bone defect.

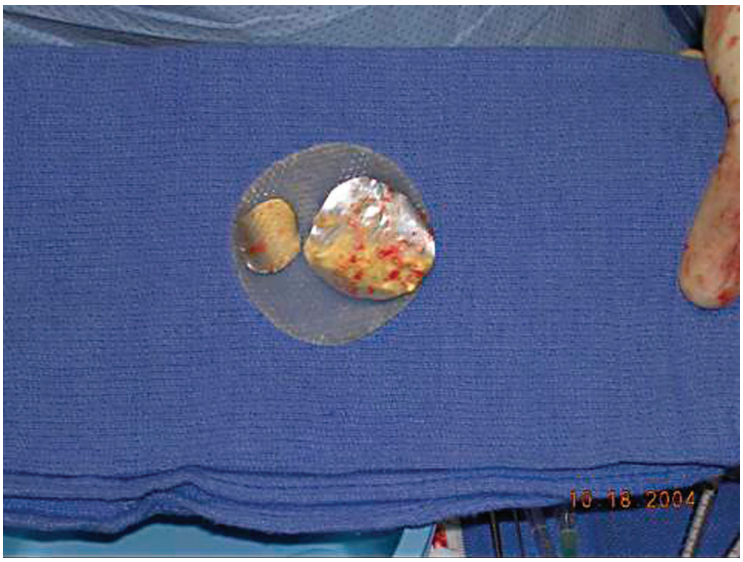


Fig. 8-D
Restore Patch (DePuy Orthopaedics, Warsaw, Indiana) with an aluminum template over the graft prior to preparation for suture fixation.

loss of adjacent cartilage with progressive follow-up.

Arthroscopic assessment remains the gold standard for postoperative evaluation. The repair is directly visualized, probe indention stiffness can be measured, and a biopsy can be done to allow histomorphologic assessment[26]. Arthroscopic probe indentation stiffness testing is useful. Vasara et al. evaluated thirty patients arthroscopically, with measurement of indentation stiffness, and clinically following autologous chondrocyte implantation[49]. The mean stiffness of the repair tissue was 62% of that of the adjacent cartilage. In six patients, the normalized stiffness was at least 80%, suggesting hyaline-like repair. The indentation stiffness following the repairs of osteochondritis dissecans lesions was less than that following repairs of lesions other than osteochondritis dissecans. Gadolinium-enhanced magnetic resonance imaging of the cartilage during the follow-up of four patients suggested proteoglycan replenishment. The authors concluded that low stiffness values may indicate incomplete maturation or predominantly fibrous repair while increased stiffness correlated with improved clinical outcomes.

The initial experience with autologous chondrocyte implantation was reported by Brittberg et al. in 1994[23]. The cases of twenty-three patients were reviewed. Fourteen of sixteen patients who had implants on the distal part of the femur had a good or excellent result, whereas only two of seven patients who had implants on the patella had a satisfactory result. Second-look biopsies revealed hyaline-like cartilage in eleven of fifteen distal femoral lesions but in only one of seven patellar lesions. The biopsy results correlated well with the clinical outcomes, suggesting a direct correlation between hyaline-like repair tissue and good to excellent function two years after surgery.

In a later review, during the intermediate to long-term follow-up period (at two to nine years), this initial trend was found to have continued[24]. This review was of the clinical, arthroscopic, and histologic results for the first 101 patients treated with an autologous chondrocyte implantation procedure. The results were better for patients who had been treated after the early series of patients, suggesting that there is a learning curve for the procedure. Graft failure occurred in seven patients, with four of the failures seen in the first twenty-three patients but only three observed in the next seventy-eight patients. Patient and physician-derived clinical rating scales; arthroscopic assessment of cartilage fill, integration, and surface hardness; biopsies; and standard histochemical techniques were utilized. Ninety-four patients underwent reevaluation, and a good or excellent clinical result was seen in 92% of those with an isolated femoral condylar lesion but in only 67% of those with multiple lesions. Patients with osteochondritis dissecans also did well, with 89% having a good or excellent result. In contrast to the findings in

the initial series, patients with a patellar lesion did relatively well, with 65% having a good or excellent result. Strict attention to patellofemoral tracking and malalignment issues were found to be important, and concomitant advancement of the tibial tubercle and trochleoplasty procedures were believed to account for the improved clinical results in the patients with a patellar lesion. Of the patients who underwent implantation in the femoral condyle with concomitant reconstruction of the anterior cruciate ligament, 75% had a good or excellent result. Periosteal overgrowth as demonstrated arthroscopically was identified in twenty-six patients, but only seven were symptomatic; the symptoms consistently resolved after arthroscopic trimming. Histologic analysis of the matrix in thirty-seven biopsy specimens to assess for type-II collagen showed a correlation between hyaline-like repair tissue and good to excellent clinical results.

An evaluation was performed on a subset, from the same series, of sixty-one patients who had been treated for an isolated cartilage defect on the femoral condyle or the patella[26]. The durability of the results was assessed by comparing the clinical status at two years with that at a mean of 7.4 years (range, five to eleven years) after transplantation. Fifty of the sixty-one patients had a good or excellent clinical result at two years, whereas fifty-one had a good or excellent result at five to eleven years. Hyaline-like repair tissue was demonstrated by eight of twelve biopsies. An electromechanical indentation probe was used to assess the grafted areas in eleven patients during a second-look arthroscopy procedure (at mean of 54.3 months [range, thirty-three to eighty-four months] postoperatively); eight patients demonstrated stiffness measurements that were ≥90% of those of normal cartilage. The mean stiffness of grafted areas with hyaline-like repair tissue, as identified with histologic assessment, was 3.0 ± 1.1 N. In contrast, the mean stiffness of grafted areas with fibrous tissue was 1.5 ± 0.35 N. Once again, good or excellent clinical outcomes were directly correlated with the demonstration of a hyaline-like repair tissue at the implantation site, whereas fibrous fill was correlated with poorer clinical outcomes. More importantly, durability of the repair tissue was clearly demonstrated, with the results at seven years equal to or better than the initial two-year results.

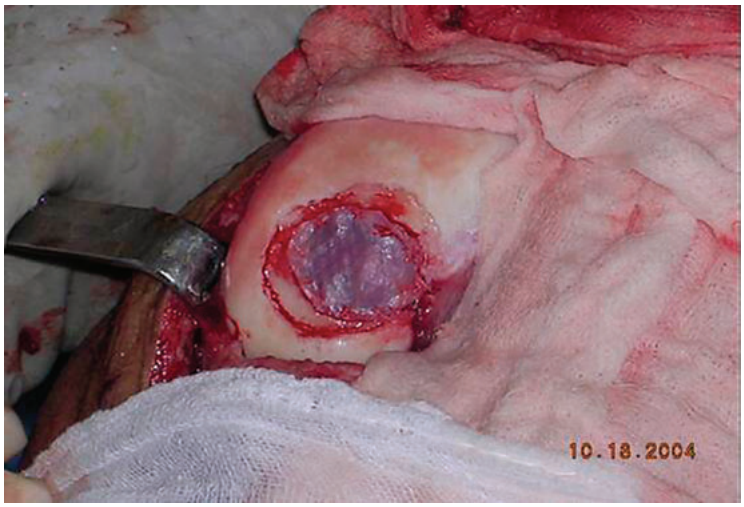


Fig. 8-E

Suture fixation of the Restore patch to the bone defect.


Fig. 8-F

Final suture fixation of the larger Restore patch and application of cells with use of the "sandwich" technique.

In 1995, Genzyme Tissue Repair (Cambridge, Massachusetts) initiated an international registry to assess the clinical effectiveness of autologous chondrocyte implantation. Data from this registry were used to evaluate the first fifty patients treated in the United States[17]. The mean patient age was thirty-six years, and the mean defect size was 4.2 $cm^2$. Thirty-nine patients had undergone previous articular cartilage repair procedures on the affected knee during the previous five years. A marrow stimulation procedure had failed in nine patients. Outcomes were measured at a minimum of three years with the modified Cincinnati Knee Rating System, and graft failure was defined as replacement or removal of the graft due to mechanical symptoms or pain. Scores derived with the modified

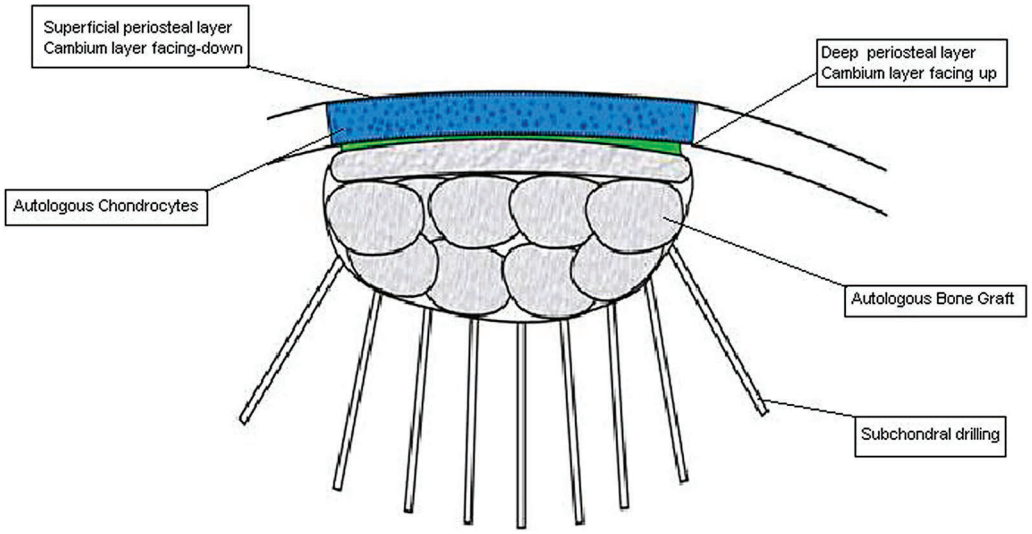


Fig. 8-G

Schematic of the "sandwich" technique, which includes drilling of the base of the lesion, application of bone graft, and placement of the bottom periosteal patch (with the cambium layer facing up) followed by cells and then the top periosteal patch (with the cambium layer facing down).

Cincinnati Knee Rating System range from 0 to 10 points, with lower scores representing poorer function and substantial pain with activities of daily living[50]. The median improvement in the score was 4 points for the clinician-based portion of the evaluation and 5 points for the patient-based portion. Neither previous treatment with marrow stimulation techniques nor the size of the defect had an impact on the results of the autologous chondrocyte implantation. The graft failed in three patients, and Kaplan-Meier analysis revealed an estimated rate of freedom from graft failure of 94% at thirty-six months.

The same registry was used to evaluate the results, at six years, in the first seventy-six patients treated with implantation in the United States[51]. The mean age of these patients was also thirty-six years. Fifty-seven patients had a single lesion, with a mean size of 4.4 $cm^2$. Nineteen patients had multiple lesions, with a mean total surface area of 10.8 $cm^2$. Nine treatment failures occurred within the first twenty-four months. Including the scores for these failures, the mean overall condition score improved from 3.1 points preoperatively to 6.0 points at six years ($p < 0.001$). Pain and swelling scores improved 2.7 and 2.6 points, respectively, compared with the baseline values.

Gillogly evaluated 112 patients with a total of 139 defects treated with autologous chondrocyte implantation over a five-year period[52-54]. The average size of the defect was 5.7 $cm^2$, and >60% of the patients had had a failure of at

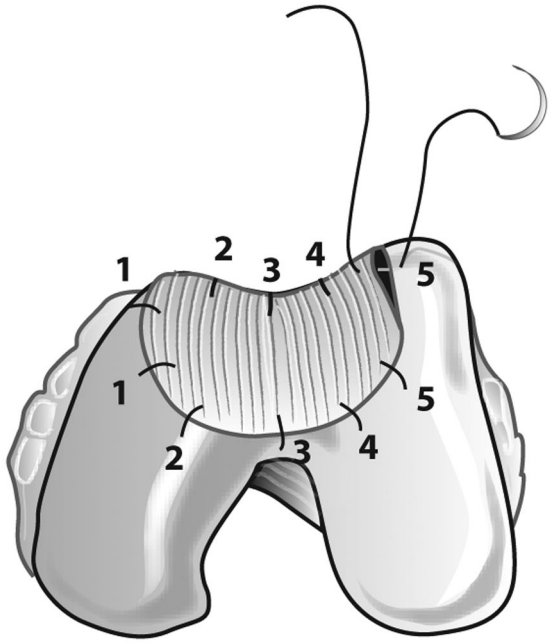


Fig. 9

With a trochlear defect, it is important to create the normal trochlear configuration. The template must be oversized by ~3 mm. The periosteal patch is then sutured sequentially from medial to lateral, as denoted by the numbers 1 through 5, with care taken to recreate the normal convex surface, thus avoiding postoperative overload to the repair site. (Reprinted, with permission, from: Minas T, Peterson L. Advanced techniques in autologous chondrocyte transplantation. Clin Sports Med. 1999;18:13-44.)

least one prior procedure. Twenty-two of the patients had multiple defects. Forty-two patients had a patellofemoral lesion, twenty-seven of which were trochlear and fifteen of which were patellar. Outcomes were measured with use of the modified Cincinnati Knee Rating System and Knee Society Clinical Rating System[55]. There were three clinical failures, and three patients were lost to follow-up. The average duration of follow-up was forty-three months. Ninety-three percent of the patients had a good or excellent outcome according to the clinician-evaluation portion of the modified Cincinnati scale, whereas 89% had a good or excellent outcome according to the patient-evaluation portion. There was no deterioration of the outcomes during the two to five-year follow-up period. Workers' Compensation claims had no effect on the clinical outcomes.

Seidner and Zaslav assessed the direct medical and nonmedical costs for, and the return-to-work status of, twenty-four patients (mean age, thirty-five years) treated with autologous chondrocyte implantation who used the same claims system of a single Workers' Compensation insurer[56]. The patients were followed until claim closure and were compared with a three-to-one matched control group of seventy-six patients treated with various other cartilage procedures. The patients' occupations ranged from light to heavy-demand. The total medical costs for the patients treated with autologous chondrocyte implantation averaged $90,235, and the indemnity costs averaged $64,704. Seventeen patients returned to work. In comparison, the total medical costs in the control group averaged $80,407 and the indemnity costs averaged $89,226, with twenty patients returning to work. The authors concluded that autologous chondrocyte implantation results in a similar return-to-work rate at an average cost savings of $15,000 per patient in comparison with controls.

Yates performed a prospective longitudinal study of twenty-four patients with Workers' Compensation claims related to lesions of >2 $cm^2$ (mean lesion size, 4.7 $cm^2$; range, 2 to 10 $cm^2$)[57]. Five lesions were on the patella, and the remaining nineteen lesions were on the distal part of the femur. Eighteen patients were followed at one year with use of the modified Cincinnati Knee Rating System. According to the clinician and patient evaluations of the modified Cincinnati Knee Rating System, the overall clinical scores improved from a mean of 3.2 points at baseline to 6.8 points at one year postoperatively. Fourteen patients had a good or excellent result. Of the twenty-one patients who were followed for more than one year, thirteen returned to unrestricted work status at a mean of seven months and an additional four returned to modified work status. This study demonstrated that autologous chondrocyte implantation can effectively enable patients in a Workers' Compensation population to return to their desired activity level.

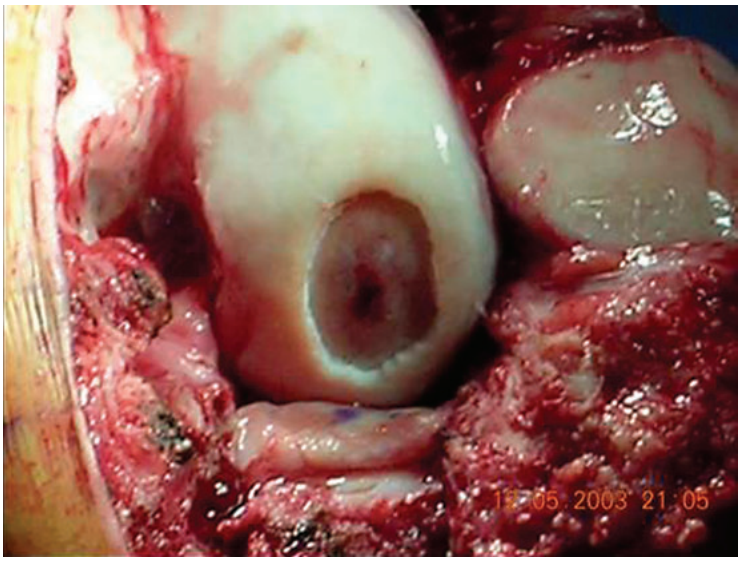


Fig. 10-A

A well-contained lesion with normal articular cartilage borders.

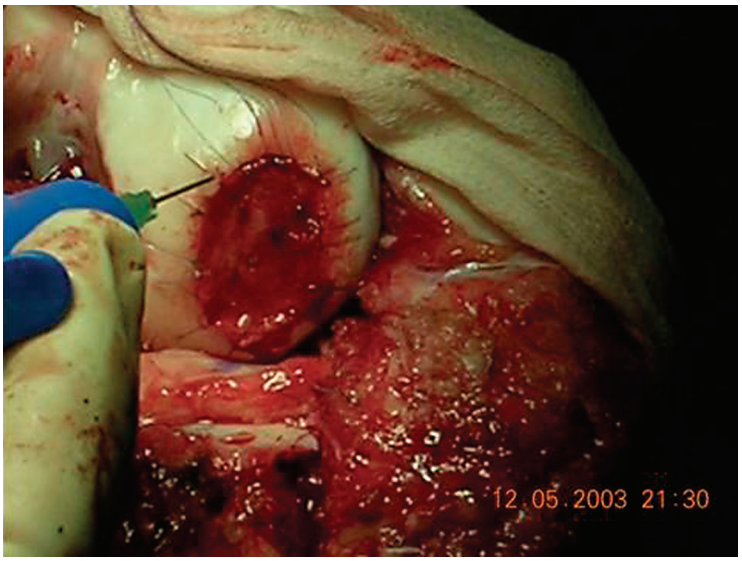


Fig. 10-B

Following implantation, the repair site is protected from damage, and a more aggressive rehabilitation program can be initiated.

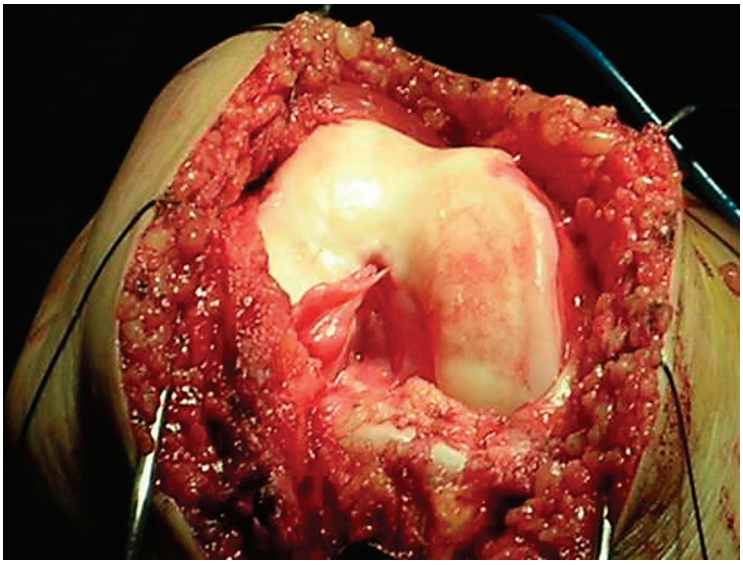

Fig. 10-C

A poorly contained lesion with limited normal articular cartilage margins.

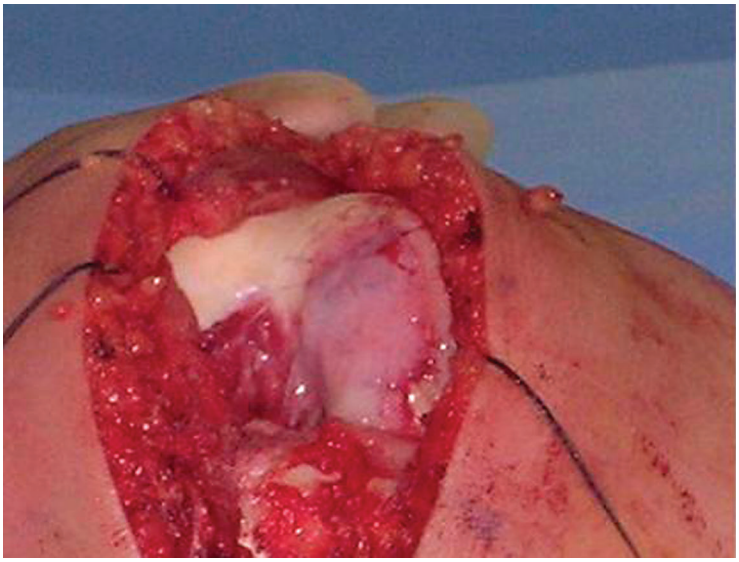

Fig. 10-D

Following implantation, the repair site is not well protected by the surrounding cartilage. Thus, a slower rehabilitation program should be initiated, with full weight-bearing allowed after eight to twelve weeks.

Minas evaluated the health economics of the autologous chondrocyte implantation procedure[58]. He prospectively examined the efficacy of treatment and quality of life of forty-four patients who had undergone the procedure and calculated the average cost per additional quality-adjusted life year. At twelve months after autologous chondrocyte implantation, there was improvement in patient function as measured with both the Knee Society Clinical Rating System (a mean improvement from 114.02 to 140.67 points, $p < 0.001$) and the Western Ontario and McMaster Universities Osteoarthritis Index (a mean improvement from 35.30 to 23.82 points, $p < 0.05$). Quality of life as measured with the Short Form-36 Physical Component Summary improved from a mean of 33.32 points prior to the biopsy to 41.48 points twelve months after implantation ($p < 0.05$). There was additional improvement in all three outcome measures during the following twelve to twenty-four months. As a result of these findings, Minas concluded that autologous chondrocyte implantation improved the quality of life of patients and was a cost-effective treatment for cartilage lesions.

There have been several studies comparing autologous chondrocyte implantation directly with other biologic reconstructive procedures. Horas et al. compared autologous chondrocyte implantation with osteochondral cylinder transplantation in a prospective, single-center study of forty patients assessed at two years[59]. The mean lesion size and the mean age were 3.86 $cm^2$ and 31.4 years in the group treated with autologous chondrocyte implantation and 3.63 $cm^2$ and 35.4 years in the group treated with osteochondral cylinder transplantation. Seven of the twenty patients treated with autologous chondrocyte implantation had undergone a previous abrasion arthroplasty. Two patients treated with osteochondral cylinder transplantation had undergone a previous abrasion arthroplasty, and two had undergone microfracture. The recovery after the autologous chondrocyte implantation was slower than it was after the osteochondral cylinder transplantation as assessed on the basis of the Lysholm score at six months. Both groups had substantial improvement at two years as assessed with the Meyers score and the Tegner activity score. The one failure in the study was of an autologous chondrocyte implantation procedure, but it occurred in the only patient in either group who had treatment of a patellofemoral lesion. This patellofemoral lesion was large (5.6 $cm^2$), and failure was thought to be due to poor rehabilitation. Gross examination revealed complete, mechanically stable resurfacing of all of the defects treated with autologous chondrocyte implantation except for the one failure. Biopsies done in the autologous chondrocyte implantation group showed predominant areas of fibrocartilage

**TABLE II Recommended Operative Treatment According to Lesion Size**

| Recommended Treatment | Lesion Size |
|---|---|
| Microfracture | 1-2.5 $cm^2$; well-shouldered, protected edges |
| Osteochondral autograft | 1-2.5 $cm^2$; grafts need to be perpendicular and flush to surface |
| Autologous chondrocyte implantation | >2 $cm^2$; background factors need to be addressed, patient must be compliant with rehabilitation |
| Osteochondral allograft | >4 $cm^2$; uncontained large lesion involving substantial osseous loss |

with localized areas of hyaline-like regenerative tissue close to the subchondral bone. In the osteochondral cylinder transplantation group, all of the biopsies showed hyaline articular cartilage that was histomorphologically similar to the surrounding cartilage. All specimens from the patients treated with osteochondral cylinder transplantation had a persistent interface between the transplant and the surrounding cartilage, however. One important limitation of the study was the small number of patients in each treatment group, which raises questions about the effect of the learning curve, particularly in association with the autologous chondrocyte implantation procedure, that occurred during the study period. This study also had a relatively short-term follow-up. With longer follow-up, the durability of the repair in both groups may be better delineated.

In a similar prospective, randomized study comparing autologous chondrocyte implantation and mosaicplasty, Bentley et al.[60] assessed 100 consecutive patients with a mean age of 31.3 years and a mean defect size of 4.66 $cm^2$. The mean duration of symptoms prior to the operative repair was 7.2 years, and the mean number of previous operative procedures (excluding arthroscopy) was 1.5. The mean duration of follow-up was nineteen months. Fifty-eight patients underwent autologous chondrocyte implantation, and forty-two patients underwent microfracture. According to the modified Cincinnati Knee Rating System, the Stanmore Functional Rating Scale, and objective clinical assessment, the result was excellent or good in 88% of the patients treated with autologous chondrocyte implantation compared with 69% of those treated with mosaicplasty[61]. Arthroscopic assessment of the lesions with the ICRS grading system at one year demonstrated a grade-I or II appearance in thirty-one (84%) of the thirty-seven patients treated with autologous chondrocyte implantation compared with only eight (35%) of the twenty-three patients treated with microfracture. Biopsies were performed at one year after nineteen autologous chondrocyte implantation procedures; three of the lesions were patellar, and sixteen were femoral condylar. Seven patients had hyaline-like cartilage, seven had a mix of hyaline-like and fibrocartilaginous regions, and five had a fibrocartilaginous material that was well bonded to the subchondral bone. There were seven poor results in the mosaicplasty group, with poor graft incorporation at the interface in four, graft disintegration in three, and exposed subchondral bone at the margin in one.

Autologous chondrocyte implantation has been compared with the Steadman microfracture technique[62] in two studies. In a prospective, concurrently controlled study, Anderson et al. compared the two techniques with twenty-three patients in each group[63]. Defects of <2 $cm^2$ as well as patellar and tibial lesions were excluded. No difference between groups was noted with regard to the overall defect area, body-mass index, number of prior procedures, or baseline scores. The improvements in overall scores from baseline measurements averaged 3.1 points in the group treated with autologous chondrocyte implantation compared with 1.3 points in the microfracture group. Two autologous chondrocyte implantation procedures and six microfracture procedures met the study criteria for failure. When the treatment failures were excluded from each group, those treated with autologous chondrocyte implantation had a mean improvement in the overall condition score of 4.7 points and those treated with microfracture had a mean improvement of 2.8 points. This difference was significant ($p = 0.023$).

In a separate study, Knutsen et al. evaluated eighty patients in whom a single symptomatic cartilage defect of the femoral condyle had been treated with either autologous chondrocyte implantation or microfracture (forty in each group)[64]. Arthroscopic biopsy was done two years postoperatively, and histologic evaluation was performed by a pathologist and a clinical scientist, both blinded to the type of operative treatment. At two years, both groups had significant clinical improvement. However, according to the SF-36 Physical Component score, the microfracture group had significantly more improvement than the group treated with autologous chondrocyte implantation ($p = 0.004$). Two failures occurred in the group treated with autologous chondrocyte implantation, and one occurred in the microfracture group. On review of the biopsy findings, the authors could not find a significant difference between the two groups, with the small numbers studied, with regard to the frequency with which hyaline or fibrocartilage was observed. No correlation between histologic appearance and clinical outcome was found in this study. One important question that arises is whether autologous chondrocyte implantation should have been used as a first-line treatment in many of these patients. The baseline clinical scores in the group treated with autologous chondrocyte implantation were somewhat higher than those in the microfracture group. This concern, combined with the relatively low mean

lesion size in both groups (5.1 $cm^2$ in the group treated with autologous chondrocyte implantation and 4.5 $cm^2$ in the microfracture group), suggests that many of these patients might have been more appropriately treated with a less invasive option. Unlike the microfracture technique, the autologous chondrocyte implantation procedure currently necessitates a concomitant arthrotomy, with its associated morbidity. As a result, most surgeons use the microfracture or mosaicplasty procedure for isolated lesions of <2 $cm^2$ and employ autologous chondrocyte implantation for more extensive lesions causing greater functional deficits[65,66] (Table II).

The experience with the traditional autologous chondrocyte implantation technique—i.e., implantation of autologous chondrocytes with an autologous periosteal patch—is promising. At the current time, minimally invasive procedures such as microfracture or mosaicplasty are probably best for lesions of <2 $cm^2$, but we recommend autologous chondrocyte implantation for lesions of ≥2 $cm^2$ or for patients with multiple lesions (Table II). The repair process is a reproducible sequence of events that occur as the tissue matures. Proper patient selection and education are important for success. Potential long-term benefits of autologous chondrocyte implantation include durable repair tissue that functions in a manner similar to that of normal hyaline cartilage, withstanding the high shear and compressive loads applied during daily and sports activities. The intermediate-term results show that outcomes can improve after the first two years. A direct correlation between biopsies showing hyaline-like repair tissue and better clinical results has been found in several studies. The future of biologic regeneration and tissue engineering for the treatment of articular cartilage defects is promising. With further modifications of the techniques, arthroscopic or minimally invasive methods hopefully will be developed to repair these defects and allow patients to return to normal activity levels on a regular basis.

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