AUTOLOGOUS CHONDROCYTE IMPLANTATION

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Autologous chondrocyte implantation (ACI) has been performed in more than 4,500 patients and, when appropriately indicated, provides durable hyaline-like repair tissue with consistent clinical results. ACI is primarily indicated for full-thickness articular cartilage injuries of the femoral condyles and trochlea. Emerging evidence suggests that it may also have a role in the treatment of patellar defects. The success of ACI is in part attributed to its ability to resolve the limitations of other techniques that are at best palliative or reparative with limited capacity to restore hyaline or hyaline-like tissue. Lesions of the femoral condyles and trochlea can be expected to respond favorably to treatment in greater than 85% of all patients, both clinically and subjectively with follow-up at 2 to 9 years. Patients with multiple lesions or lesions involving the patella have not responded as well, but up to 70% still show improvement with more consistent results if ACI is accompanied by a patellar realignment procedure when indicated.

KEY WORDS: articular cartilage, chondral injury, autologous chondrocyte implantation, cartilage restoration

Treatment of articular cartilage injuries is an evolving science and presents one of the most intriguing challenges in orthopaedics today. Although we do not as of yet have a full understanding of the natural history of articular cartilage lesions, once they become symptomatic, they lead to diminished knee function and progressive deterioration over time with no appreciable inherent healing response. Classic symptoms include pain on weight-bearing, pain associated with swelling after activities, locking, catching, and crepitation.

As part of the overall treatment algorithm described in the article in this issue entitled, "Atlas of Chondral Injury Treatment," there are several treatment options for the symptomatic chondral lesion that are predicated upon patient- and lesion-specific factors. Each option, however, has specific indications and limitations, and thus appropriate decision making is critical to success.[1-3]

Arthroscopic debridement and lavage will effectively reduce inflammatory mediators and temporarily stabilize chondral flaps or fissures, but the clinical results are at best, palliative. Reparative tissue that results from marrow-stimulating techniques, although often quite successful in relieving symptoms from acute and relatively small lesions, tends to deteriorate in larger chronic lesions in physically demanding patients. Osteochondral autografts and allografts are excellent options for certain-sized lesions, but they do require conversion of a superficial chondral lesion into an osteochondral lesion, which may limit the success of future restorative treatment options should these methods fail. Additionally, autografts are limited by potential donor site morbidity, and fresh allografts are fraught with availability limitations and the inherently small but positive risk of disease transmission.

This article specifically discusses the basic science, indications, technique, rehabilitation, results, and complications of autologous chondrocyte implantation (ACI). The initial peer-reviewed publication in 1994 showed good and excellent results in 14 of 16 patients treated on the weight-bearing femoral condyle,[4] since the Food and Drug Administration's approval of the procedure in 1997 based on agreement that ACI provides clinical benefit to patients with symptomatic chondral injury, ACI has been performed in more than 4,500 patients worldwide with more than 9 years of follow-up and has emerged as an accepted treatment option for full-thickness chondral injury. The success of ACI is in part attributed to its ability to resolve the limitations of other techniques that are at best palliative or reparative but have limited capacity to restore hyaline or hyaline-like tissue. When appropriately indicated and with strict adherence to surgical technique, the compliant patient should expect a predictably good or excellent clinical result after ACI.

BASIC SCIENCE OF AUTOLOGOUS CHONDROCYTE IMPLANTATION

Chondrocytes within their natural environment actively synthesize and maintain their surrounding matrix. Because mature chondrocytes have limited ability to proliferate, they are often mislabeled as dormant. In cell culture, however, human chondrocytes regain their ability to proliferate.[5] Thus, the basic premise behind ACI is to overcome the inherent limitations of mature chondrocytes to effectively restore an injured articular surface.

Clinically, the process begins with a biopsy of healthy articular cartilage. The cartilage then undergoes enzymatic degradation, releasing chondrocytes from the surround-

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ing matrix. In monolayer culture, these cells respond by undergoing rapid proliferation. Histologically, these chondrocytes reversibly dedifferentiate, assuming a fibroblastic appearance, and express type I collagen as opposed to type II collagen normally seen in articular cartilage. Once removed from the monolayer culture and placed in suspension or returned to the articular cartilage environment, the cells undergo a redifferentiation process into normal-appearing chondrocytes and again produce type II collagen and proteoglycan aggregates. Importantly, these chondrocyte cells, unlike cells derived from the periosteum or perichondrium, do not express type X collagen, a marker of chondrocyte hypertrophy and bone formation.[5] Therefore, it is less likely that implantation of cultured chondrocytes will result in the endochondral ossification seen after perichondrial or periosteal grafting alone.[6,7]

Limitations in our ability to study the response of implanted cultured chondrocytes in humans have necessitated reliance on the findings of several important animal studies. Rabbit studies evaluating tritiated thymidine–labeled chondrocytes show that in vitro cultured chondrocytes are largely responsible for the repair tissue formed in vivo.[8] Additional studies determined that the combination of autologous chondrocytes and periosteum is superior to periosteum alone in the quantity and quality of the repair tissue formed.[9]

Canine studies show that implanted chondrocytes undergo a sequential pattern of healing including proliferation, transition, and remodeling with maturation.[10] The proliferation stage (0 to 6 weeks) is marked by the rapid filling of the defect with a poorly integrated and mechanically vulnerable primitive repair tissue predominately consisting of type I collagen. This corresponds with the protected weight-bearing phase of the postoperative rehabilitation.

The transition stage (7 to 12 weeks) is characterized by the progressive production of extracellular matrix and type II collagen, with a gradual increase in tissue firmness resembling a firm gelatin. Similar to the proliferation stage, this tissue is poorly integrated and continues to be soft and ballotable. Clinically, this corresponds with a gradual increase in patient weight-bearing and restoration of muscle function.

The remodeling stage begins at about 3 months and the tissue continues to mature for at least 3 years. The tissue integrates and stabilizes to the surrounding cartilage and subchondral bone showing increased mechanical strength due to increased cross-links between matrix proteins and stabilization of the collagen framework into the subchondral bone. Clinically, this corresponds to significant symptom relief and increased function. Over the course of 9 to 18 months after implantation, the tissue becomes firmer, achieving equal firmness to the surrounding cartilage. At this point, high-level pivoting activities are tolerated with minimal symptoms.

Serial second look arthroscopies confirm that the hyaline-like cartilage forms after ACI and progressively stiffens over time. Continued maturation has been observed for up to 3 years after ACI. Excessive activities leading to recurrence of symptoms, however, may be cause for concern because of the potential for repair tissue degeneration during maturation.[11]

INDICATIONS

Current indications for ACI consider patient- and defect-specific factors. Patients between 15 and 50 years of age who are motivated and compliant with at least moderate symptoms caused by full-thickness chondral injuries of the distal femur limiting athletic and daily living activities are basic considerations for ACI. Not uncommonly, these patients have failed previous treatment attempts including debridement and lavage, marrow stimulation, or osteochondral autograft procedures.

ACI is currently indicated for symptomatic, unipolar, full-thickness (ie, Outerbridge[12] grade III or IV) articular cartilage lesions of the distal femur (ie, medial and lateral femoral condyles or trochlea) ranging in size between 2 to 12 cm^2. Osteochondritis dissecans (OCD) is also an indication for ACI providing bone loss is limited to less than 6 to 8 mm. Greater depths of bone loss should be bone grafted before ACI, or alternative techniques, such as osteochondral allografts, should be considered. Reciprocal lesions, when present, should be no more than Outerbridge[12] grade I or II. Experience with the treatment of patellar and tibial lesions is increasing, and specific indications are currently undergoing refinement. Patellar lesions may require concomitant correction of existing patellofemoral malalignment to increase the success of ACI.

Osteoarthritis, as indicated by joint space narrowing best seen on preoperative 45° flexion posteroanterior weight-bearing radiographs,[13] with or without subchondral sclerosis, cyst formation, and marginal osteophytes are relative contraindications to ACI. ACI may be performed in patients with malalignment or ligament instability provided that the associated pathology is addressed through bony realignment or ligament reconstruction either before or concomitantly with ACI. Earlier subtotal or total meniscectomy is another relative contraindication, and allograft meniscal transplantation is considered as a concomitant procedure when necessary.

PATIENT ASSESSMENT

Typical patient complaints include knee pain localized to a particular compartment that is aggravated by activities that stress the involved region. Weight-bearing activities may exacerbate medial and lateral compartment disease, and sitting or climbing may exacerbate patellofemoral disease. A review of available operative notes and arthroscopic pictures is particularly helpful to define previous treatment and defect characteristics.

The physical examination includes assessment for significant lower limb malalignment and gait abnormalities. Localized tenderness related to the articular lesion is inconsistent. A positive patellar grind test may indicate a trochlear lesion, whereas joint line tenderness may indicate an associated meniscal tear. A thorough ligament examination is performed for sagittal plane (ie, anterior or posterior cruciate ligament); coronal plane (ie, medial or lateral collateral ligament); or rotational instability (ie, pos-

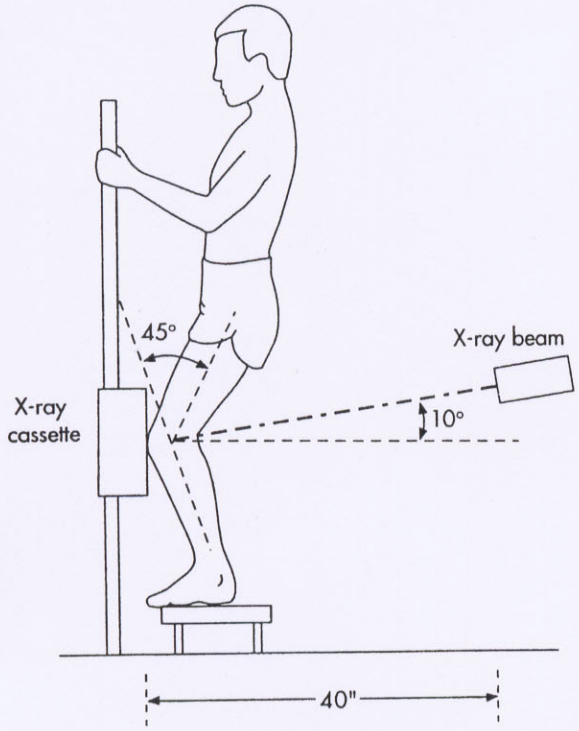


Fig 1. An example of the technique for obtaining the 45° flexion weight-bearing posteroanterior radiograph. (Adapted and reprinted with permission[13]).

terolateral corner). Evaluation for excessive lateral retinaculum tightness or for apprehension with lateral patellar glide is performed to rule out patellofemoral problems.

Radiographic evaluation should include an extension weight-bearing anteroposterior, supine lateral, 45° flexion weight-bearing posteroanterior view (Fig 1) and a merchant or skyline view. Assessment of bone quality and involvement (ie, OCD), alignment, and the degree of arthritis is performed. If malalignment is of concern, a full length weight-bearing mechanical-axis view should be obtained.

Magnetic resonance imaging (MRI) of the knee does not reliably add to the overall assessment of the cartilage surfaces. Some cartilage lesions may be seen with MRI, but currently the sensitivity and specificity are not sufficient to warrant its routine use for preliminary assessment of cartilage lesions.[14] MRI is helpful, however, in the assessment of the subchondral bone (ie, avascular necrosis and OCD) and for determining associated ligament or meniscal injuries.

ARTHROSCOPIC ASSESSMENT

Arthroscopic evaluation of the joint surfaces is currently the gold standard for assessment of chondral lesions. At the time of arthroscopy, a careful and systematic assessment of the entire joint is performed. The chondral surfaces are probed gently and areas of softening or fissuring are noted in addition to any grossly visible defects. Defect assessment includes measuring its dimensions, location, depth, the quality of the surrounding tissue, the condition of the opposing surface, and the knee flexion angle leading to lesion contact with the opposing surface (Fig 2). The quality of the tissue along the defect boundaries is documented because it directly affects periosteal patch suturing at the time of ACI. The menisci and cruciate ligaments are probed for any tears. Meniscal tears, when relatively small (ie, 20% to 30% of the ipsilateral meniscus), are not considered a contraindication to ACI and are usually managed at the time of arthroscopy and cartilage biopsy.

CARTILAGE BIOPSY

A biopsy is performed with the explicit intention to treat a cartilage lesion with ACI and should otherwise be delayed until clear indications exist because of the significant resources associated with a routine biopsy. Once the criteria for ACI are met, a full-thickness biopsy of the host articular cartilage is arthroscopically performed with a sharp ring curette or gouge. Loose or ectopic articular cartilage originating from the defect is not suitable as it may be biologically compromised. The primary site for cartilage biopsy is the superior medial edge of the trochlea (Fig 3). Occasionally, the medial facet of the patella may overhang this region, and the superior lateral edge of the trochlea may be a more suitable biopsy location. The senior author (B.J.C.) prefers the lateral intercondylar notch in the region where anterior cruciate ligament (ACL) notchplasty is regularly performed (Fig 4). An additional site includes the superior transverse margin of the proximal femoral articular surface adjacent to the supracondylar synovium obtained through a separate superior portal.[15]

The biopsy specimen should be 200 to 300 mg in total weight, normally containing between 200,000 to 300,000 cells. This represents a full-thickness area of articular cartilage of approximately 5 mm × 10 mm, which is enough to cover the bottom of the biopsy specimen medium container. The biopsy specimen is placed into the sterile me-

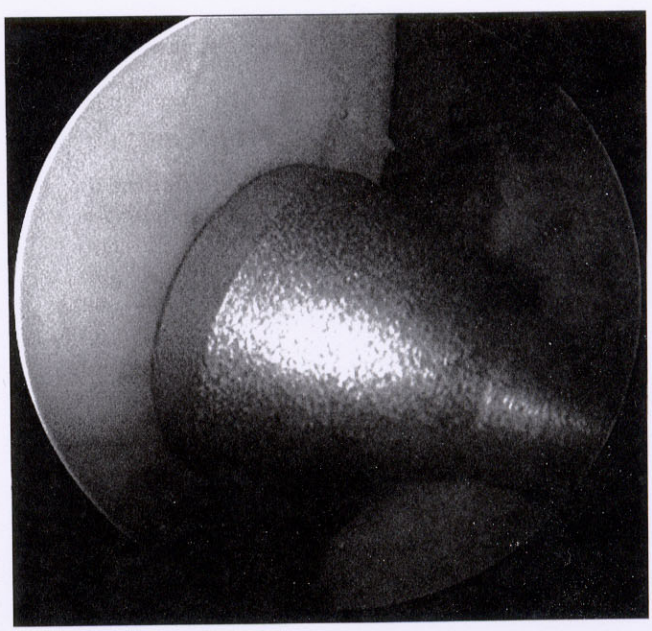


Fig 2. An example of symptomatic focal chondral defect measured with a commercially available sizing tube (Arthrex Corp, Naples, FL).

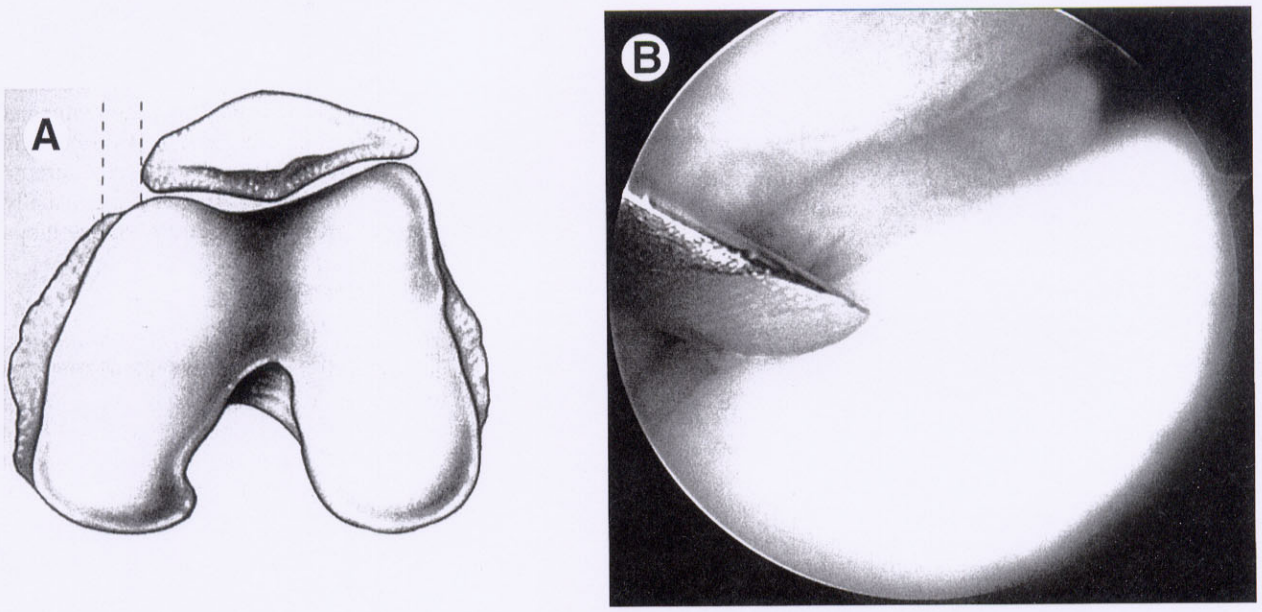


Fig 3. (A) An example of the traditional site for chondral biopsy, the superior medial trochlear ridge. (Adapted and reprinted with permission[15]). (B) This shows arthroscopic technique that uses a curved gouge placed through the inferomedial arthroscopic portal.

dia and sent overnight at 4°C to Genzyme Biosurgery Corporation (Cambridge, MA) for processing.

The cartilage biopsy specimen can be maintained under strictly sterile condtions for up to 18 months until it is processed and undergoes cellular expansion over the course of 3 to 5 weeks. The result is a suspension of autologous-derived chondrocytes on the order of 12 million cells per 0.4 mL of culture media. Multiple defects (each 6 to 10 cm^2) require that multiple vials of cells be processed from the same original biopsy specimen.

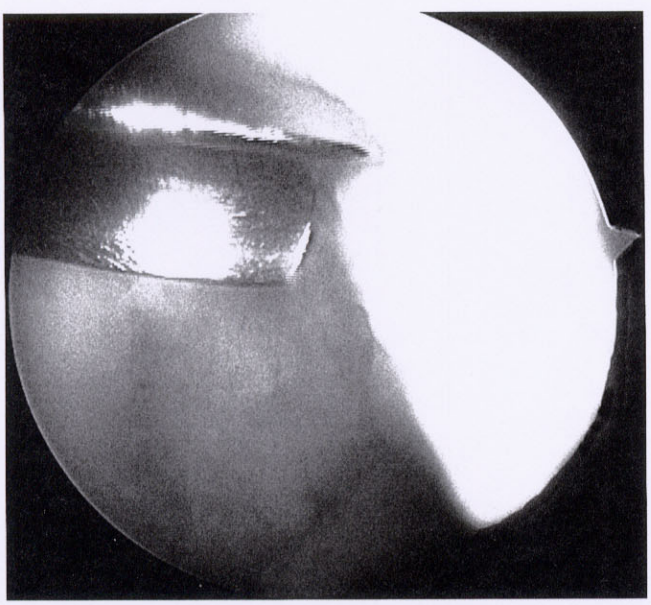


Fig 4. An example of the author's preferred biopsy site, the lateral intercondylar notch in the region where ACL notchplasty is regularly performed.

IMPLANTATION OF AUTOLOGOUS CHONDROCYTE CELLS

Surgical Exposure

Prophylactic antibiotics are administered and the patient is positioned supine on the operating table with entire lower extremity sterilely prepped and draped, allowing full mobility of the knee into extreme flexion. If the tourniquet is used during the initial portion of the procedure, it should be deflated after periosteal patch harvest to ensure hemostasis. If more than 12 to 16 weeks have passed from the time of cartilage biopsy, a brief arthroscopic evaluation will confirm that the knee still meets the criteria for ACI.

We prefer a midline incision because of its greater utility for future procedures should they be necessary. Depending on the compartment involved, a medial or lateral parapatellar arthrotomy is made through the midline incision. Medial femoral condylar defects typically require larger incisions than trochlear or lateral condylar defects because of the position and mobility of the patella. Posteriorly located lesions will require additional knee hyperflexion and may require a larger arthrotomy with subluxation or dislocation of the patella to facilitate exposure. A commercially available lower extremity positioning device is also helpful in this regard.

Defect Preparation

Defect preparation requires that the remaining cartilage walls be healthy, full thickness, and firmly attached. Fissured or delaminated cartilage will not provide a secure platform for suturing and containment of the implanted cells and must be debrided. A fresh no. 15 scalpel blade and sharp ring curettes are used to incise the defect border

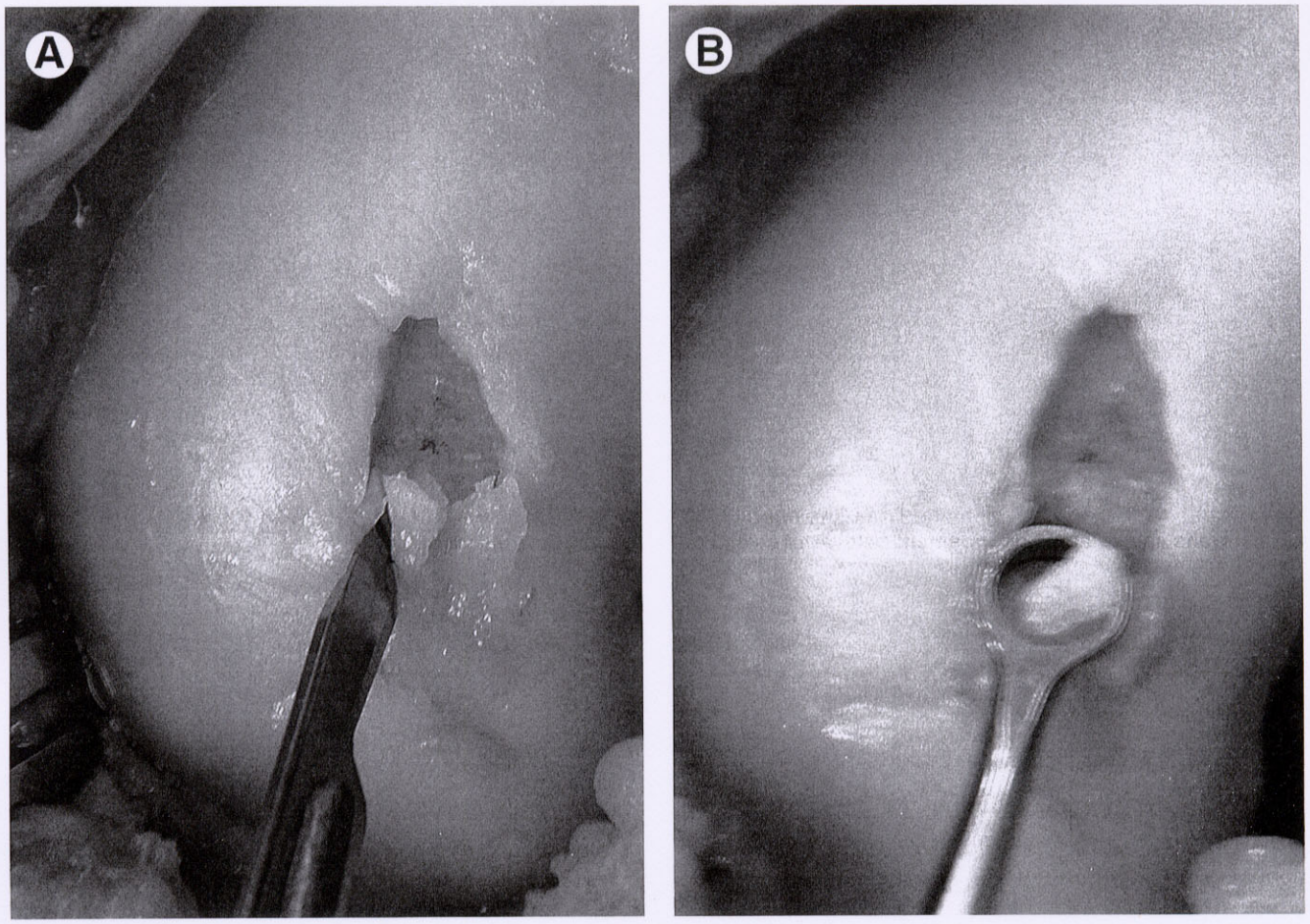


Fig 5. (A) A fresh no. 15 scalpel blade and (B) sharp ring curette are used to incise the defect border through the cartilage down to the level of, but not into, the subchondral bone. Care is taken to ensure the walls of the remaining cartilage are vertically oriented.

through the cartilage down to the level of, but not into, the subchondral bone to prevent bleeding into the defect, which may adversely affect implanted chondrocytes. Care is taken to ensure the walls of the remaining cartilage are vertically oriented (Fig 5, 6). If the defect lies close to the border of the articular surface, it may be better to leave mildly injured articular cartilage at the edge of a lesion to maintain a contained defect, rather than remove it and create an uncontained defect.

Obtaining Hemostasis

Hemostasis is controlled with the use of neuro-patties soaked with a dilute 1 to 1,000 epinephrine and sterile saline solution. Applying thrombin directly to the site of bleeding may be helpful if hemostasis is still not achieved. Bleeding may be especially difficult to control in patients who have previously undergone a marrow-stimulating technique (Fig 7A-E). As a last resort, hemostasis can be obtained by using a needle tipped electrocautery device to cauterize only the bleeding points, not the entire base of the defect.

Defect Sizing

Defect dimensions are measured and documented by using a sterile ruler. A template of the defect can be made by placing a sterile tracing material (ie, sterile transparent x-ray film) over the defect and outlining the defect with a marking pen. The template is cut and used during periosteal patch procurement (Fig 8).

Harvesting the Periosteal Patch

The periosteal patch is harvested through a 3-cm incision on the subcutaneous medial border of the proximal tibia, 2 finger breadths distal to the pes anserine tendon attachments (Fig 9). Gentle blunt dissection is used to develop the plane between the periosteum and overlying subcutaneous fat and fascia. Electrocautery should be used only superficially, if absolutely needed, and never on or near the periosteum. The outer surface should be marked to distinguish it from the inner cambium layer. Because the periosteum has a tendency to shrink slightly after harvest, oversizing the patch template by 2 mm in each dimension ensures an adequate fit.

A fresh no. 15 scalpel blade is used to incise the periosteum down to the underlying bone. A sharp curved-tip periosteal elevator is used to slowly and carefully perform subperiosteal dissection off of the underlying bone from distal to proximal, minimizing side-to-side motion to prevent inadvertent tearing of the patch (Fig 10). Smooth forceps are used to provide

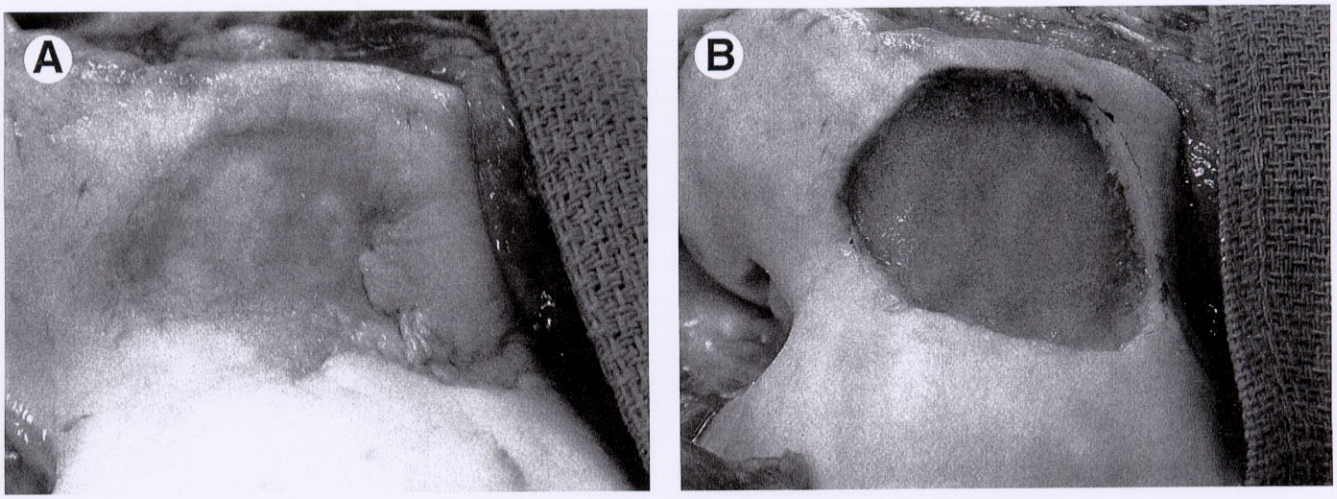


Fig 6. (A) An example of trochlear defect before debridement and (B) immediately after debridement. Care is taken to create vertical walls and to avoid debridement below the calcified layer to prevent bleeding.

countertraction and raise the leading edge of the periosteum. Just enough force is used to elevate and incise the patch at the junction of the bone and Sharpey's fibers while avoiding penetration of the underlying bone. If the periosteum does tear during harvest, it can be repaired during suturing. In the event that the patch is inadequate, a second patch can be harvested from an adjacent area of periosteum. It should be noted that the periosteum tends to become thinner with age and as one moves distally down the tibia.

Securing the Periosteal Patch

At this point the tourniquet should be deflated and hemostasis obtained within the defect. The periosteum should be kept moist at all times, both to minimize shrinkage and to maintain the viability of the cambium layer. The patch should be trimmed to sit within the edges of the defect, not overlapping them. The periosteum is secured with 6-0 absorbable Vicryl suture on a P-1 cutting needle. The suture should be coated in sterile glycerin or mineral oil to facilitate smooth passage through the periosteum and cartilage and to prevent tearing of either tissue.

Proper suturing technique begins with the passage of the needle through the periosteum from outside to inside approximately 2 mm from the tissue edge. The needle is then placed from inside to outside through the cartilage. The needle should enter the cartilage perpendicular to the inside wall of the defect at a depth of 2 mm below the articular surface and exit the articular surface 3 mm from the edge of the defect. Following the curve of the needle will avoid bending or breaking the needle and prevent the needle from tearing through the tissue. The sutures are tied gently, with the knot placed over the periosteal patch at the junction of the patch and articular cartilage. The most efficient method is to start with sutures placed at the 4 corners of the defect. The sutures are then placed alternately around the defect, maintaining equal tension across the periosteum and leaving a space underneath for placement of the chondrocyte cells. The sutures are spaced approximately 3 to 4 mm from each other to provide a watertight seal (Fig 11). Uncontained defects may require suturing through the surrounding synovium, cruciate ligament edge, or small drill holes made with a Kirshner wire. A small opening, about 6 mm in width, is left at the proximal end of the defect to facilitate access with the 18-gauge catheter used for water-tightness testing and later, for injection of the cells.

Water-tightness testing is performed with a saline-filled tuberculin syringe and 18-gauge catheter to ensure cell containment and to prevent defect contamination from the postoperative hemarthrosis (Fig 7F,G). Leakage seen around the periphery should be sealed with additional sutures. After confirmation of a watertight periosteal patch, the saline should be aspirated from within the defect, leaving a dry bed. This will prevent dilution of the cells and promote cell adherence.

Sealing with Fibrin Glue

The periosteal patch may then be sealed with fibrin glue. Autologous fibrin glue is formed with the cryoprecipitate prepared from 1 U of whole donated blood, combined with a mixture of bovine thrombin and calcium chloride. Alternatively, commercially available fibrin glue (Tisseel, Baxter Healthcare Corporation, Glendale, CA) may be used and is the preferred method of the senior author (B.J.C.) because of the convenience and quality of the sealant. The surrounding articular cartilage is dried gently, and the fibrin glue is applied along the edges of the defect, augmenting the watertight seal verified by a second water-tightness test performed as previously described.

Chondrocyte Handling and Injection

The autologous chondrocyte cells arrive in a small vial with enough cells and solution to fill a defect or defects totaling approximately 6 to 10 cm^2. If the total defect size is greater than this, additional vials may be requested before surgery. The suspension medium should be clear and the cells appear as an off-white pellet at the bottom of the vial (Fig 7H). If the solution is turbid or cloudy before resuspension, the vial should be discarded. The exterior of the vial is not sterile, and careful handling is required to

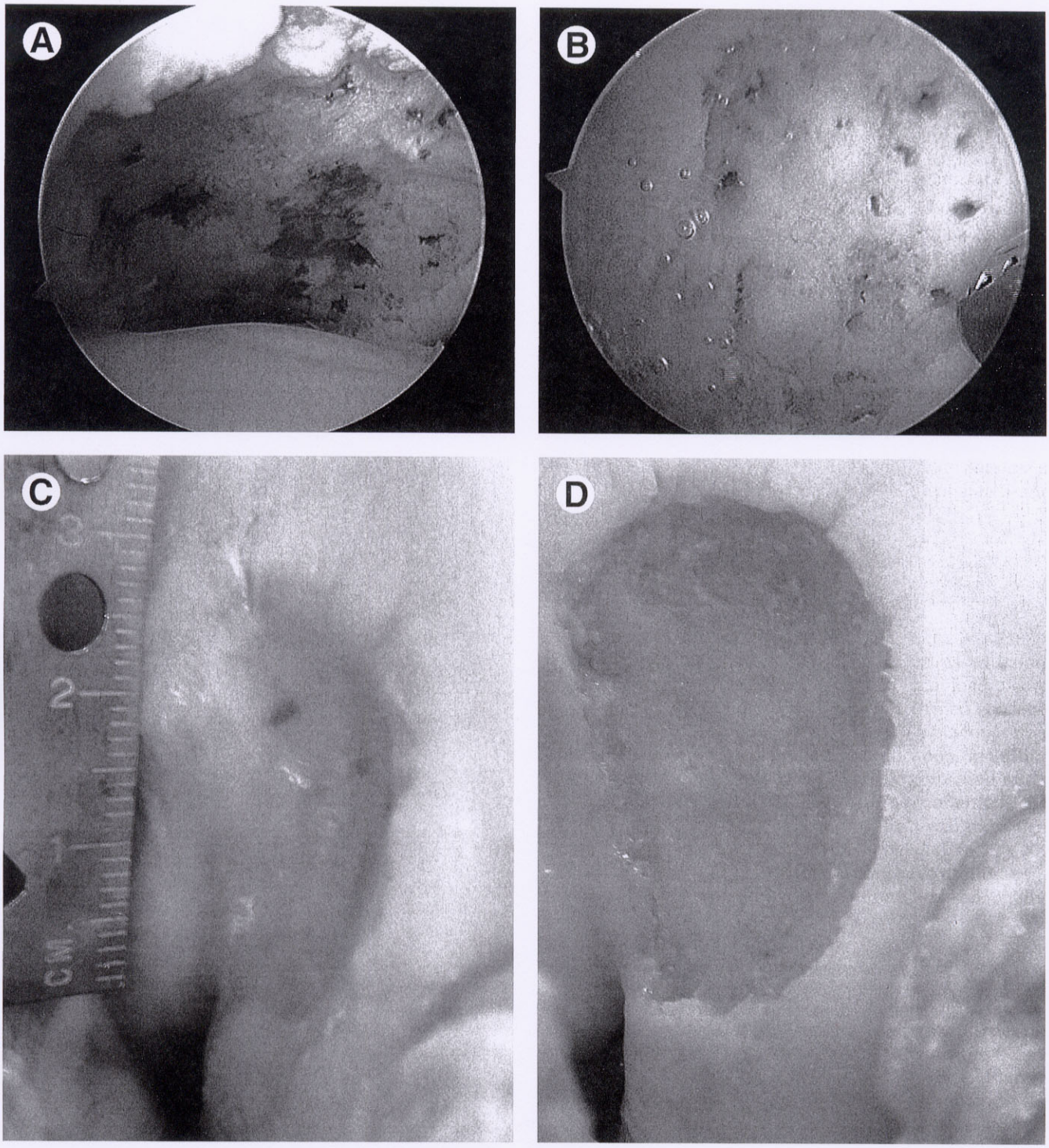


Fig 7. A treatment series for lateral femoral condyle defect. (A) Index defect at time of arthroscopy. (B) Microfracture treatment of index defect. (C) Fibrocartilage fill of defect at 12 months seen at time of arthrotomy for ACI because of persistent symptoms. (D) Defect after debridement at the time of ACI. (E) Hemostasis obtained with neuro-pattie soaked in 1:1000 ratio of epinepherine and sterile saline solution. (F) Periosteal patch sewn into place and tested for water tightness through remaining proximal opening. (G) Fibrin glue applied to edges at patch-cartilage junction. (H) Cells at time of implantation before resuspension. (Figures 7E through H are on the next page.)

ensure sterility of the contents during resuspension, aspiration, and implantation.

The vial is held in a vertical position, the lid is removed, and the top is wiped with alcohol. A sterile 18-gauge catheter with the metal needle in place is inserted into the vial and advanced until the tip lies just above the fluid. (Smaller gauges will damage the cells.) The metal needle is withdrawn, leaving the plastic catheter tip within the vial. A sterile tuberculin syringe is reattached to the catheter, and the fluid is aspirated into the syringe, leaving the cells

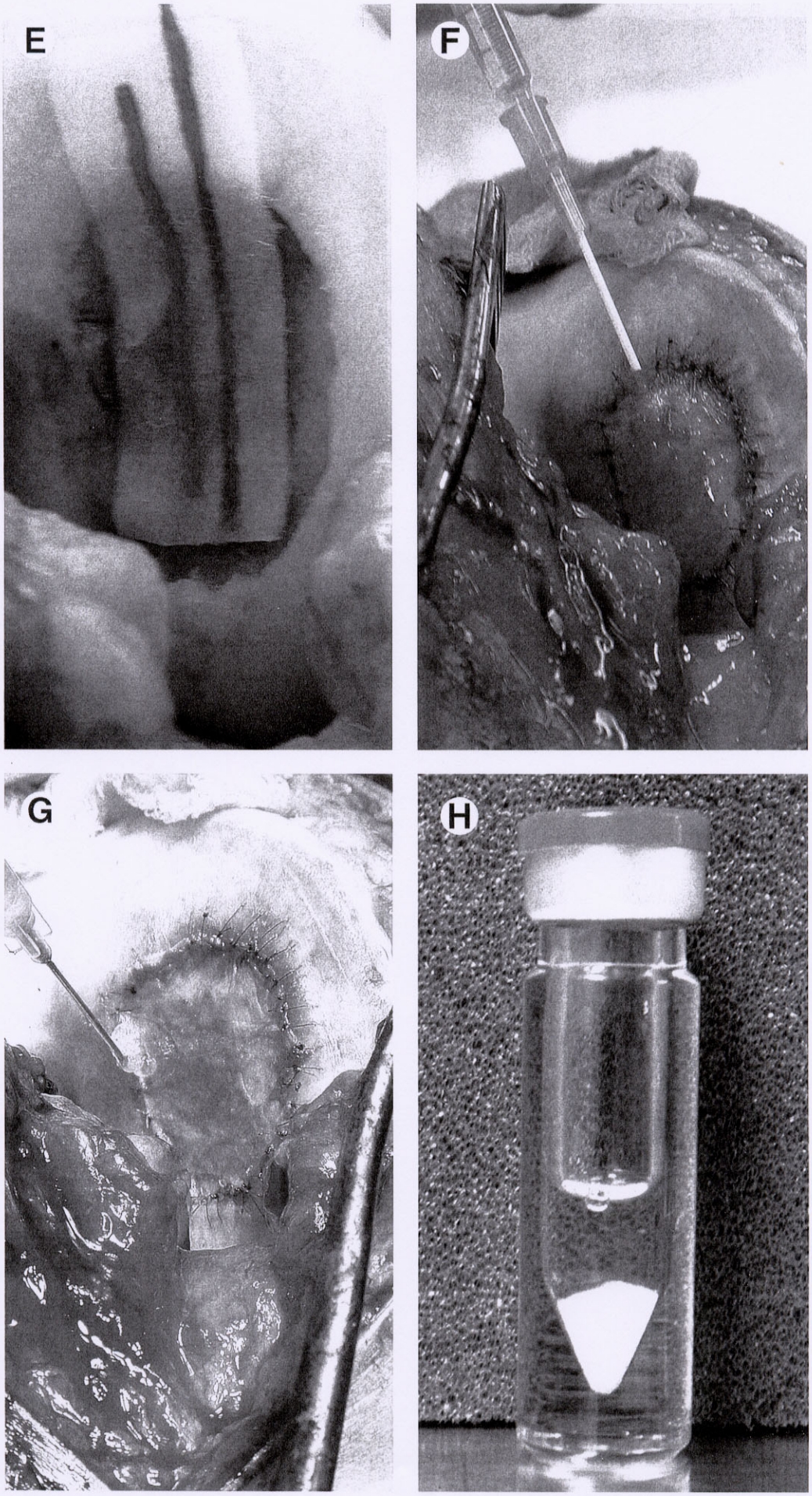
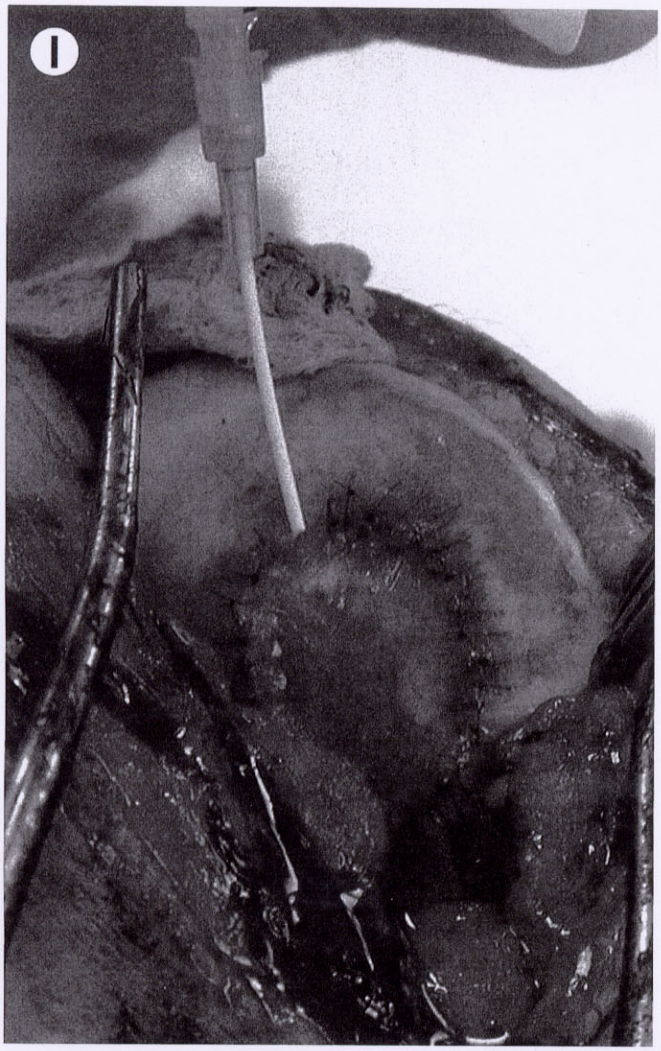


Fig 7 (cont'd).



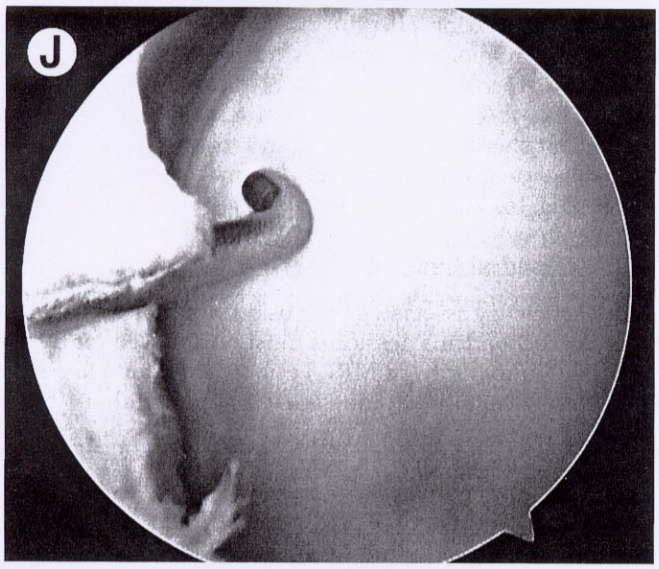


Fig 7 (cont'd). (I) Cells injected beneath patch before defect closure. (J) Second-look arthroscopy at 12 months showing firm hyaline-like cartilage with excellent integration with surrounding articular cartilage.

behind, and then the fluid is gently injected back into the vial, resuspending the cells within the fluid. The process is repeated until a uniform suspension is achieved whereby entire contents of the vial are aspirated into the syringe and the syringe and catheter are carefully withdrawn from the vial. The syringe is maintained vertically with the tip down to maintain the air pocket proximal to the cell solution. Inadvertant syringe detachment during withdrawal can lead to contamination or critical cell loss.

The catheter is then placed through the opening at the top of the defect and advanced to the distal end. The cells are slowly injected into the bed of the defect with a side-to-side motion while the catheter is slowly withdrawn to the opening of the defect (Fig 7I, J). If multiple defects are treated with a single vial, care must be taken to distribute the volume of cells proportionally, 1 vial at a time. The opening at the proximal end of the defect is closed with additional sutures and sealed with fibrin glue. Arthrotomy closure is carried out in a layered fashion, and a soft sterile dressing is applied to the knee. The use of drains is avoided to prevent damage to the periosteal patch and loss of the implanted chondrocytes.

ADVANCED TECHNIQUES

Malalignment

Severe varus or valgus malalignment is addressed before or at the time of ACI to reduce the mechanical load placed across the involved region (Fig 12). If performed concomitantly, fixation must be sufficient to allow postoperative rehabilitation to proceed without modification, including continuous passive motion (CPM) and early active range of motion. The timing of such procedures is often difficult to determine, but the senior author (B.J.C.) will often first perform an osteotomy in patients over aged 40 to 45 years and then reassess the need for cartilage restoration over the ensuing postoperative 3 to 6 months based on the patient's initial treatment response.

Patellofemoral Lesions and Malalignment

Patellofemoral lesions require special consideration. Lesions of the trochlea should be prepared with the periosteal patch sewn in such a fashion to maintain the biconcave anatomy of the normal trochlear groove. Placing sutures in a generously oversized periosteal patch at the apex of the proximal and distal extent of the lesion will help to prevent tenting of the patch over the entire defect, which may inadvertently lead to abnormal trochlear anatomy after cartilage restoration (Fig 13). Similar considerations are relevant to certain lesions of the patella. Additionally, patella lesions should be prepared such that the angle of the proximal and distal cartilage walls are incised obliquely at a 30° to 45° angle to minimize shear stress during proximal-distal excursion that occurs with knee motion (Fig 14).

Trochlear and patellar lesions may be associated with abnormalities of the extensor mechanism complex including patellofemoral instability, lateral retinacular tightness, increased quadriceps angle (ie, Q angle), or more rarely, trochlear hypoplasia. Isolated tibial tubercle anteromedi-

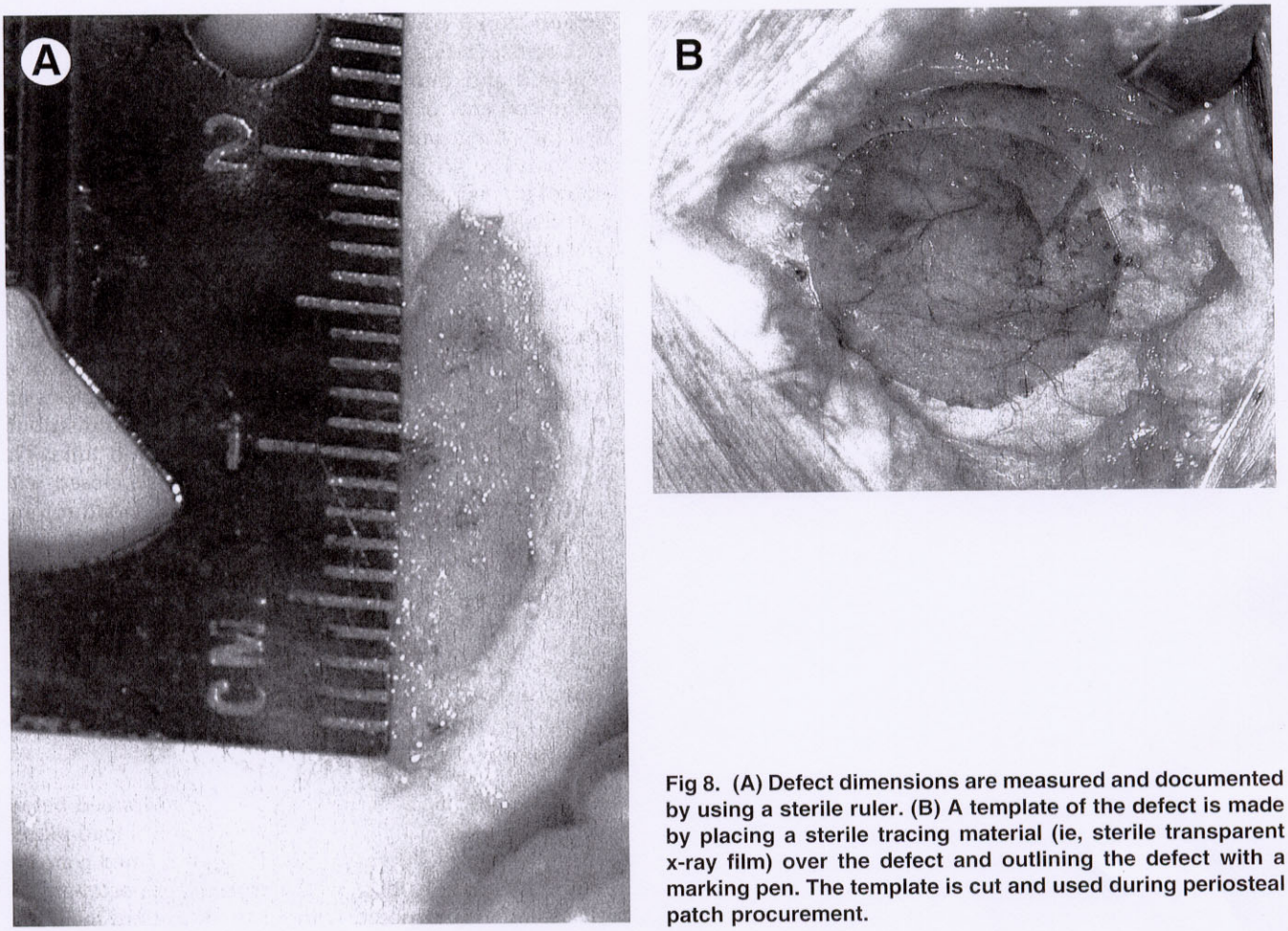


Fig 8. (A) Defect dimensions are measured and documented by using a sterile ruler. (B) A template of the defect is made by placing a sterile tracing material (ie, sterile transparent x-ray film) over the defect and outlining the defect with a marking pen. The template is cut and used during periosteal patch procurement.

alization as popularized by Fulkerson et al[16] is an excellent treatment option for patellofemoral instability associated with articular cartilage defects of the patella, but performed in isolation, is less successful for trochlear defects.

The senior author (B.J.C.) favors combining this operation with the majority of trochlear lesions (especially when laterally based) and all patellar defects with any history of patellofemoral instability. Typically, a more vertical osteotomy is performed to maximize anteriorization in combination with a lateral release and medial reefing with severe patellofemoral instability (Fig 15).

Concomitant Ligament Tears

Ligamentous insufficiency is best treated with a ligament reconstruction, as indicated, before or concomitantly with the resurfacing procedure to optimize healing of the articular defect and to minimize shear forces on the ACI graft. In general, when performed concomitantly, rehabilitation should respect the ACI for the first 6 to 9 months, after which more aggressive rehabilitation can be undertaken. If the procedures are staged, we recommend waiting at least 4 months after ACL reconstruction (Fig 12) and 6 months after posterior cruciate ligament reconstruction before ACI is performed.

Meniscal Deficiency

Minimal meniscectomy (ie, central or involving 20% to 30% of the meniscus) is not a contraindication to ACI. Significant ipsilateral meniscal deficiency is a relative contraindication to ACI because of loss of the load sharing role and stabilizing effect of the meniscus, and thus we will perform allograft meniscus transplantation as a concomitant procedure. Before the arthrotomy required for ACI, all arthroscopic steps required for the meniscus transplant should be performed and the meniscus is sewn into place to avoid iatrogenic trauma to the periosteal patch (Fig 16).[17]

Osteochondral Lesions

Bony deficiency associated with osteochondral fractures or with osteochondritis dessicans must be assessed for depth by plain radiographs or MRI. Lesions less than 6 to 8 mm in depth generally respond well to ACI without bone grafting. Lesions deeper than 1 cm should be grafted before ACI, followed by a 6- to 9-month interval to allow for bone graft maturation. Alternatively, a fresh osteochondral allograft may be an excellent option, especially in relatively older individuals with larger lesions.

POSTOPERATIVE REHABILITATION

A balance between knee function and protection is achieved through a 4-phase rehabilitation protocol. Adherence to strict guidelines regarding motion, weightbearing, and strengthening will provide the best opportunity to achieve full range of motion, and functional

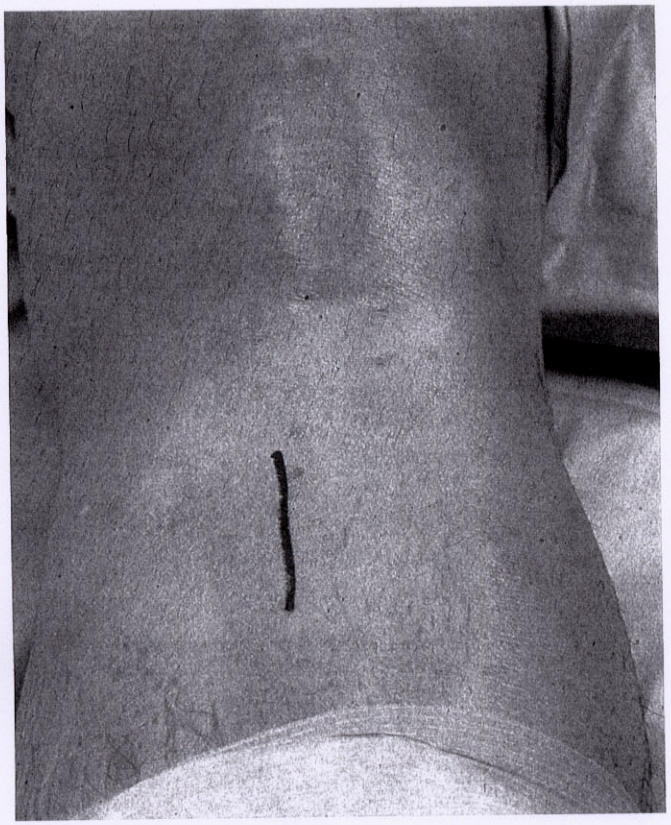


Fig 9. The periosteal patch is harvested through a 3-cm incision on the subcutaneous medial border of the proximal tibia, 2 finger breadths distal to the pes anserine tendon attachments.

recovery while minimizing the risk of mechanical overload during graft maturation.

Early Phase (Postoperative 0 to 6 Weeks)

CPM is started as early as 6 hours after surgery because cell adherence had occurred by that time. CPM has a beneficial effect on the quality of the repair tissue and on the degree of defect fill.[18-20] CPM is performed for 6 to 8 hours per day at 1 cycle per minute in 2-hour increments during the early phase. For femoral condyle lesions, CPM begins initially from 0° to 45° of flexion and is gradually increased as tolerated. Trochlear lesions are initially limited to 45° of flexion to minimize patellofemoral contact forces. A brace maintains the leg in extension, and touch-down weight-bearing with crutches for femoral condyle lesions and partial weight-bearing for trochlear lesions are allowed. Strengthening focuses primarily on quadriceps reactivation with isometric contraction and modalities to limit pain and effusion while promoting return of quadriceps function. Progressive resistance exercises begin and the brace is discontinued once the extension lag is eliminated during straight leg raise.

Transition Phase (Postoperative 6 to 12 Weeks)

Full knee motion is achieved and weight-bearing is progressed 20% per week until full with simultaneous weaning of crutches to a cane until normal gait is obtained. Strengthening exercises include short-arc closed chain activities (ie, bicycling, leg press, and squats). Patients with trochlear lesions should avoid deep knee flexion during strengthening exercises and should continue to focus on straight leg raises and short-arc closed chain activities. Functional training begins and focuses on a return to sport-specific activities and cardiovascular, proprioceptive, and plyometric training techniques.

Maturation Phase (Postoperative 3 to 5 Months)

Full motion is maintained during this phase. Strengthening may continue to progress to wider arcs of motion with increased resistance. Trochlear repairs are still restricted from deep flexion exercises. Open chain extension is avoided in all patients. Functional training is advanced within the guidelines established for weight-bearing and strengthening.

Final Phase (Postoperative Month 6)

The final phase continues until a full return to activities is allowed. This may be as soon as 12 months for small and moderate-sized condylar lesions, or as much as 18 months in larger condylar lesions or after trochlear repairs. The progression is governed by the individual's healing response and symptom profile. Weight-bearing is progressed from walking to jogging, and finally, to running. Strengthening continues to progress, as does the functional training program, to achieve a functional level at or above 85% of the uninvolved extremity. Symptoms of pain, chronic effusions, locking, or catching may indicate that the rehabilitation program may be progressing too quickly for that patient. A reduction in activities to a level tolerated by the patient should be implemented, followed by a gradual progression.

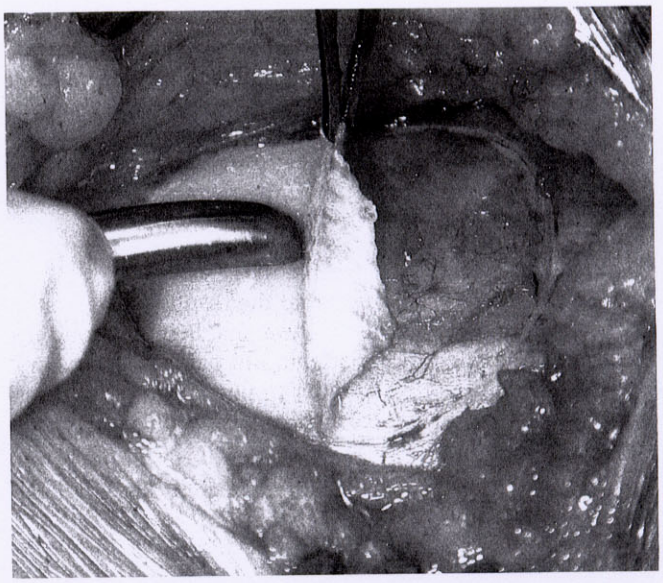


Fig 10. A fresh no. 15 scalpel blade is used to incise the periosteum down to the underlying bone. A sharp curved-tip periosteal elevator is used to slowly and carefully perform subperiosteal dissection off of the underlying bone from distal to proximal, minimizing side-to-side motion to prevent inadvertent tearing of the patch.

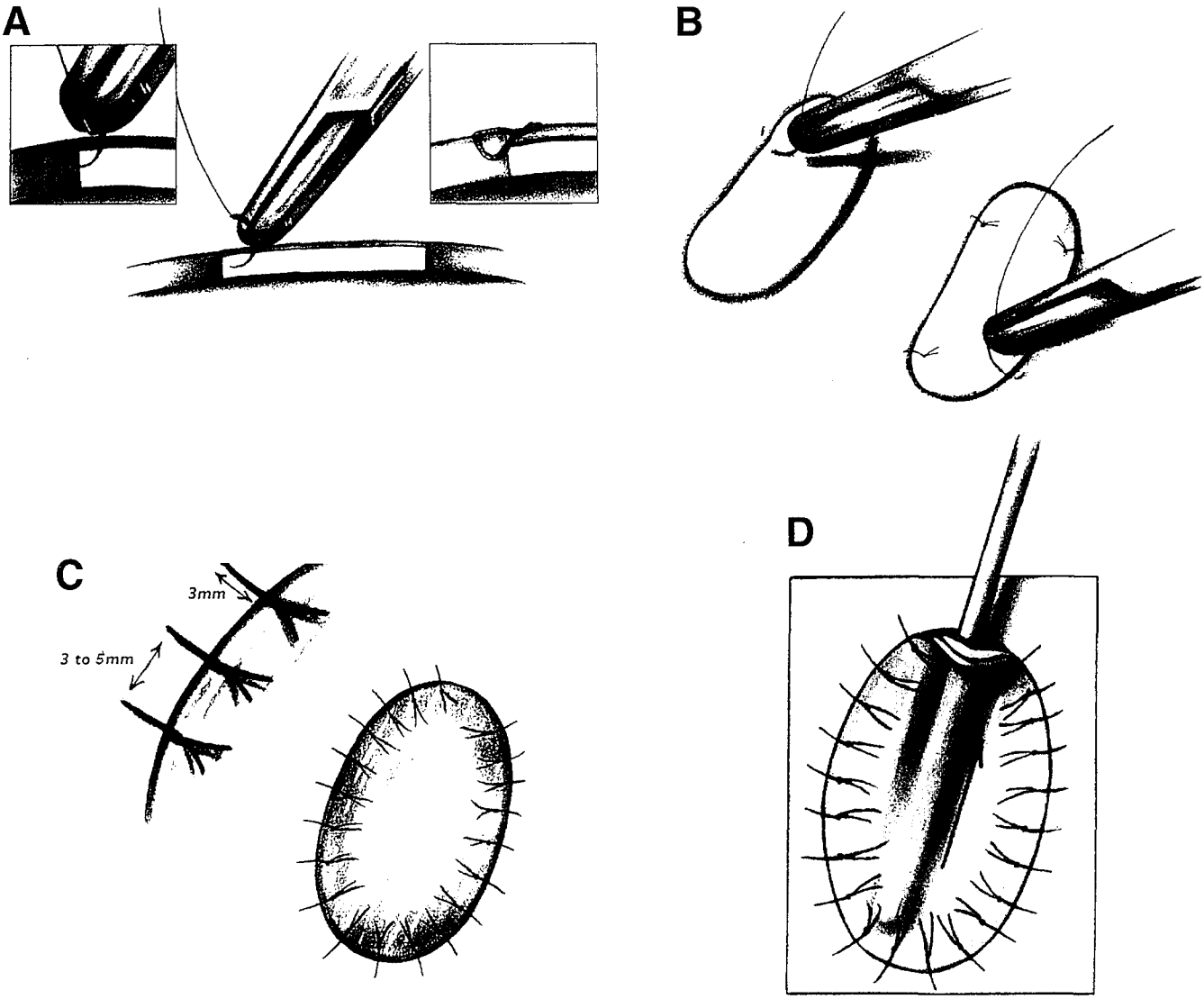


Fig 11. (A) Periosteal suturing is performed such that the knots are tied on the periosteal surface at the junction of the cartilage border. (B) Alternating suture technique to ensure balanced tightening of the periosteal patch. (C) Sutures are placed at a distance of 3 to 5 mm apart to ensure water tightness as as shown in (D). (Adapted and reprinted with permission[15]).

RESULTS

The Swedish Experience

In 1994, Brittberg et al[4] presented the results of the first 23 ACI procedures performed in humans. Femoral condylar lesions were treated in 16 patients and patellar lesions in 7. Follow-up averaged 39 months (range, 16 to 66 months) and included second-look arthroscopy with biopsy performed in 22 of 23 cases.

In 16 patients treated for condylar defects at average follow-up of 2 years, 14 had good or excellent results. Of the 15 biopsies, 11 showed hyaline-like tissue, and 4 showed a more fibrous appearance. Of the 4 defects showing fibrous repair tissue, 2 were noted to have good clinical results, and 2 represented treatment failures. All patients receiving an excellent clinical grade were noted to have hyaline-like repair tissue. Five specimens underwent immunohistochemical testing showing type II collagen. Arthroscopy of the 2 failures caused by mechanical symptoms showed severe central wear within the repair tissue at 11 and 14 months, respectively. In the 7 patients treated with patellar defects at average follow-up of 3 years, only 2 patients experienced clinical results graded as good or excellent, with 6 of 7 biopsy specimens showing fibrous tissue. Poor results were explained by the failure to address patellar malalignment at the time of implantation.

Recently, Peterson et al[11] published the results of their first 101 patients treated with ACI. Ninety-three of 94 patients were available for follow-up at 2 to 9 years. Sixty-five patients underwent second-look arthroscopy. Repair tissue was graded on a 12-point scale based upon the degree of defect fill, integration, and macroscopic integrity. Biopsy specimens were obtained from 37 patients. Histologic examination of the tissue was performed, and the tissue was categorized as either hyaline-like, fibrous, or a mix of hyaline and fibrous tissue. The patients were categorized into 5 groups.

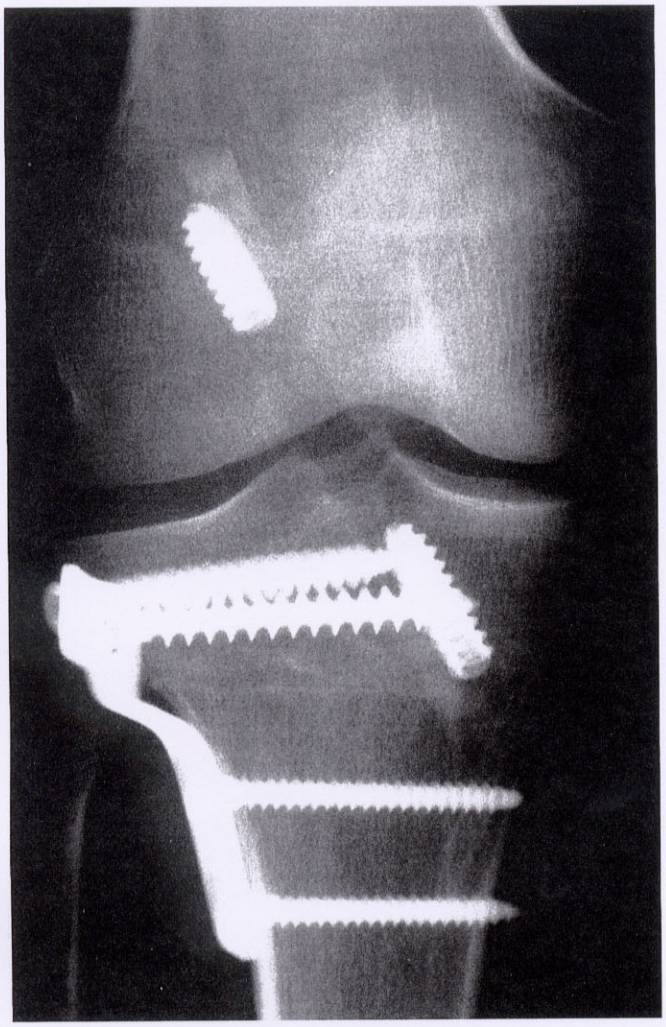


Fig 12. Four-month postoperative anteroposterior radiograph of a patient after ACL reconstruction and concomitant high tibial osteotomy for varus deformity in preparation for second stage ACI to treat a symptomatic focal chondral defect of the medial femoral condyle.

Group 1 consisted of 25 patients treated for isolated femoral condyle lesions. Twenty-four of 25 patients were graded good or excellent on clinical evaluation, and 23 noted subjective improvement. Mean functional scores improved significantly. Arthroscopic appearance averaged 10.3 (range, 4 to 12). Histologic evaluation of 13 biopsy specimens showed hyaline cartilage in 9, fibrous cartilage in 3, and a mix of hyaline and fibrous cartilage in 1. Graft failure occurred in 2 patients.

Group 2 had 15 of 16 patients treated for multiple femoral condyle lesions, including trochlear lesions, and "kissing" lesions of the patella. Clinically, 9 patients were graded good or excellent, and 6 were graded fair or poor. Subjectively, 10 patients believed their symptoms had improved and 5 patients believed they had no improvement or were worse after the procedure. There were no graft failures in this group.

Group 3 consisted of 18 patients treated for femoral lesions related to OCD. Sixteen of 18 were graded clinically as good or excellent, with all 16 reporting subjective symptom improvement. Mean functional scores improved significantly. Arthroscopic appearance averaged 10.5, and histologic evaluation of 4 biopsy specimens showed hyaline cartilage in 2 and fibrous or mixed tissue in 2. Graft failure occurred in 2 patients.

Group 4 had 19 patients treated for isolated patellar lesions, the latter 14 of which received a patellar realignment procedure at the time of ACI. Eleven of 19 patients were graded clinically as good or excellent, and 13 reported subjective improvement. In the 14 patients with patellar lesions who were treated with more aggressive debridement and patellar realignment, 11 were clinically graded good to excellent, compared with just 2 of the 7 patellar lesions included from the original pilot study.[4] Graft failure occurred in 2 patients.

Group 5 consisted of 16 patients who underwent an ACL reconstruction in addition to ACI. Twelve of 16 patients were graded clinically as good or excellent, and 12 patients reported subjective improvement. Mean functional scores were significantly improved. Arthroscopic appearance averaged 10.9. There were 4 biopsies performed, and all 4 revealed the presence of hyaline cartilage within the specimen. Graft failure occurred in 1 patient.

Of 52 adverse events, half involved hypertrophy of the periosteum and repair tissue within the defect, with only 7 symptomatic cases, all of which, experienced relief after arthroscopic debridement. Ten patients experienced intra-articular adhesions, and 8 improved after arthroscopic debridement. Three patients suffered superficial infection that resolved with antibiotic treatment. Three patients experienced synovial hypertrophy, which responded to arthroscopic debridement. The remaining adverse events were considered minor and required no intervention. Graft failure occurred in 7 patients. Four of these failures occurred in the initial pilot group of 23 patients,[4] whereas failure occurred in only 3 of the subsequent 78 patients.

This large series of patients shows a high level of clinical success and patient satisfaction with durable results at up to 9 years after ACI, especially for isolated lesions of the femoral condyle, including OCD. It shows the importance of correcting all concomitant disease including patellofemoral malalignment when treating patellar defects. Serious adverse events were infrequent and responded well to arthroscopic treatment.

The United States Experience

Genzyme Biosurgery Corporation (Cambridge, MA) maintains a cartilage repair registry to track the results of patients receiving ACI outside of Sweden. The results are updated on a continuous basis and released yearly, with the most recent results released in March, 2000, with a 4-year follow-up.[21]

For treatment of 33 femoral lesions, including the medial and lateral condyle, as well as the trochlea, statistically significant clinical improvement was noted in 85% of all patients, and subjective improvement was noted in 81% of all patients. These results were maintained, or even improved, when compared with the 2-year and 3-year follow-up data.[21] Symptoms of pain, swelling, and joint-line pain all improved over the baseline values, and these improvements were maintained over time. When lesions outside the femur were added to the results, for a total of

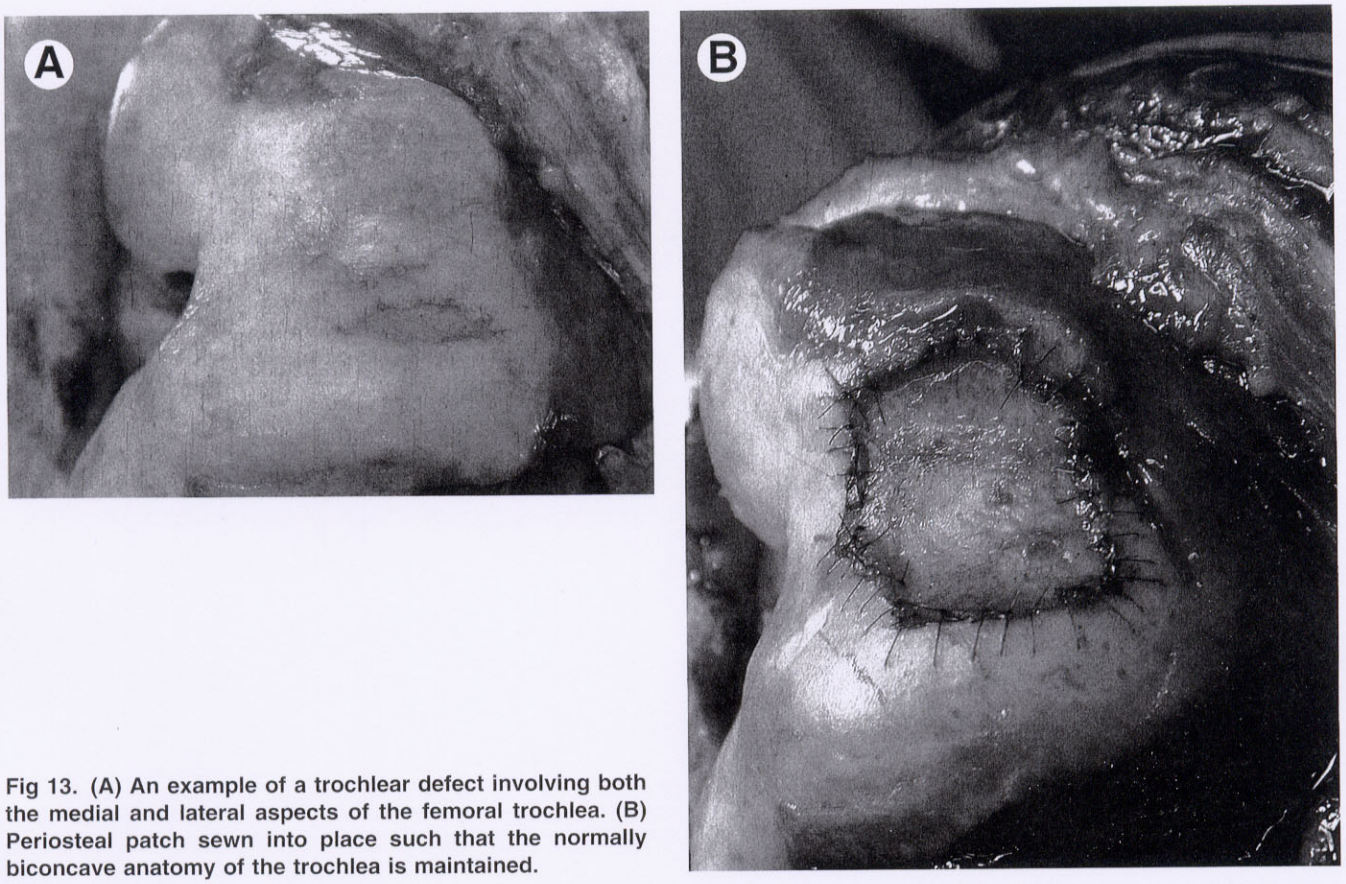


Fig 13. (A) An example of a trochlear defect involving both the medial and lateral aspects of the femoral trochlea. (B) Periosteal patch sewn into place such that the normally biconcave anatomy of the trochlea is maintained.

44 lesions, the overall clinical improvement decreased to 71%, and subjective improvement decreased to 70%. Adverse events were noted in only 7.6% of patients. The incidence of graft failure was 3.2% at 4 years. Adhesions were noted in 1.9% of all patients, while the incidence of hypertrophy of the repair tissue was 1.3%. Additional surgery was required in 6.3% of patients and included athroscopic debridement with or without manipulation.

Our Experience

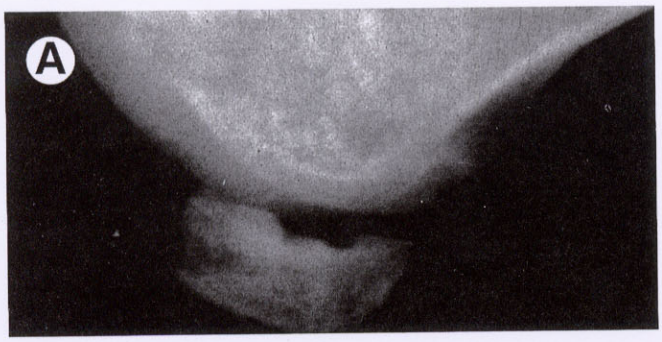
Since 1977, the senior author (B.J.C.) has performed 322 ACI procedures. The average patient age is 34.5 years (range, 16 to 48 years), with a mean of 2.6 (range, 1 to 5 years) procedures performed before treatment with ACI excluding the articular cartilage biopsy.

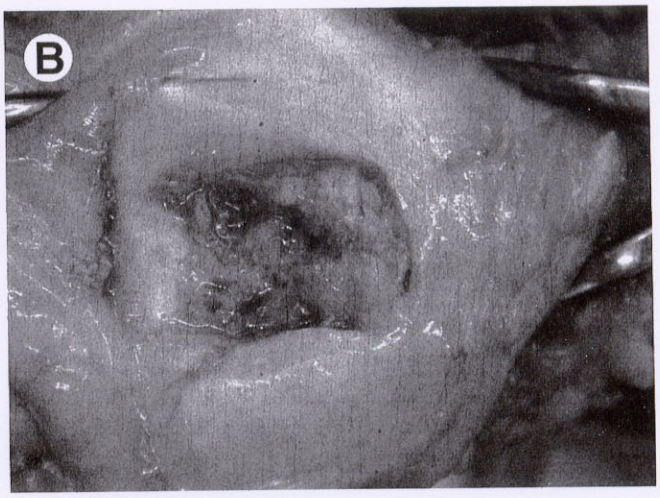
Eleven patients have had follow-up of more than 12 months (mean, 21; range, 12 to 36 months), including 8 men and 3 women. Of these, there were 7 lesions of the medial femoral condyle, 3 lesions of the lateral femoral condyle, and 3 lesions of the trochlea. Two patients had 2 lesions treated that consisted of either a medial or lateral femoral condyle with a trochlear lesion. One patient underwent a concomitant ipsilateral meniscus transplant, 1 patient had a concomitant ACL reconstruction, and 2 patients with trochlear lesions underwent a Fulkerson osteotomy of the tibial tubercle. Five of 11 patients had work-related injuries, and the remaining were caused by either sport-related injury or blunt trauma to the knee. The mean time from symptom onset to treatment was 17 months (range, 2 to 108 months).

Mean lesion size was 3.55 cm^2 (range, 2.0 to 10 cm^2). The mean patient-rated improvement in the modified Cincinnati score (scale, 0 to 10) was 4.8 (SD $\pm$ 1.2). The mean patient-reported decrease in pain rating based on a 10-point visual analogue scale was 2.5 (SD $\pm$ 3.3). All worker's compensation-related cases (5 of 11) returned to their original level of employment, and 6 of 7 non–worker's compensation cases (ie, sports-related injuries) returned to their preinjury activities at the same level. Adverse events included a total of 3 repeat arthroscopies required for intra-articular adhesions associated with motion loss and 1 arthroscopy for tissue hypertrophy.

In summary, lesions of the femoral condyles and trochlea can be expected to respond favorably to treatment with ACI in greater than 80% of all patients, both clinically and subjectively. Patients with multiple lesions or lesions involving the patella have not responded as well but up to 70% still show improvement, with more consistent results if ACI is accompanied by a patellar realignment procedure if indicated. OCD can be treated successfully with ACI. The number of significant complications is low. Overt graft failure occurs in 3% to 7% of all patients. Symptomatic graft hypertrophy occurs in 1% to 7% of all patients. The incidence of arthrofibrosis ranges from 2% to 10%.

A cost analysis of autologous chondrocyte implantation was published in November, 1998.[21] The estimated cost per additional quality-adjusted life year averaged $6,791. This compares favorably to knee arthroplasty ($11,560), and was considerably less costly than other commonly administered surgical and medical interventions.[22,23]





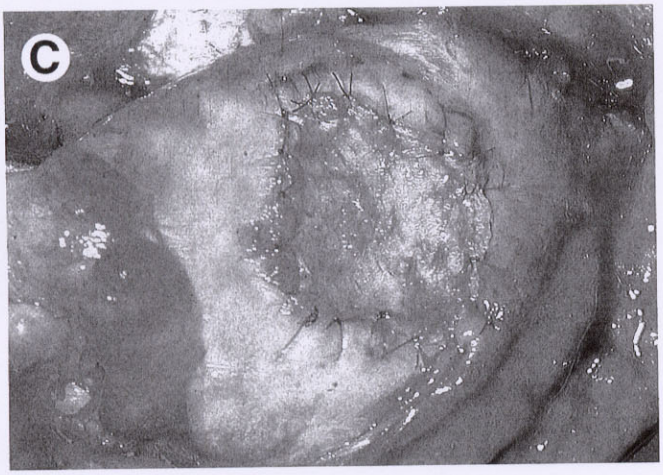


Fig 14. (A) Axial radiograph of a symptomatic central patellar osteochondral injury after a patellar dislocation. (B) An example of patellar defect preparation with the proximal and distal cartilage walls incised obliquely at a 30° to 45° angle to minimize shear stress during proximal-distal excursion that occurs with knee motion. (C) Periosteal patch sewn into place.

Fig 15. An example of a Fulkerson-type osteotomy performed concomitantly with an ACI of the trochlea in a 32-year-old female patient. In general, patients without frank patellar instability benefit most from a more vertical osteotomy to minimize patellofemoral contact forces during range of motion. This is typically performed with all trochlear and patellar lesions in combination with a lateral release and occasionally, medial reefing of the medial patellofemoral ligament depending on the severity of the patellofemoral instability.

COMPLICATIONS

Complications after ACI are typically treatable, and with the exception of graft failure (3% to 7%), rarely compromise the long-term outcome of the procedure. Graft failure is typically a result of delamination with variable degrees of defect fill or central degeneration of the repair tissue. The former may benefit from sharp excision of only the loose fragments, whereas the latter may need to be revised entirely by either ACI or osteochondral grafting (ie, allograft or autograft). If a patient is a candidate for repeat ACI, the original biopsy specimen may be used to culture additional cells if the time period for revision lies within the 18-month window from the date of the original biopsy.

Graft hypertrophy and arthrofibrosis are the most common complications after ACI. Graft hypertrophy typically occur between 3 and 7 months postoperatively and may result from abrasion of the periosteal patch with motion, especially with patch overlap at the host cartilage edge. Treatment for symptomatic lesions requires careful arthroscopic debridement of the hypertrophic tissue, leaving a smooth surface level with the surrounding host cartilage. Mechanical shavers should be avoided, if possible, to prevent inadvertent damage of the residual cartilage tissue. Arthrofibrosis unresponsive to physical therapy is best treated no earlier than 3 months postoperatively with arthroscopic lysis before manipulation to minimize the risk of iatrogenic graft delamination.

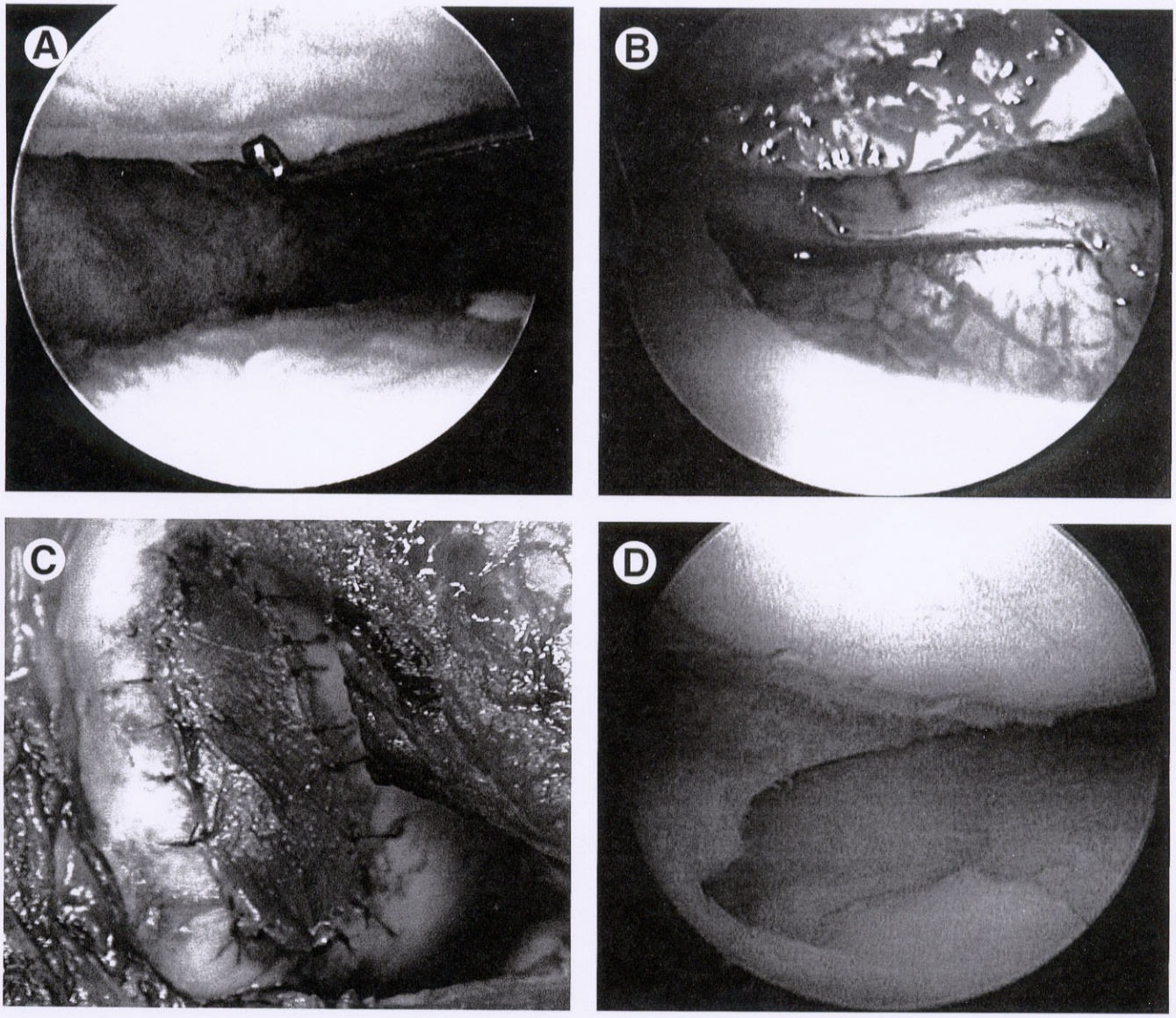


Fig 16. (A) An index defect of the lateral femoral condyle in a 36-year-old male patient who also underwent complete lateral meniscectomy 10 years previously. (B) Lateral meniscus transplant and (C) ACI performed concomitantly. (D) Second-look arthroscopy at 18 months shows excellent hyaline-like cartilage defect fill with peripheral healing of the lateral meniscus allograft with a small degree of shrinkage of the central meniscal rim.

CONCLUSION

Treatment of articular cartilage injuries remains a difficult problem with an evolving treatment algorithm. Surgical procedures developed to treat these problems have, in the past, met with moderate results at best with long-term follow-up. For relatively young patients, the option of waiting for the inevitable knee arthroplasty is not appealing, and fortunately, alternatives now exist. The results of ACI are encouraging for lesions of the femoral articular surface and appear to be improving as our experience with the procedure increases. Clearly, this procedure offers a favorable alternative to the majority of procedures currently available, and hopefully, further research into the factors mediating the healing response of articular cartilage will lead to greater improvements in cell-based technology. Less invasive techniques to deliver cell-based technology are likely to emerge and will inevitably lead to their reduced surgical morbidity. Over the ensuing 5 years, data will emerge from an ongoing prospective study of ACI performed in patients who have failed previous attempts at cartilage restoration. This type of study will further validate ACI for use in the treatment of symptomatic chondral lesions when proper indications are respected.

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