Current Concepts Review

The Healing and Regeneration of Articular Cartilage*

BY SHAWN W. O'DRISCOLL, PH.D., M.D., F.R.C.S.(C)†, ROCHESTER, MINNESOTA

It is well established that damaged articular cartilage has a very limited potential for healing, and articular defects larger than two to four millimeters in diameter rarely heal even with such advances as the use of continuous passive motion[26,36,70,98,101,128,130,138,162,163,208]. Damage to articular cartilage is a common problem: in one study, it was associated with 16 percent (twenty-one) of 132 injuries of the knee that were sufficient to cause intra-articular bleeding[88]. Furthermore, damage to a joint surface can lead to premature arthritis[128]. Twyman et al. prospectively followed twenty-two knees in which osteochondritis dissecans had been diagnosed before skeletal maturity; at an average of thirty-four years, 32 percent had radiographic evidence of moderate or severe osteoarthritis[235]. Only 50 percent had a good or excellent functional result.

Elderly patients (those who are sixty-five years of age or older) who have an arthritic condition can obtain dramatic relief from pain and restoration of function after total joint replacement. However, such procedures have higher rates of failure in young and early-middle-aged patients (those who are less than forty years old and those who are forty to sixty years old, respectively) than in elderly patients[194]. This leaves a large group of patients spanning a broad age-group, many of whom are in their prime, for whom there is no currently acceptable and reliable treatment. A typical example is that of a young, healthy individual who has arthrosis or osteochondritis dissecans following an injury to a joint. It might be possible to solve this patient's problems if the lost or damaged segment of articular cartilage inside the involved joint could be regenerated. After it had been restored, the joint might function indefinitely or until the patient reached the age at which joint replacement was appropriate. The implications of such possibilities are great in terms of the number of patients affected, their quality of life, and ultimately the decrease in the long-term costs of health care related to joint replacement and multiple revisions.

Thus, there is a need for a method for biological healing and regeneration of cartilage if arthritis is to be prevented in patients who have these injuries and disorders. The purpose of this paper is to review the current concepts and data, both biological and clinical, that are related to the healing and regeneration of articular cartilage.

Pathophysiology of Cartilage

Articular cartilage in adults possesses neither a blood supply nor lymphatic drainage. Furthermore, no neural elements connect it to the remainder of the homeostatic systems within the body. In fact, after they are surrounded by their extracellular matrix, articular chondrocytes are sheltered even from immunological recognition. Although the cells continue to produce new extracellular matrix throughout life, they are ineffective in responding to injury. Wounds that are limited to the cartilage itself, without penetration of the subchondral bone, stimulate only a slight reaction in the adjacent chondrocytes. Cell replication and increased matrix turnover are briefly induced.

Not until the subchondral bone is penetrated is the usual inflammatory wound-healing response observed in a damaged joint surface. Cells that are recruited from the marrow elements then attempt to fill the defect with new tissue. The extent to which the new tissue resembles articular cartilage depends on the age and species of the host as well as the size and location of the defect. However, complete restoration of the hyaline articular cartilage and the subchondral bone to a normal status is rarely seen, and, to date, no treatment has been shown to be predictable in this regard.

Treatment Options for Damaged or Lost Cartilage: the Four R's

The options for operative treatment after a joint surface has been damaged or a portion has been lost can be grouped according to four concepts or principles. The articular cartilage can be restored, replaced, relieved, or resected (the four r's). Restoration refers to healing or regeneration of the joint surface, including the hyaline articular cartilage and the subchondral bone. Replacement can be accomplished with use of an allograft or a prosthesis. A damaged joint surface can be relieved by an osteotomy that unloads and decreases the stresses on it. The final option is resection with or without an interposition arthroplasty. If the four r's fail or are not appropriate, an arthrodesis

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†Cartilage and Connective Tissue Research Laboratory, Department of Orthopedic Surgery, Mayo Clinic, 200 First Street S.W., Rochester, Minnesota 55905. E-mail address: odriscoll.shawn@mayo.edu.

can be performed as a salvage procedure.

The focus of this paper is on the restoration of articular cartilage. Biological healing and regeneration of cartilage, which have been elusive for so many years, have recently generated a great deal of interest among clinicians, researchers, patients, and the media. A review of the current status of this exciting field is appropriate as many questions are being posed not only by patients and the media but also by orthopaedic surgeons and residents or fellows in training.

Strategies for Restoration of the Joint Surface

On the basis of the premise that biological restoration of articular cartilage (as well as the underlying subchondral bone) is the goal toward which investigative efforts must be directed, two possible strategies can be logically considered. The first strategy is to enhance the intrinsic capacity of the cartilage and the subchondral bone to heal themselves. An alternative approach is to regenerate a new joint surface by transplanting chondrocytes or chondrogenic cells or tissue that have the potential to grow new cartilage. These two strategies will be discussed in turn.

Enhancement of Intrinsic Healing Capacity

Attempts to enhance the intrinsic healing potential of cartilage have traditionally been focused on recruiting pluripotential cells from the bone marrow by penetrating the subchondral bone or providing a mechanical, electrical, laser, or other stimulus for healing. More recently, the use of bioactive agents such as growth factors and cytokines, sometimes in combination with scaffolds on which healing can be structured, has been investigated.

Subchondral Drilling, Abrasion, or Microfracture

Articular chondrocytes reside in an avascular environment and do not usually effect healing when damage to the joint surface is limited to the layer of cartilage[27,47,129]. Many investigators have attempted to stimulate cartilage-healing by drilling, abrading, or producing so-called microfractures in the subchondral bone[2,3,19,70,102,116,130,138,191,236]. All of these techniques have in common the goal of recruiting pluripotential stem cells from the marrow by penetration of the subchondral bone. Meachim and Roberts performed a number of such perforations in each defect in twenty-one knees of adult male rabbits after the knees had been denuded of cartilage[130]. For as long as two years after the procedure, the cartilage never fully healed, and even complete covering of the denuded bone with noncartilaginous tissue was rarely seen. Mitchell and Shepard made similar observations after drilling thirty-one-millimeter holes through the subchondral bone in twenty-five adult rabbits[138]. Vachon et al. showed that, for healing with fibrocartilage to occur in horses, the subchondral bone should be penetrated[236]. Similarly, Kim et al. found that, for abrasion to have any benefit, it must extend into the subchondral bone[116]. Thus, penetration of subchondral bone might have some benefit with regard to small defects, although a benefit has not been proved in relation to large defects, osteoarthritic joints, or older adults[87,116].

Abrasion chondroplasty was shown, by Altman et al., to stimulate a cartilage-healing response that was inadequate to result in functional hyaline cartilage[3]. Friedman et al. found that abrasion arthroplasty offered a benefit, after short-term (average, one-year) follow-up, in 60 percent of 110 patients who had a full-thickness cartilage defect in the knee; the results were better in patients who were less than forty years of age[68]. Rand reported on twenty-eight patients who had had exposed bone[193]. At an average of 3.8 years after an abrasion arthroplasty, eleven patients had no improvement, eight had no change, and nine had worsening of the condition. Fourteen patients had a total knee arthroplasty for salvage at an average of three years after the abrasion procedure.

In a retrospective, comparative study of 126 patients who were evaluated an average of sixty months after operative treatment of unicompartmental gonarthrosis, Bert and Maschka reported a satisfactory result in 67 percent of fifty-nine patients who had been managed with an abrasion arthroplasty combined with débridement compared with 79 percent of sixty-seven who had been managed with arthroscopic débridement only[16].

Steadman popularized the so-called microfracture technique, in which multiple small holes are made by hand with use of small picks rather than drills or pins[226]. This technique is based on the theory that use of an awl results in microfracture of the trabeculae rather than destruction of bone; thus, the microfractures induce a healing response. Moreover, heat necrosis is avoided. This technique is easier and probably as effective as drilling; however, data from comparative studies, which are not yet available, are needed to confirm or refute its efficacy.

The current role of penetration of subchondral bone is somewhat controversial. This method is best considered as a treatment option that has little likelihood of harming, and some chance of helping, the patient. On the basis of current knowledge, it is a reasonable first step in the management of a patient who has a previously untreated cartilage defect. Clinical studies have suggested that patients often respond to arthroscopic procedures because of a nonspecific effect related to joint lavage[109,169].

Continuous Passive Motion

Salter introduced and investigated the biological concept of continuous passive motion of joints for the postoperative treatment of many types of articular injuries[48,116,119,141,159-164,207-210,248,254,255]. In a series of studies spanning two and one-half decades, he and his colleagues

demonstrated that healing of articular cartilage was enhanced in rabbits by the postoperative use of continuous passive motion. In one series, multiple (four) small (one-millimeter) drill-holes were made in one knee of each rabbit; after four weeks, healing with predominantly hyaline cartilage was seen in 60 percent of the forty defects in ten adolescent rabbits and in 44 percent of the forty defects in ten adult rabbits that had been treated with continuous passive motion, whereas such healing was seen in 10 percent or fewer of the defects in rabbits that had had postoperative immobilization in a cast or had been allowed free movement in their cages[208]. Subsequent studies showed that, although continuous passive motion enhanced cartilage-healing, the effect was much less pronounced in defects that were larger than three millimeters in diameter[162,163]. However, the beneficial effect of continuous passive motion on the regeneration of cartilage after periosteal transplantation was confirmed[116,141,142,162-164]. The current role of continuous passive motion is generally accepted to be adjunctive to procedures directed toward cartilage-healing.

Electrical Stimulation

Electrical stimulation for cartilage-healing has not received as much attention as has electrical stimulation for fracture-healing[11,124,126]. Lippiello et al. demonstrated slightly improved healing of cartilage defects in the knees of rabbits after treatment with pulsed direct current[124]. Maximum efficacy was seen after four hours of exposure per day. Baker et al. reported that electrical stimulation improved healing, but their sample sizes (three or fewer per group) were insufficient[11]. More importantly, the effect was not seen in the articular defects but rather in the surrounding cartilage. The role of electrical stimulation in cartilage-healing is unclear, and further definition of parameters as well as testing in a wider variety of experimental and clinical settings is required.

Lasers

Most discussions of treatment with lasers have focused on damaged articular cartilage, but there have been some reports on the effect of lasers on cartilage repair[9,28,35,75,89,196,232,246,247]. Hardie et al. found no beneficial effect on cartilage-healing in association with low doses of neodymium:yttrium aluminum-garnet (Nd:YAG) laser therapy in twenty knees of adult dogs that had a partial or full-thickness cartilage defect[89]. Similarly, Reed et al. found no benefit with use of an excimer (308-nanometer xenon-chloride ultraviolet) laser compared with that of arthrotomy and lavage in eighteen knees of adult rabbits that had mechanically induced osteoarthritis[196]. Whether lasers will make a contribution in this area remains to be determined.

Pharmacological Agents

Drugs that might enhance cartilage-healing can be administered systemically, intra-articularly, or locally. Although many investigators have hoped for a systemic agent that can counteract generalized osteoarthritis, no such agent has yet been identified. Intra-articular injections, which have been used both clinically and experimentally, fall into three basic categories: corticosteroids, hyaluronic acid, and growth factors. There has been some suggestion that corticosteroids can enhance cartilage-healing[179], but other authors have found that they impair the physiology of normal cartilage and induce arthropathy[14,127,206,217,218]. Hyaluronic acid has been used widely, in several countries, as a so-called viscosupplement[1,8,49,51,105,182,184]. Its mechanism of action is probably more than simply that of a lubricant. It is possible that it has a direct biochemical effect[105]. In experimental models of arthritis, hyaluronic acid binds to, and penetrates into, damaged articular cartilage, potentially providing a protective coating[224].

The intra-articular injection of growth factors, such as transforming growth factor-β1, insulin-like growth factor-1, and bone morphogenetic proteins, has been studied on the basis of abundant data from *in vitro* studies demonstrating the chondrogenic effects of these agents[50,51,241-244]. Cuevas et al. reported preliminary data suggesting an early stimulating effect from basic fibroblast growth factor that had been injected with an osmotic pump into the knees of rabbits in which small (two-millimeter) defects had been created[42]. Neidel found that intra-articular injections of insulin-like growth factor-1, fibroblast growth factor, or epidermal growth factor had no effect on the healing of standard cartilage defects[153]. Although the data are still somewhat sparse, problems such as formation of osteophytes in association with intra-articular administration of transforming growth factor-β1 might limit the usefulness of this technique[51,97,240-242,244]. In a series of experiments in mice, van den Berg[244] as well as van Beuningen et al.[240-242] showed that intra-articular injections of transforming growth factor-β1 stimulated the formation of osteophytes that were similar, in morphology and location, to those seen in osteoarthritis. A single injection of transforming growth factor-β1 stimulated a persistent increase in cartilage proteoglycan synthesis and content, but multiple injections induced substantial synovitis and synovial hyperplasia[242].

For the effective delivery of growth factors or other bioactive agents, a more attractive concept than intra-articular injection is local implantation into a defect in the joint surface with use of a carrier matrix[99]. This idea currently is being investigated and shows great promise on the basis of preliminary data, which must still be substantiated. Tanaka et al. implanted allogenic demineralized bone plugs into four-millimeter osteochondral defects in the knees of adolescent rabbits[230]. Over a four to thirty-week period, healing of the cartilage and the subchondral bone in the defects that had been treated with the grafts was superior to that in the controls. However, those investigators concluded that the extract dis-

solved rapidly after placement in the defect, necessitating a delivery system that could maintain the extract in the defect during the healing process. Dahlberg and Kreicbergs similarly concluded that the technique had to be improved before it could be used in order to enhance cartilage-healing[45]. Billings et al. also showed that demineralized bone stimulated subchondral bone regrowth and provided a surface for cartilage-healing[17].

Most current efforts are being directed toward the implantation of scaffolds containing growth factors. (These will be discussed in the next section.)

A thought-provoking approach is related to the concept that wound-healing may be inhibited in articular cartilage. The normal response associated with wound-healing, including vascular invasion, cell migration, and inflammatory reaction, is seen in full-thickness defects that extend through the subchondral bone but not in partial-thickness injuries that are limited to the articular cartilage[128]. Although this could be due to the absence of blood vessels in the cartilage itself, it is also possible that the extracellular matrix contains an inhibitor of wound-healing that impairs cell migration or adherence to the damaged surface[99,100]. If this is true, then digestion of the extracellular matrix with proteolytic enzymes, such as trypsin or chondroitinase, might enhance cartilage-healing. Lack et al. compared the effect of injection of trypsin and blood with that of injection of trypsin alone, injection of blood alone, or no injection in fifty-four knees of rabbits that had five by 1.5-millimeter partial-thickness cartilage defects in the femoral condyle[122]. Cartilage-healing was seen in eight of twelve defects that had been treated with injection of trypsin and blood but in none of the others. Injection of trypsin and blood seemed to block the apparent inhibition of wound-healing that occurs in cartilage. On the basis of the hypothesis that proteoglycans may prevent mesenchymal cells from adhering to and migrating over the surfaces of partial-thickness defects, Hunziker et al. studied enzymatic treatment with chondroitinase ABC; they found that it evoked an initial increase in the coverage of partial-thickness cartilage defects with mesenchymal cells, presumably from the synovial tissue[99,100].

There is currently interest in the enzymatic digestion and exposure of the edges of cartilage defects to promote incorporation of neocartilage produced by whatever method is used for the regeneration of cartilage. Even when there is excellent regeneration of cartilage, there is incomplete remodeling at the junction between the neocartilage and the adjacent cartilage[162,164]. This approach of enzymatic digestion may improve the bonding of such regenerated tissue to the edges of the defect.

Use of Scaffolds and Composites for Healing

Scaffolds have been used both alone and in combination with growth factors or cells for the healing of joint defects[31,51,63,79,112,123,155,156,189,195,197,205]. The many substances that have been tested include nonabsorbable materials, such as carbon fiber[21,111,136,137,200], Dacron, and Teflon[131-133]; porous metal plugs; absorbable polymers or copolymers[31,189,205], such as polyglycolic acid and polylactic acid; fibrin[155]; and collagen[156,250]. Meniscal allografts have been used as a tissue to induce healing, but they have not restored the original joint surface[158,228].

The nonabsorbable materials have not proved successful in restoring cartilage. The use of carbon fiber alone has been shown to promote healing with only fibrous tissue in animals[21,111,136,137,200]. Similarly, Teflon and Dacron have not effected healing of cartilage in rabbits[131-133]. Other materials, such as absorbable polymers, have shown promise, especially when used as a matrix in which to transplant cells and deliver growth factors.

On the basis of the hypothesis that proteoglycans may prevent mesenchymal cells from adhering to and migrating over the surfaces of partial-thickness defects, Hunziker et al. used a fibrin clot to contain locally applied mitogenic growth factors (basic fibroblast growth factor, transforming growth factor-β1, epidermal growth factor, insulin-like growth factor-1, and growth hormone) and to furnish a matrix or scaffold for the migration of cells therein[99,100]. When this method was combined with enzymatic treatment of partial-thickness cartilage defects with use of chondroitinase ABC, it evoked an initial increase in coverage with mesenchymal cells, presumably from the synovial tissue. At forty-eight weeks, the entire cavity of the defect remained filled with fibrous connective tissue.

In the mid-1970s, Chvapil and colleagues described a collagen-sponge technology for cartilage-healing[34,94]. The initial concept involved use of a collagen sponge as a scaffold on which repair cells from the defect could grow and synthesize extracellular matrix components. Wakitani et al. later developed a technique employing collagen gels as a carrier in which to transplant and maintain chondrocytes in articular defects[250]. Freed et al. noted cartilage-healing following implantation of a polyglycolic acid scaffold in three-millimeter defects extending just into the subchondral bone of the knees of adult rabbits, but they did not compare the results with those in controls[64]. Oka et al. found that a synthetic composite consisting of polyvinyl alcohol hydrogel on titanium fiber integrated into the subchondral bone better than did pure titanium or alumina[178].

Biological and technical aspects that are currently being studied include the targeting of cells in specific zones (cartilage and subchondral bone) in a vertical organization with use of different growth factors and with the timed release of the growth factors. Sellers et al. reported success with use of a collagen sponge impregnated with five micrograms of recombinant human bone morphogenetic protein-2 for the healing of full-thickness osteochondral defects in adult rabbits[214]. This treatment accelerated the formation of new subchondral bone and substantially improved the histolog-

ical appearance of the overlying articular cartilage. At twenty-four weeks, the thickness of the healing cartilage was 70 percent of that of the normal adjacent cartilage and a new tidemark usually had formed between the new cartilage and the underlying subchondral bone.

The concept of a two-phase scaffold (collagen matrix or copolymer) containing growth factors or chondrocytes for the healing of articular defects has been investigated; the objective is to separately influence the restoration of the subchondral bone and the cartilage[10,67]. Athanasiou et al. studied the potential benefit of combining local growth-factor delivery with implantation of a scaffold, with use of transforming growth factor-β1 in a two-phase biodegradable polymer[10]. The scaffold consisted of 50:50 poly-DL-lactide-co-glycolide, with a stiffer phase in the region of the subchondral bone and a softer phase for interfacing with the cartilage. Transforming growth factor-β1 (180 or 1800 nanograms) was delivered in these implants, which stimulated partial healing of osteochondral defects in mature goats; however, there was no significant difference in the histological appearance compared with that of the controls.

It is widely believed that the science of scaffolds or matrices for delivery of bioactive agents and transplantation of cells will play a fundamental role in the development of what recently has been termed tissue engineering for restoration of the cartilage and the joint surface. For the purpose of this discussion, tissue engineering can be defined as the application of engineering science and technology to the combined field of cellular and molecular biology with the goal of regulating the growth, differentiation, and metabolic activity of cells that are either transplanted or recruited to heal or regenerate a joint surface.

Regeneration: Growth of New Cartilage

Because of the limited capacity of cartilage to heal, a more attractive approach is to transplant cells or a tissue with chondrogenic potential into the joint (so-called biological resurfacing). Bentley and Greer were apparently the first to show that chondrocytes could be transplanted into articular cartilage defects and improve healing compared with that in controls[15]. Chondrocytes[15,91,92,155], stem cells[71,103,104,139,165-167,251], an undifferentiated tissue (such as periosteum or perichondrium) containing stem cells or chondrocyte precursors, or any combination of these can be used[22].

Use of Isolated Cells Compared with Use of Whole Tissue Grafts with Chondrogenic Potential

Cells that have been isolated from their matrix can be explanted to culture dishes and increased in number *in vitro*. This makes it possible to start with a relatively small quantity of tissue as a source of cells. The main challenge of this approach is the need to maintain the transplanted cells in the damaged area of the joint surface after implantation; the challenge is greater with large defects or whole joint surfaces than it is with small, circumscribed defects[15]. This technical concern poses less of a problem with whole tissue grafts, which can be used to resurface most shapes and sizes of articular defects as well as whole joints. The graft can be retained on the joint surface by anchoring it to the subchondral bone with sutures pulled out through tunnels under the adjacent joint surfaces. My clinical experience with use of periosteum for biological resurfacing of joints in humans has confirmed the technical feasibility of this approach. The technique also has been proved successful in experiments involving animals[162,164]. Therefore, the use of tissue grafts will be discussed first, followed by a discussion of cell transplantation.

Investigators in several countries have provided confirmation of the chondrogenic potential of periosteum[7,46,60,71,83,84,106,107,140,143,144,154,161-164,166,201-204,216,231,233,237-239] and perichondrium[4-6,17,25,31,33,39-41,52,95,110,117,120,121,172,175,181,198,219,221,222,249,252]. Perichondrial arthroplasty was described by Skoog, and he and his colleagues extensively investigated this technique, as did Engkvist et al.[52-59,170-177,181,219-223,225,252,253]. Periosteal arthroplasty, initially described by Rubak et al.[201-204], also has been extensively investigated[46,141,154,161-164,188,199,254,255]. Both periosteum and perichondrium can survive, grow, and differentiate to produce a cartilaginous extracellular matrix in organ culture, thereby permitting their use in tissue engineering[25,55,71,140,166].

Periosteal Arthroplasty

Osteochondral defects in the knees of rabbits that were resurfaced with use of autogenous periosteal grafts healed with predominantly hyaline cartilage containing more than 90 percent type-II collagen and normal water, proteoglycan, chondroitin, and keratan sulfate contents[162,164]. The quality of the healing tissue was enhanced significantly ($p < 0.001$) by postoperative continuous passive motion, whereas it was impaired in older animals or when the cambium layer of the periosteal graft was placed so that it faced the subchondral bone. At one year, the nature and structural quality of the regenerated tissue in the defects that had been treated with continuous passive motion had not degenerated compared with those at four weeks ($p > 0.1$), although there were slight early degenerative changes. The restoration of the subchondral bone was complete; this is important if the regenerated cartilage is to remain intact because alteration of the biomechanics of the subchondral bone leads to degeneration of the overlying cartilage[190]. Curtin et al. found normal ultrastructural characteristics in cartilage that had been regenerated with use of periosteal grafts in rabbits, although there was variability among the results[43].

Periosteum has been used alone for biological resurfacing arthroplasty in humans for more than a decade[69,93,118,154]. Niedermann et al. reported a successful result, after one year of follow-up, in the knees of all

of four patients who had osteochondritis dissecans and in that of one patient who had avascular necrosis[154]. Four patients had no pain, and one had dull aching. Arthroscopy performed twelve months postoperatively revealed firm cartilaginous tissue on visualization and probing. Hoikka et al. used periosteal grafts to resurface patellar defects in thirteen patients[93]; according to the scoring system of Freeman et al.[66], the result was good for eight patients, fair for four, and poor for one.

Since 1986, I have cautiously applied what has been learned from laboratory investigations about periosteal transplantation to the care of approximately forty patients. The initial goals were to clarify the technical aspects of the operative procedure, to determine the likelihood of clinical success on a broader scale, and to establish reasonable guidelines for indications and contraindications. Although the purpose of the current review is not to present unpublished data, I have made a number of observations that might help others to avoid failure. Periosteal grafting requires meticulous procurement and handling of the graft, which must be placed deep enough in the subchondral bone to avoid shear forces due to articulation in the first week or two. I used the periosteal transplants in patients who had severe symptoms and had had failure of at least one previous operation. Twenty-three of the forty patients who were so managed had osteochondral defects in the knee; the others had defects that involved the elbow, ankle, shoulder, or hand. The defects ranged in size from 1.5 by 1.5 centimeters to four by ten centimeters and were as deep as two centimeters, but generally they were large and full-thickness, penetrating the subchondral bone. Some defects were treated with bone-grafting simultaneously. My results with periosteal grafting have not yet been evaluated by peer review, but they are encouraging.

Perichondrial Arthroplasty

Perichondrial resurfacing in humans, which apparently was first described by Skoog et al.[219-222] for the resurfacing of joints in the hand, enjoyed initial popularity and has been reported on by a number of authors[25,52,58,96,171,181,198,215,219-222]. Homminga et al. reported on twenty-five patients who had thirty osteochondral defects that were treated with perichondrial grafts from the ribs; repeat arthroscopy revealed that twenty-eight defects were filled with tissue resembling cartilage[96]. The average knee score of The Hospital for Special Surgery[192] improved from 73 points preoperatively to 90 points postoperatively. Although the duration of follow-up was less than two years for eleven patients, the fourteen patients who were evaluated after a minimum of two years had no deterioration in the knee score over time. Bouwmeester et al. reported the long-term results for eighty-eight patients who had been managed for articular defects in the knee with use of perichondrial grafts inserted with fibrin glue[18]. After an average of four years, the result was good for 38 percent of the patients, fair for 8 percent, and poor for 55 percent. The poor results were related to overgrowth of the graft, calcification, or the presence of osteoarthritis preoperatively. Those authors immobilized the knee postoperatively to ensure adhesion of the graft and concluded that better fixation was necessary.

Vachon et al. compared the use of periosteum for chondrogenic grafts with that of perichondrium in horses[237]. Chondrogenesis was observed significantly more frequently ($p < 0.05$) and in greater amounts in free intra-articular periosteal grafts than in perichondrial autogenous grafts. Cartilage was found in five of six periosteal grafts and in one of six perichondrial grafts. Periosteum is readily accessible in large enough amounts and has been used clinically to totally resurface smaller joints such as the elbow. The morbidity associated with obtaining periosteum adjacent to the knee is less than that associated with obtaining perichondrium, which requires a second incision on the chest wall.

Coutts et al. and Amiel et al. reported a number of investigations involving the use of perichondrium as a chondrogenic tissue for the resurfacing of articular defects in the knees of rabbits and noted concerns primarily with the technical aspects of implantation of the grafts[4,6,17,31,39-41,120,121,249]. In a long-term study of 100 rabbits that were followed for a maximum of one year, 37 percent were eliminated from the final analysis of the data as only grafts that were considered to be "biologically acceptable" were included[121]. Biologically acceptable, as defined by those authors, meant that, on gross inspection, "the defect was filled with firm, cohesive cartilaginous tissue."[4] In a subsequent study, the use of periosteum wrapped onto a biodegradable polylactic-acid scaffold as well as the combination of cells in absorbable polymers were investigated as means for delivering and maintaining the cells in the defect in order to improve cartilage-healing[249].

My experience with use of periosteum in rabbits and humans has confirmed that it can be accurately and securely transplanted into defects of various sizes, shapes, and depths. For reasons that include the accessibility and amount of available tissue as well as its chondrogenic potential, periosteum appears to be preferable to perichondrium for the biological resurfacing of joints.

Use of Fully Differentiated Chondrocytes Compared with Use of Undifferentiated Chondrocyte Precursor Cells

Many investigators have chosen to use chondrocytes for cell transplantation for the regeneration of cartilage[12,15,22,62-65,76-78,80,91,92,155-157,186,189,212,213,234,250]. Other investigators have preferred to use undifferentiated (perhaps better termed incompletely differentiated) pluripotential cells (often referred to as mesenchymal stem cells)[24,29,61,71,90,103,140,145-152,161-164,166,185,251,254]. The concept of multipotentiality is well substantiated in the literature[81,187].

Bone marrow, periosteum, or perichondrium can be used as a source of such cells, although it is not clear that perichondrial cells are truly pluripotential or that they can produce bone[31,32]. Each approach has advantages and disadvantages. Differentiated chondrocytes produce cartilage under appropriate conditions. They are ideal if the damage to the joint surface is limited to the cartilage alone. However, many articular defects involve the subchondral bone, and in these instances the transplanted cells or tissue also must be capable of either forming or permitting the formation of bone. Radin et al. reported that the health of articular cartilage depends on maintenance of the normal biomechanics of the subchondral bone[190]. Thus, restoration of the subchondral bone should be an integral concern with regard to any method used for cartilage-healing. Chondrocytes do not possess the capacity to induce bone-healing, whereas periosteal or bone-marrow stem cells do have the potential to regenerate both the cartilage and the underlying subchondral bone[162,164].

Large, deep articular defects present a special challenge as it is not sufficient simply to replace the cartilage. Restoration of the structural integrity of the joint surface requires correction of the architecture, including the lost subchondral bone. One approach is to restore the bone first and then to regenerate the cartilage. In an experimental model, van Dyk et al. impacted autogenous cancellous bone into large, cylindrical articular defects measuring ten by ten millimeters in the femoral trochlea of the knees of twenty adult dogs[245]. Similar lesions in the contralateral knees served as controls. During a two to twenty-four-week period, marked improvement in healing was observed in the knees that had been treated with a graft compared with those that had not. Interestingly, those authors also noted a difference in the reparative surface overlying the new bone, with much more cartilaginous tissue covering the defects that had been treated with a graft. This finding suggests that the graft may have provided a scaffold on which mesenchymal stem cells from the bone marrow could differentiate into chondrocytes and produce a matrix.

Transplantation of Autogenous Chondrocytes

This technique was originally developed in experiments involving rabbits, by Grande et al.[76,78] and more recently by Brittberg et al.[23]. Chondrocytes that had been isolated from biopsy specimens of cartilage were grown in monolayer culture to increase the cell population. These cells then were suspended in a liquid medium and placed beneath a periosteal graft sewn over the defect. With this technique, the periosteal graft is transplanted with the cambium layer facing down into the defect. Chondrocytes labeled with tritiated thymidine before transplantation accounted for 8 percent of the total number of cells in the healing tissue that filled the defects[78]. In the study by Brittberg et al.[23], cultured chondrocytes that had been increased in number for two weeks *in vitro* were transplanted into patellar chondral lesions in four-month-old New Zealand White rabbits. The lesions were three millimeters in diameter and extended down to the calcified zone. Fifty-two weeks later, the lesions that had been treated with transplantation of autogenous chondrocytes under a periosteal flap had much more and better repair tissue than did untreated, control lesions or lesions that had been covered by a periosteal flap with or without a carbon-fiber pad seeded with chondrocytes. However, the incorporation of the healing tissue into the defect tended to be incomplete. A gradual maturation of the hyaline-like tissue, with more pronounced columnarization, was noted as late as one year after operative treatment. Although Brittberg et al. stated that the rabbits were adults, no radiographic or histological evidence of physeal closure was provided. This might be important; Kaweblum et al. found that physeal closure in the distal aspect of the femur in New Zealand White rabbits occurred between 4.4 and 5.5 months, with growth remaining until 4.2 months[115].

This technique also was investigated with use of a chondral defect model in dogs, without penetration of the subchondral bone, by Breinan et al.[20]. Twelve to eighteen months after the operation, those authors were unable to confirm that articular cartilage had been regenerated in the defects that had been treated with transplantation of chondrocytes under a periosteal flap, those that had been treated with a periosteal flap alone, or those that had been left untreated. Furthermore, they could detect no significant differences with regard to any of the parameters that had been used to assess the quality of healing ($p > 0.05$). Damage to adjacent cartilage was attributed to suturing of the periosteal flap to the cartilage. Additional experiments will be needed to confirm the scientific validity of transplantation of chondrocytes with use of this technique. Perhaps enzymatic preparation of the exposed surfaces will allow for better bonding of the neocartilage, as was suggested by Hunziker and Kapfinger[100].

The results of transplantation of autogenous chondrocytes in humans were reported by Brittberg et al.[22]. Twenty-three patients, ranging in age from fourteen to forty-eight years, were managed with a patch of periosteum sewn over an articular defect in the knee. A small volume of autogenous chondrocytes, which had been grown in culture for two to three weeks after having been isolated from biopsy specimens of cartilage obtained during an earlier arthroscopy, was injected beneath the patch. The second stage of the procedure was performed through an open arthrotomy. At a maximum of sixty-six months postoperatively, according to a subjective scoring system based on pain, swelling, and locking, the clinical result was good or excellent after the treatment of fourteen of sixteen condylar and two of

seven patellar defects. At the time of an arthroscopic assessment at twelve to forty-six months postoperatively, the defects generally appeared to have healed, although the edges were still visible. Histological evidence of cartilage formation was seen in thirteen biopsy specimens (57 percent).

Since the report by Brittberg et al.[22], this technique has received much attention. As with all initial reports, there are some limitations that should be resolved with additional documentation. Peterson[183] reported on a larger series of ninety-four patients who had been followed for two to nine years, and his findings were similar to those that have been published. Half of the patients had not had previous operative treatment, and, as mechanical symptoms were prevalent, it is not known how many would have responded to arthroscopic débridement or subchondral drilling. The results would be easier to interpret if there had been a control group or if all previous standard operative procedures had failed. The disparity between the subjective clinical results and the biological results raises questions regarding the specific contribution of the grafted cells. The injected volume was very small, only 0.3 milliliter. The number of transplanted chondrocytes may be an important factor. Chen et al. used an *in vitro* model to study the incorporation of cultured chondrocytes onto articular cartilage and found that matrix synthesis was directly related to the number of transplanted cells[30].

There is some controversy regarding the potential contribution of the periosteum in the technique of chondrocyte transplantation. Investigators[78] have compared chondrocyte transplantation with periosteal transplantation alone, but the technique of periosteal transplantation has differed among studies. The periosteum, in the absence of transplanted chondrocytes, should be placed facing into the joint[162] and deep enough in the defect to prevent articulation with the opposing surface during the first week or two, until matrix is produced to protect the cells[141,163]. Room is needed to accommodate the new, growing tissue or it will be proud, above the adjacent cartilage, and it will break down. In the studies of chondrocyte transplantation, the periosteum was placed directly on the subchondral bone with its cambium layer facing down[78,183]. The defects were too shallow to permit the regeneration of cartilage by periosteum alone. Fitzsimmons and I demonstrated that proper technique for obtaining and handling periosteum is a critical determinant of its chondrogenic potential[61]. If the cambium layer is not preserved, the procedure will fail. These observations[61] can be considered preliminary until additional scientific evidence is accumulated.

Autogenous Compared with Allogenic Transplantation of Cells

Cell and tissue transplantation can be autogenous or allogenic, and each technique has advantages and disadvantages. Allogenic transplantation of chondrocytes has been used with some success in experiments involving rabbits[64,250] but not in those involving horses[212,213]. Also, Kawabe and Yoshinao identified an immune rejection response in rabbits, which was associated with premature degeneration of the newly formed healing tissue[113]. Freed et al. noted only a slight immune response to allogenic chondrocytes that had been cultured in polyglycolic acid scaffolds for one month and then implanted in defects in the knees of rabbits[64]. Those authors suggested that culturing might have permitted sequestering of the cell-surface antigens by extracellular matrix production. Noguchi et al. found no difference in the healing of osteochondral defects in rabbits that had been treated with isogeneic chondrocytes compared with those that had been treated with allogenic chondrocytes, both of which were carried in collagen gels[157]. Both treatments were more successful than the use of collagen gels alone. However, caution must be used in interpreting the results of those studies as some strains of rabbits are inbred and the genetic differences between two rabbits from the same breed may be less than those between two unrelated humans. Finally, viability and chondrogenic potential must be ensured post mortem and should not simply be assumed. For example, a postmortem viability study in my laboratory demonstrated a decrease of more than 90 percent in the viability and chondrogenic potential of periosteum that had been obtained from rabbits four hours after death[168]. Whether allogenic (as opposed to only autogenous) cells can be used remains uncertain.

An interesting variation on the theme of chondrocyte transplantation was reported by Takahashi et al., who used early fracture callus to induce healing of osteochondral defects in skeletally mature rabbits, with excellent results[229]. The transplanted piece of bone and adjacent callus from the site of an osteotomy of the iliac crest that had been performed ten days earlier integrated into the defect and restored the subchondral bone and overlying cartilage. Although it is easy to envision some important limitations to the clinical application of this concept, such as the need for two procedures at the iliac crest and one at the involved joint, the concept is of biological interest.

Use of a Scaffold Compared with Use of a Matrix

Bentley and Greer, in their initial report on chondrocyte transplantation, stated that retention of the cells in the defect was a problem[15], and this has been a concern in subsequent studies[250]. For this reason, scaffolds and matrices have been used for cell transplantation. The ideal material has not yet been identified, but the many that have been tried include fibrin, collagen, ceramics, and synthetic polymers that are absorbable (such as polyglycolic or polylactic acid) or nonabsorbable (such as Dacron and Teflon). In general,

biodegradable matrices are thought to have the most promise. The polymer composition is probably important. Freed et al. found that chondrocytes grown on polyglycolic acid scaffolds *in vitro* grew at twice the rate of those grown on polylactic acid[62]. The polyglycolic acid-based composites also continued to accumulate glycosaminoglycans for six weeks, whereas the response in the polylactic acid-based composites reached a plateau after one week.

Wakitani et al. described a technique employing collagen gels as a carrier in which to transplant and maintain chondrocytes in articular defects[250]. They reported what they referred to as complete healing at four weeks in seven of nine defects that had been treated with a graft compared with none of two controls. Nixon et al. found that allogenic chondrocytes on collagen scaffolds were optimally ready for transplantation after ten to fourteen days in culture[156]. Neither Sams and Nixon[212] nor Sams et al.[213] confirmed these results in horses with large (fifteen-millimeter) defects that had been treated with allogenic transplantation of chondrocytes with use of collagen scaffolds. At four and eight months postoperatively, no differences were detected between these defects and the controls with regard to the findings on analysis of synovial fluid, the gross appearance, the histological or histochemical appearance of the new tissue at the surface of the defect, or the percentage of type-II collagen[156,212,213]. The tissue was disorganized and fibrous, containing only 30 percent type-II collagen. Those authors concluded that collagen scaffolds have limited usefulness for chondrocyte-grafting in large defects. Kawamura et al. recently showed that a collagen gel containing cultured allogenic chondrocytes could be used to induce healing of full-thickness articular cartilage defects in the knees of rabbits[114].

Hendrickson et al. transplanted allogenic chondrocytes from a nine-day-old foal into large (twelve-millimeter) defects in eight knee joints of horses, with use of fibrin as the matrix to carry the cells[92]. At eight months, healing was superior in the defects that had been treated with a graft, which contained 61 percent type-II collagen compared with 25 percent in the controls. The advantage of this approach is that it can be performed arthroscopically in one operation with minimum patient morbidity. It is not clear what limitations regarding the size or shape of the defect may preclude this type of treatment.

Replacement of Damaged Cartilage with Use of Osteochondral Transplants

An alternative to biological regeneration of the joint surface is to replace it with a substitute: either partially, with a series of small osteochondral plugs (mosaicplasty), or completely, with a matched osteochondral transplant. The former usually are obtained from a relatively non-weight-bearing region of the knee, while the latter usually is obtained from an unrelated donor.

Mosaicplasty and Osteochondral Autogenous Grafts

Mosaicplasty involves the autogenous transplantation of at least one cylindrical osteochondral plug from a relatively non-weight-bearing region of the knee into an articular defect. The donor site is usually the edge of the patellar groove or the area just proximal to the intercondylar notch. In concept, this technique is analogous to that of hair transplantation. Its recent dramatic rise in popularity is based on extensive experience in Hungary, where the originators have successfully used it to treat lesions of the knee and the talar dome[85,86]. This technique often can be performed arthroscopically, although it is technically demanding. The procedure requires the use of multiple plugs, which must be obtained, and inserted, perpendicular to the joint surface. Studies will be needed to evaluate the tissue in the repaired joint surface and to compare the results with those for controls. I am not aware of any reports of major complications at the donor site, but the possibility of such complications remains a concern.

Outerbridge et al. reported that ten patients with a large osteochondral defect of the weight-bearing surface of the femoral condyle had successful treatment with use of an autogenous osteochondral graft obtained from the lateral facet of the patella[180]. At an average of six and one-half years after the operation, six patients had no symptoms and four had mild pain in the knee anteriorly. Small osteophytes were present in five patients, and two had mild patellofemoral incongruity. This procedure is probably useful only in carefully selected patients because of the structural alterations created at the donor site.

Osteochondral Allografts

Reports from three different centers have documented the use of fresh osteoarticular allografts for the treatment of isolated posttraumatic articular defects or lesions of osteochondritis dissecans in the region of the knee[13,37,44,72-74,82,125,134,135]. Garrett reported clinical improvement in all ten patients who were followed for two to four years after transplantation of an osteochondral allograft into an articular defect of the femoral condyle[72]. Ghazavi et al. reported clinical success in 85 percent of 126 knees at an average of 7.5 years after they had received similar treatment for a posttraumatic osteochondral defect[74]. Survivorship analysis revealed a 95 percent rate of survival of the graft at five years, a 71 percent rate at ten years, and a 66 percent rate at twenty years. (The 95 percent confidence intervals were not reported.) The criteria for success included an age of less than fifty years, a unipolar defect (involving only one side of the articulation), and normal alignment or unloading by means of an osteotomy. It is difficult to

distinguish the beneficial effects of osteotomy from those of grafting as an unloading osteotomy was performed in 54 percent of the knees.

Chondrocyte viability was demonstrated in articular cartilage that had been refrigerated for twenty-four to forty-eight hours[211] and in retrieved specimens at a maximum of twelve years after transplantation of fresh allografts[38,44,74]; however, the immune response to fresh allografts was more intense than it was to frozen allografts in experiments involving dogs[227]. In experiments involving goats, Jackson et al. found that fresh cartilage allografts contained viable chondrocytes for as long as one year after transplantation, but viability decreased after three weeks[108]. Replacement of a missing portion of the joint surface with a small-fragment osteochondral allograft is a good option for symptomatic patients in whom attempts to induce healing or regeneration of the articular surface are inappropriate or have failed.

Present Status and Future Challenges

At present, efforts to induce healing and regeneration of cartilage are being directed toward enhancing the natural healing potential of cartilage or replacing the damaged cartilage with tissues or cells that can grow cartilage. These approaches have shown promise, but they are still far from reliable and are not sufficiently versatile to be employed in many clinical settings. The ideal patient for most of the current procedures is less than forty-five years old, has an isolated symptomatic chondral or osteochondral lesion in the femoral condyle, and has no evidence of osteoarthritis or malalignment. I believe that the treatment of asymptomatic lesions, including those discovered coincidentally at the time of an operation on the anterior cruciate ligament or the meniscus, should be considered experimental.

Future treatments will likely involve the implantation of tissues and cells that respond to local stimuli by growing and differentiating into mature chondrocytes capable of producing extracellular matrix that will integrate into surrounding tissue. This will probably involve *in vitro* conditioning of the transplant as well as regulating it after implantation. The key to success will be determined by our ability to understand and take advantage of natural processes.

The current limitations and future challenges with regard to the healing and regeneration of articular cartilage are both technical and biological. Technically, it will be necessary to develop appropriate scaffolds and adhesives as well as methods for the local and temporal delivery of growth factors and cytokines. Ideally, these techniques should be adapted so that they can be performed arthroscopically and be made less demanding. Biological challenges include the variable quality and quantity of the cartilage that is produced, decreasing responsiveness with age, bonding to the adjacent cartilage, and restoration of the subchondral bone. Most importantly, it will be necessary to clarify the process of chondrogenesis and its regulation at the cellular and molecular levels so that we can most intelligently control and optimize it.

As with all new developments, there is both skepticism and excitement. There are plenty of reasons for us to be excited, but a healthy degree of skepticism also is appropriate. Not all of the statements and claims that are being made can be substantiated by data. All current methods for the healing and regeneration of cartilage should be considered investigational until they can be proved in rigorous clinical trials, which, ideally, should be randomized, controlled, and blinded.

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