A critical analysis of cartilage repair

Sir—In 1987, Shimizu et al. (1987) stated that *There is no way to assess the repair of cartilage that is universally applicable, generally accepted and beyond criticism.* This statement is applicable to our report (Brittberg et al. 1994a) regarding cartilage repair with autologous chondrocytes that was so critically reviewed by Messner and Gillquist in *Acta Orthopaedica Scandinavica* 1996; 67 (5): 523-529. A critical review of cartilage repair techniques could be beneficial to the field, but, alas, an unbalanced review is not. As advocated by Messner and Gillquist, the conclusion and discussion should be scientific—i.e., well documented and based on facts. Conclusions of Messner and Gillquist, such as *repair enhancement methods have failed to improve cartilage repair mechanisms more than that found after natural repair of an untreated defect* are unacceptable if such arguments are used. Furthermore, it is not helpful that the authors use words like *flaws* and *ignorance* regarding references in our paper to other studies or *erroneous conclusions* and *false interpretation of data.* Such statements are far from scientific and are questionnable in a journal of the quality of *Acta Orthopaedica Scandinavica.* The authors not only show ignorance of their colleague's work, but also appear to impute incompetence to the referees and editors of one of the world's most prestigious medical journals. One should note that the report by Brittberg et al. (1994a) was awarded recognition as one of the 10 best scientific papers in 1994 by the *Harvard Health Letter* (Thomas 1995).

Arthrosis means organ failure (Radin 1995) and the etiology of the disease in most cases is unclear (Dieppe 1995). Genetic susceptibility may be a cause, but the literature often discusses posttraumatic causes (Dieppe 1995). To what extent a single cartilage lesion could develop into arthrosis is not known; the natural course of a single or focal cartilage lesion has yet to be fully determined. In experimental studies, incongruity and step-off in joint articulation lead to degenerative changes in the cartilage and subchondral bone that mimick the appearance of arthrosis (Lefkoe et al. 1992). Incongruence in the cartilage could lead to symptoms such as locking or catching of the knee, localized pain and swelling. Filling a defect with a repair tissue can reduce symptoms but it may not prevent further deterioration of the cartilaginous tissue. Our article regarding autologous chondrocyte grafting deals with the treatment of focal cartilage defects of the knee joint which were causing a chronic disability, demonstrable for at least three years prior to the cell-grafting. It was an experimental study based on the results of an animal model used in several rabbit experiments (Peterson et al. 1984, Brittberg et al. 1989, Grande et al. 1989, Brittberg et al. 1996). Our aim was to explore whether this model could be applied to human problems. We think that the human experimental study is an adequate scientific step for evaluating the feasibility of the treatment before going on to randomized studies. The first successful use of cultured cells in the treatment of tissue damage, where nature is unable to heal itself, was the life-saving use of cultured skin cells demonstrated by Dr Howard Green in 1984, which was published in the *New England Journal of Medicine (NEJM)* and not in a dermatology journal (Gallico et al. 1984). We sent our paper to the *NEJM* because there exist similarities between the two cell-repair techniques—not because of a breakthrough in the repair of cartilage defects or in treatments of arthrosis but because it demonstrated the use of cultured autologous chondrocytes as an example of tissue engineering that could be used to repair cartilage injuries. *NEJM* is a journal enjoying world-wide respect and has readers among all medical specialities. Tissue engineering has attracted experts from many research fields, including chemical engineering, material science, surgery, genetics, etc. The results were evaluated in the first 23 patients treated with autologous chondrocyte transplantations; this was a prospective study in which the patients served as their own controls. It is well accepted that new treatments may be approved for publication without double-blinded randomized controlled trials. The article was rewritten, as proposed by the editors of *NEJM*. Reviewers suggested that the amount of degenerative disease in the USA should be stated. Thus figures regarding arthrosis were mentioned in the report, but it is not suggested that cartilage resurfacing with chondrocytes could eliminate the need for 500,000 artificial joint replacements per year in the USA. In the text it is said that if the treatment of cartilage injuries of the knee at an early stage could prevent the development into arthrosis, the need for a total joint replacement might be postponed or eliminated. The concept of treating body defects by growing committed cells for its own replacement parts was considered the most interesting aspect of the article. However, we were surprised by the enormous impact of the article throughout the world. In any case, the

media interest initiated a public discussion and, we fear, created premature or unrealistic dreams of a treatment for disabling arthrosis regardless of its etiology and the age of the patients. On the other hand, the enormous media interest also aroused greater interest in cartilage research, which we believe is potentially beneficial for the field. The article by Homminga et al. about perichondrial resurfacing evoked little interest in 1990 and it is likely that if our article had appeared in an ordinary orthopedic journal the interest might also have been limited.

Messner and Gillquist appear astonished that we did not mention our own work on carbon fiber (Brittberg et al. 1994b) or Homminga's experience with human perichondrial resurfacing (Homminga et al. 1990). According to the rules as to citations in *NEJM*, such references must have been published, the carbon article did not fullfil these criteria at that time. Furthermore, that carbon fiber report involved early arthrosis of the knee and patients who were *salvage cases*. These patients had widespread lesions and should not be compared to patients with focal lesions. In regard to the carbon article, Messner and Gillquist mentioned that no arthroscopies were done, but if the authors had read the article carefully they should have noted that 20 of the 37 patients were examined by arthroscopy. The work by Homminga was not mentioned in the *NEJM* report, which we agree was unfortunate. Ironically, now two years after the release of our *NEJM* paper, Messner and Gillquist themselves fail to provide full information regarding the clinical results of perichondrial resurfacing. The first 14 patients in Homminga's perichondral series were assessed at a mean time of 24 months at which time their mean knee score increased slightly from 85 to 87. In a later follow-up in a larger study group of 88 patients in the Homminga's perichondrial series, 18 of the patients suffered graft failure and only 33 of the patients had good results after 8 years. As early as 1992, 2 years before the *NEJM* paper, Beckers and colleagues analyzed their clinical results after perichondrial transplantation for cartilage defects of the knee (Beckers et al. 1992). Their series included a mixture of patients with focal defects as well as arthrosis. After a mean follow-up period of 32 months, of 80 studied patients, 42 patients were classified as failures and lost grafts. Failure occurred at an average of 18 months after the operation, especially in the patients with arthrosis. The problem of detachment of the perichondral graft tissue has also been reported as early as in 1981 when Kon reported in an animal study that 16 of 50 grafts failed to attach to the underlying bone. Although, it was not proven that the calcification was the only cause of the bad results, graft fixation and graft calcification are major problems in perichondrial grafting, and produce poor clinical outcome in a majority of the cases. In the *NEJM* paper, we could also have mentioned periosteal resurfacing, as described clinically by Korkala and Hukkanen (1991) regarding patellar and medial condylar resurfacing, Hoikka et al.'s (1990) treatment of patellar surface, Angermann and Riegels-Nielsen's regarding periosteal resurfacing of osteochondritis dissecans (1994). Unfortunately, the customary brevity of the *NEJM* did not allow for such extensive discussion, particularly since the essence of the paper was a description of the method of autologous cells as the source for repair.

It is now a well-known fact that the results using the perichondrium deteriorate with time. Homminga himself has started to study the technique of chondrocyte grafting and is collaborating with our group in Göteborg. The available knowledge regarding problems with graft fixation and possible related calcification should be mentioned in an article on cartilage repair techniques. The Messner and Gillquist article can be viewed as a direct criticism of our work rather than a review of cartilage repair. Our ongoing long-term study has been continually examined by unbiased persons (Chiltern International) and hitherto the percentage of good results remains high and without evidence of mineralization of grafts.

Messner and Gillquist attempted to compare different treatment methods and their related clinical outcomes. However, as mentioned previously, patients with widespread degenerative lesions (Brittberg et al. 1994b, Brittberg 1996) should not be compared to patients having focal well-contained defects with surrounding good cartilage. Resurfacing techniques for the finger joints (Engkvist and Johansson 1980) should not be compared to the treatments of the knee joints. In our paper on the treatment of cartilage defects with chondrocytes, all the patients had deep lesions with exposed bare bone. Such lesions are known to be difficult to treat (Dzioba 1988). Partial-thickness lesions are reported in several papers to do well after debridement and shaving procedures (Shariaree 1986, Hubbard 1987, Dzioba 1988). Messner and Gillquist refer to the good results in the article by Messner and Maletius (1996) concerning 28 patients who were retrospectively examined at a mean of 14 years after their inital joint trauma with chondral damage. This article was solely based on the high Lysholm-scores and not on pain scores or radiographic images and none of the patients had a second arthroscopic evaluation. 25 of the 28 patients had partial thickness defects and 3 had bare bone. The study shows that 11 of 28 patients did not have pain when

they were included in the study—do the authors really consider this group represents *severe* cartilage damage? Of note, after 14 years, the majority of the patients experienced pain during daily activities. Only 6 of 28 patients had no symptoms of pain, swelling or locking. Moreover, 19 patients underwent some kind of surgical treatment, such as Pridie drilling, shaving or removal of a free body. Furthermore, there was a high incidence of joint-space narrowing at follow-up and in 16 of the patients, radiographic signs of arthrosis. Do these results warrant the conclusion that the outcome is strikingly good? We do not support the statement that the natural course is favorable. In the article no information is provided whether the defects were superficial, medium or deep partial lesions, critical information for interpretation of the clinical outcome (Ogilvie-Harris and Jackson 1984, Dzioba 1988). Our patients had bare bone defects known for more than 3 years which had not responded to conventional treatment. If Messner and Gillquist wish to discuss the importance of clear and unflawed articles, it is of utmost importance to the credibility of the critical review that the authors at least try to follow their own guidelines. Otherwise, even in an orthopedic journal, the information given to our colleagues who are treating cartilage defects could be misleading.

So far as we know, no common evaluation system of postsurgery results in cartilage repair and no accepted classification system regarding the description of the cartilage defects exist. It is difficult to compare the results of different cartilage treatments and a complete evaluation of cartilage repair technique is possible only if biopsies are taken. Some series include patients with advanced degenerative lesions, while others include patients with focal cartilage defects in otherwise normal joints. These are not randomized, controlled studies and the follow-ups vary greatly, as also does the measurement of outcome. Not mentioned in the Messner-Gillquist article is the fact that we have started a multicenter, randomized study of the treatment of focal cartilage defects on the medial femoral condyle. Three treatment groups are to be randomized. Patients 18–48 years of age with focal cartilage lesions down to the bone (1–10 cm in diameter) will be randomized into either multiple subchondral drilling transarthroscopically with a 2 mm drill, periosteal resurfacing without opening of the subchondral space but with additional injections of nutrional medium or periosteal resurfacing and additional injections of autologous chondrocytes and nutrional medium. The last two groups are *blinded* and thus neither the physician nor the patients will know the content of the injected medium. Furthermore, at the Universities of Lund and Malmö, a similar study will be started with identical criteria and follow-ups, but with two groups: subchondral drilling versus autologous cell transplantation (cells grown in our lab).

In Stockholm, a group at St. Göran's Hospital has started to grow their own cells (not yet validated in Göteborg) and they are ready to start a randomized study where the postoperative results are to be followed by surgeons at Huddinge Hospital. In England at Agnes Hunt and Robert Jones Hospital, Ostwestry, a randomized study is planned with cells prepared by Genzyme, where cell transplantation will be compared to debridements. These studies are of extreme importance. Hopefully, other centers could join us in similar studies—for example, in the study of perichondrial resurfacing.

The pilot study shows that the effects of repair seen in the rabbits are transferrable and could also apply to wear in humans. We have never claimed that our results are better than those with other similar techniques.

In medicine, we often discuss symptom-modifying and disease-modifying antirheumatic drugs. For arthrosis, no disease-modifying drug exists. In operative procedures for the treatment of local cartilage defects, we could use the terms of "symptom-modifying operative procedures and disease-modifying operative procedures". Our technique could be viewed as one symptom-modifying operative procedure among others. It needs further evaluation like that in the randomized prospective studies. The use of tissue engineering with committed chondrocytes is new, other techniques use cells of primitive origin with chondrogenic properties.

The commercial availability of the technology may be contentious and therefore we also think that reliable validated measurements of outcome in well controlled studies using the different available clinical resurfacing techniques should be done before a technique is launched on the market as a commercial product (Jackson and Simon 1996). However, several bioengineering companies have long been working in this field and it is therefore important to present results that can stimulate the ongoing research. The cell technique is available for many but cell culture procedures should also be validated. The Genzyme technique for cell cultures is the only cell-culturing laboratory considered by our cell laboratory to be efficient.

Techniques for multiple autologous osteochondral grafting, such as the mosaicplasty produced by Smith & Nephew (Hangody et al. 1996) and OATS (Osteochondral Autograft Transfer System) by Arthrex (Bobic 1996) have recently appeared on the market. These are less expensive to use, but there are few pub-

lished data and also no controlled studies regarding the technique. Because of the controversies regarding chondrocyte transplantation and the increasing awareness and demands to treat chondral injuries, we think the use of these methods will spread rapidly. It would have been interesting to have heard Messner and Gillquist's views about such techniques in a review article on cartilage repair.

Hopefully, we shall be able to use the great interest in cartilage as something positive. The critical review by Messner and Gillquist, despite its misunderstandings, has given us the opportunity to discuss our goal of presenting more knowledge as clearly as possible, in order to reveal the secrets of cartilage and enhance its poor reparative capacity.

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Sir–The cartilage resurfacing technique with autologous chondrocytes described by Brittberg et al. (1994a) has no adequate scientific foundation yet. The authors directly admit that in their letter to the editor *(Our technique...needs further evaluation...)*. In the future, it may be shown to be a success or a failure, but when it was introduced with an enormous media coverage and also commercialized, there was not a proper background for the method. We are not criticizing the method as such, but the way in which the authors have presented and used their limited results. We also criticize the fact that they make it appear that the technique was superior to other techniques by not discussing relevant references. In their discussion (Brittberg et al. 1994a), they state that: *The tissue that results from these reparative techniques* (= techniques other than chondrocyte transplantation, our comment) *is disorganized fibrocartilagenous tissue with type I collagen fibers that is unable to restore the biomechanical properties of normal articular cartilage.* Regarding their own technique, they state: *Our results indicate that cultured autologous chondrocytes can be used to repair articular cartilage defects in the femorotibial joint and that this treatment restores the function of the joint by forming predominantly hyaline-like cartilage containing type II collagen.* The authors imply that autologous chondrocyte transplantation is much better than other techniques. It is interesting to find that the data for the collagen II analysis are used to prove the superiority, even if they are not presented in the article (data not shown, pages 891 and 893, Brittberg et al. 1994a). This is a strange practice that is usually not allowed by scientific journals.

In the letter to the editor, the authors also continue to confuse an isolated chondral defect with arthrosis. This is not the same thing. It has not been shown that chondral defects lead to arthrosis. The authors also try to blame the editorial process of *New England Journal of Medicine* both for this confusion and for the lack of certain references as well as the exaggerated importance of their results *(The article was rewritten, as suggested by the editors of NEJM. Reviewers suggested that the proportion of degenerative disease in the USA should be mentioned)*. However, the authors of an article are solely responsible for its contents and should reject any attempt by an editor or reviewers to skew the information, as will happen when important references are left out and when isolated chondral defects are confused with arthrosis. This is especially important in a journal with a large impact on media and public opinion.

We find it very interesting that the article by Brittberg et al. on carbon fiber implants (1994b) describes clinical results similar to those after autologous chondrocyte transplantation, although the patients had more serious problems. The authors' remark to the editor that *The patients had widespread lesions and should not be compared to patients with focal lesions* is interesting. On page 72 in his thesis (1996), Brittberg states: *Clinical signs noticed in chondrocyte grafting and in carbon fiber resurfacing were the disappearance of the different degrees of locking of the knee. The leveling out of the lesions with high-quantity engineered repair tissue, able to withstand loads of axial and radial forces, appears to be the explanation of this effect.* Brittberg states the following on page 69: *Both of our articular cartilage resurfacing techniques make use of an autologous source of repair cells; exogenous, expanded, mature, autologous chondrocytes or autologous repair cells invading the defect in an ordered fashion via the carbon filaments*

implanted in the subchondral bone. Extending either of these techniques to treat widespread global joint damage is not possible ... It seems that the authors compare the two techniques to a much greater extent than we ever did! How it is possible to avoid joint arthroplasty (*New England Journal of Medicine* article), if the techniques cannot be *extended to widespread ... joint damage?*

A survey of a research field should be based on information from published articles as much as possible since abstracts from conferences and various meetings usually do not contain enough solid information for a detailed analysis. In that regard the *Acta Orthopaedica Scandinavica's* practice of publishing general tables with all the data is of great importance. Therefore it is a pity that any negative results with the periosteum transplantation technique (Homminga et al. 1990) have not been published by Homminga et al., except in a symposium that is not accessible to everyone.

With regard to printed publications the studies planned by the authors and other groups to examine carefully the effect of autologous chondrocytes cannot be discussed until they are published. We can hardly be blamed for not knowing what the authors plan to do in the future. It is good that studies like these are planned, but they should have been done in the first place!

Nor is it possible to discuss any other commercial techniques that may exist on the market if there is so little supporting evidence in scientific studies.

We share Jackson and Simon's (1996) concern about the commercialization of this area and agree with their conclusion about the chondrocyte transplantation technique: *Meanwhile, until more information is available on the safety and efficacy of these new treatments, caution should be used in the widespread and uncontrolled application of this technology.* We stated the same view in our review article: *Certainly, the step from animal experiments on cartilage repair to a clinical application is a step too far, too soon* (p 527) (Messner and Gillquist 1996).

Rapid commercialization is not the best way to guarantee that caution is exercised in patient selection and indications. Instead, a commercial party always needs to increase profits so much as possible. As researchers in a world of increasing commercialism we must keep a clear borderline between science and industry, until facts from randomized trials show that the proposed treatment really is superior to other treatments. This is especially important in a new treatment that increases the costs of medical care, without any proven better effect than previous treatments.

Contrary to the facts listed above, Brittberg et al. (1997) state in their letter to the editor that they never said that the results with chondrocyte transplantation were better than any other treatment. Then, what is the point?

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