ARTICULAR CARTILAGE CHANGES IN CHONDROMALACIA PATELLAE

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Full thickness samples of articular cartilage were removed from areas of chondromalacia on the medial and "odd" facets of the patellae of 21 adults and examined by histology, autoradiography and electron microscopy. Surface fibrillation, loss of superficial matrix staining and reduced $^{35}\text{SO}_4$ labelling was seen, with little change in the deep zone.

Ten cases showed "fibrous metaplasia" of the superficial cartilage with definite evidence of cell division and apparent smoothing of the surface. Scattered chondrocyte replication appeared to occur in the surrounding intact cartilage. The findings suggest that early lesions in chondromalacia patellae may heal either by cartilage or fibrous metaplasia and that this may account for the resolution of clinical symptoms.

The term chondromalacia patellae, meaning softening of the patellar cartilage, is widely used to designate a clinical syndrome of retropatellar pain, often with giving-way, patellofemoral crepitus and wasting of the quadriceps, which is associated with softening or fibrillation of the articular cartilage of the patella. The macroscopic, histological and electron microscopic appearances are almost indistinguishable from those of osteoarthritis (Meachim and Fergie 1975) but definite progression from one to the other has not been recorded. Karlson (1940) followed a group of patients with chondromalacia patellae for 20 years and found little evidence of degenerative change in the patellofemoral joint, while older patients with osteoarthritis of this or the whole knee joint rarely give a history of the symptoms of chondromalacia patellae in adolescence or early adult life. This suggests that the condition does not progress and in about two-thirds of patients the symptoms do in fact resolve without operation (Bentley 1970).

The clinical observations that symptoms are self-limiting and may settle spontaneously, and that chondromalacia patellae does not progress to fully developed osteoarthritis in later life, suggest that the two diseases are different entities. They also suggest that the pathological changes in the articular cartilage may be self-limiting. This raises the interesting question of possible reversal of early cartilage changes and even of complete healing. Theoretically this is unlikely; adult articular cartilage was reported not to heal by William Hunter in

1743 and by numerous authors since then (Redfern 1851; Fisher 1922; DePalma, McKeever and Subin 1966; Mankin and Boyle 1967; Meachim and Osborne 1970; Bentley 1972). The suggestion that articular cartilage may heal is particularly interesting since chondromalacia patellae is the only common clinical condition of articular cartilage which presents with symptoms before gross breakdown has occurred. Since the early diagnosis of breakdown of articular cartilage is now possible by methods such as arthroscopy, it may become possible to enhance healing at an earlier stage by drugs, prophylactic operation or other means.

It is surprising that there are few descriptions of the appearances of the articular cartilage of the patella. The gross appearances of the areas affected by spontaneous degeneration were described in detail by Bennett, Waine and Bauer (1942), and the mechanical properties by Hirsch (1944). Outerbridge (1961) defined the sites of fibrillation and erosion in chondromalacia patellae on the medial and the "odd" facet and described four grades according to the extent of macroscopic involvement. Ficat (1973) described the rarer involvement of the lateral facet in the "hyperpression externe" syndrome. Lund and Telhag (1978) examined articular cartilage from patients with chondromalacia patellae and found that although there was some increase in synthesis of DNA and RNA, autoradiography provided no direct evidence of cellular replication. This suggested that healing could not occur since this would require both cellular replication and new matrix formation.

In several investigations of patients with chondromalacia patellae and persistent retropatellar pain, full thickness cartilage has been carefully removed from the underlying bone and examined with particular interest in evidence of cell division or healing of matrix, and in signs

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Fig. 1

Specimen of the full thickness of articular cartilage from an area of chondromalacia patellae of the medial facet, showing surface fibrillation and loss of matrix staining in Zones I and II. Normal staining is seen in the deep Zone III, with several scattered chondrocyte clusters. (Toluidine blue, $\times 10$).

of repair of articular cartilage by tissue other than hyaline cartilage (Bentley, Leslie and Fischer 1981; Bentley and Dowd 1984).

MATERIALS AND METHOD

Full thickness specimens of articular cartilage were removed from the undersurface of the patella in 21 adult patients at exploration of the knee for persistent retropatellar pain. The 16 women and 5 men had all failed to improve with treatment by physiotherapy, quadriceps strengthening and avoidance of provocative activities. At arthroscopy the area affected had been estimated to be greater than 1 cm in diameter, and arthrotomy was performed through a medial parapatellar incision. All 21 patients had Grade 2 or 3 involvement (Outerbridge 1961) of the odd or medial facet or both. The macroscopically fibrillated area of cartilage was excised by vertical cuts with a scalpel and careful separation from the subchondral bone with a small gouge.

The specimens were then placed in tubes containing

Eagle basal medium to which had been added 100 microcuries of either $^{35}\text{SO}_4$ or $[^3\text{H}]\text{thymidine}$ and 100 units of penicillin with 100 mg of streptomycin. The tubes were then incubated at 37 C for 12 hours after which the specimens were washed several times in the medium, fixed in formalin and prepared for section cutting by mounting in paraffin blocks. Sections 6 μm thick were cut, mounted on glass slides and stained with haematoxylin and eosin and with alcoholic toluidine blue to show the general distribution of glycosaminoglycans in the matrix.

Autoradiographs were prepared by the dipping technique of Jofte (1959) using Kodak NTB3 emulsion. After drying, the slides were maintained in light-proof boxes at 4 C for two weeks and developing and fixing was followed by staining with haematoxylin and eosin. For ethical reasons normal cartilage was not removed to serve as control material.

RESULTS

All of the patellae showed macroscopic fibrillation or obvious softening of the surface cartilage, but no separation from the subchondral bone, and considerable pressure with a gouge was required to detach the specimens from the subchondral bone.

Microscopy. A constant feature was surface fibrillation with reduction in the number of superficial cells, some of which were dead, with loss of staining of the superficial matrix with toluidine blue (Fig. 1). This indicates a primary defect in either the superficial cells or the surface collagen (Freeman 1974). In most cases the fibrils were alongside deep clefts, but in a few cases they were of the short type, similar to those seen in osteoarthritis. In all except one case the deep matrix was normal in appearance. The "cartilage thinning" phenomenon described by Meachim (personal communication 1983) in which cartilage was eroded to a certain level and then smoothed off, was not obvious.

"Fibrous metaplasia" of chondrocytes. A surprising finding in the superficial zone was a greatly increased number of small cells lacking typical chondrocyte lacunae and showing all the appearances of fibroblasts (Figs 2 and 3).

Fig. 2

Fig. 3

Figure 2—Full thickness articular cartilage showing "fibrous metaplasia" of the superficial Zone I and upper middle Zone II. Cells are very numerous and the tissue appears to be fibrous. The deep cartilage has a normal appearance. (Toluidine blue, $\times 10$). Figure 3—A high power view of part of Figure 2 to show the fibrous metaplasia of the superficial cartilage (Toluidine blue, $\times 20$).

Fig. 4

Fig. 5

Figure 4—Full thickness specimen of articular cartilage viewed by polarised light showing “fibrous metaplasia” extending into Zones I and II, but not into Zone III. (Toluidine blue, $\times 5$). Figure 5—From the same specimen as Figure 4 showing the obviously fibrous nature of the affected cartilage in comparison with the normal appearance. (Toluidine blue, $\times 20$).

Such changes were present in 10 of the 21 cases. Care was taken to exclude confusing these cells with those which may appear from subchondral bone marrow after full thickness cartilage loss or from synovial cell encroachment across the damaged surface. In association with these changes the surface of the cartilage appeared to have repaired and smoothed off.

The cells appeared to have undergone metaplasia to a more primitive fibroblast cell type; examination by polarised light confirmed the fibrous nature of the tissue (Figs 4 and 5). In one case only this fibrous metaplasia filled the whole thickness of the cartilage and could

therefore have arisen from underlying bone marrow cells.

Chondrocyte clusters. These were seen frequently, scattered throughout the cartilage presumably either as a response to matrix loss or as a degenerative phenomenon. In eight cases obvious labelling of the clusters with [^3H]thymidine suggested that cell division was a regenerative response to loss of matrix (Figs 6 and 9).

Autoradiography. $^{35}\text{SO}_4$ labelling. The appearances of sections labelled with $^{35}\text{SO}_4$ was consistent with the histological appearances of slides stained with haematoxylin and eosin and with toluidine blue. The superficial

Fig. 6

Fig. 7

Figure 6—Low power autoradiograph of articular cartilage showing scattered chondrocyte clusters in Zones I and II. S = surface. (Haematoxylin and eosin, $\times 20$). Figure 7—An autoradiograph with $^{35}\text{SO}_4$ to show the absence of label in Zone I and upper Zone II of articular cartilage with normal labelling in Zone III. (Haematoxylin and eosin, $\times 5$).

Fig. 8

Fig. 9

Figure 8—Tritiated thymidine autoradiograph from the same specimen as Figure 3 showing frequent labelling of the cells (arrows) within the area of "fibrous metaplasia". (Haematoxylin and eosin, $\times 20$). Figure 9—Tritiated thymidine autoradiograph of articular cartilage from the same specimen as Figure 6, seen at high power. The labelling of the chondrocyte clusters indicates cell division. (Haematoxylin and eosin, $\times 50$).

zones (Zone I and upper Zone II) generally showed extensive cell death; the absence or reduction of labelling indicated extensive cell damage and the absence of production of sulphate-containing glycosaminoglycans (Fig. 7). In no instance was there any excessively heavy labelling with $^{35}\text{SO}_4$ which would have suggested increased matrix production of glycosaminoglycans.

Tritiated thymidine labelling. Labelling with $[^3\text{H}]$ thymidine over the nuclei of the cells was seen at three main sites. First, in areas of fibrous metaplasia, where cells frequently showed labelling which indicated impending or recent cell division (Fig. 8). Secondly, scattered labelling was seen in a random distribution, in the deeper zones of cartilage, presumably indicating a general response of

the cartilage cells to matrix depletion. Thirdly, in 50% of clusters there was labelling with $[^3\text{H}]$ thymidine, confirming that these clusters were the result of cell division (Fig. 9).

In summary, microscopic changes included depletion of glycosaminoglycans in the matrix in Zones I and II, and response by cell division in the damaged cartilage giving the appearances of metaplasia-in-situ to fibrous tissue. Some proliferative cell activity was also seen in intact cartilage close to areas of damage. This is an extremely interesting finding, since mature cartilage has generally been considered to undergo cell division rarely. It is contrary to the findings of Lund and Telhag (1978), but the labelling of the areas of fibrous metaplasia with $[^3\text{H}]$ thymidine does strongly suggest active replication of cells.

Electron microscopy. Fourteen samples of cartilage, each 2 mm by 2 mm, were removed from typical areas at operation, fixed with gluteraldehyde and prepared for electron microscopy. They were examined in a Jeol T8 electron microscope, and the main findings are listed below.

- The absence of chondrocytes in the extensively damaged superficial cartilage was confirmed. Typical chondrocytes and matrix were seen in the deeper layers of the cartilage (Fig. 10).
- Elongated cells in the areas of fibrous metaplasia showed the appearance of fibroblasts; in one instance a long cellular process was considered to be typical of this type of cell. Coarse collagen typical of fibrous tissue was found in these areas, helping to confirm the fibrous nature of the matrix (Figs 11 and 12).
- Chondrocyte clusters of active cells and paired cells were seen quite frequently (Fig. 13) and in some cases probably resulted from cell division (Fig. 14).

Fig. 10

A typical chondrocyte from Zone II in a lacuna which shows cross banded collagen randomly orientated and some matrix vesicles, mv. ($\times 6500$, reduction to 50%).

Fig. 11

Fig. 12

Two parts of a cell from an area of cartilage showing "fibrous metaplasia". The matrix is of fibroblastic type with dense bundles of collagen fibres and the elongated process (*P* in both views) is a feature of fibroblasts. ($\times 4000$, reduction to 40%).

DISCUSSION

Relationship of chondromalacia patellae to progressive osteoarthritis. Meachim (1982) made a necropsy study of 88 knees in European subjects and drew attention to the distribution of changes in the articular cartilage of the patellae. Although macroscopic lesions usually first appeared on the medial or central segment of the patella and with increasing age tended to affect all three segments (medial, central and lateral), he noted that macroscopic lesions on the lateral and central segments were more likely than medial lesions to progress to bone exposure. This observation correlates with our findings and suggests that there is little evidence that chondromalacia

of the medial and "odd" facets of the patella progresses to osteoarthritis in later life.

Fibrous metaplasia and articular cartilage. The findings in this study indicate that a sequence of changes may occur in articular cartilage in chondromalacia patellae. Surface breakdown leading to fibrillation may be caused either by trauma and collagen fatigue failure or by matrix depletion from the effect of cathepsins released from the lysosomes of chondrocytes. This results in cell injury and death in the areas of immediate damage. The cells in these areas which survive respond either by cellular proliferation or by undergoing metaplasia to a more primitive tissue resembling fibrocartilage (Figs 2 and 3).

If for any reason the trauma to the articular carti-

Fig. 14

Fig. 13

Figure 13—Chondrocyte cell cluster of four active cells separated by fine filamentous material and showing prominent mitochondria, *M*. ($\times 2000$, reduction to 40%). Figure 14—Two chondrocytes with no matrix between them suggesting they arise from recent cell division. ($\times 4000$, reduction to 40%).

lage is reduced, for example by reduced activity, intensive quadriceps exercises or by a realignment operation, repair of cartilage may occur. If the damage has been minimal complete surface repair may result. Where it is more extensive surviving chondrocytes undergo metaplasia to fibroblasts and the vigorous cellular activity and replication results in a fibrous tissue repair of the defect, which may produce a smooth surface macroscopically indistinguishable from normal articular cartilage.

This theory is supported by observations on chondrocytes in cell culture by Aston and Bentley (1982), who found that multiplication of cells accompanied by modulation of chondrocytes to a more primitive type of fibroblastic cell is normally seen unless the cells are maintained at high density. It is proposed that when matrix or cell loss occurs in intact cartilage, the situation is similar to that in cell culture. As the cells become more sparsely distributed, and more deprived of normal matrix and nutrients, they de-differentiate and multiply to form fibroblast-like cells which are more primitive and have much less specialised nutritional requirements.

Lund and Telhag (1978) studied articular cartilage from cases of chondromalacia patellae and compared this with normal and osteoarthritic cartilage by histology and by quantitative radioactive labelling. They found that there was no labelling of cells with [³H]thymidine either singly or in cell clusters. They also found that the DNA content was decreased compared with normal cartilage and correlated this with reduced cell density and the absence of cells labelled with [³H]thymidine. An explanation for these findings may be that the decrease in total content of DNA was caused by extensive cell death even though the relatively few remaining cells were producing an increased amount of DNA. In support of this argument, in this study definite [³H]thymidine labelling on autoradiography was seen in 15 of the 22 cases either within fibrillated cartilage (4 cases), in deep cartilage (7 cases), in both (2 cases) or in cell clusters (2 cases). In a further four cases [³H]thymidine labelling of cells in fibrous tissue was observed. These findings indicate DNA synthesis in the remaining cells whether they were cartilage cells or a more primitive type. Electron micrographs also confirmed the presence of fibroblast-like cells and a fibrous matrix occurring *in situ*, providing strong presumptive evidence of cell division in intact cartilage close to fibrillated areas.

These findings indicate that there is a capacity for cellular multiplication within articular cartilage in chondromalacia patellae. Whether small defects may heal to produce complete restoration of normal hyaline cartilage remains unknown; it appears more likely that

any but the smallest defects are repaired by fibrous metaplasia and the formation of fibrous tissue. The implications of these findings for the early treatment of joints affected by chondromalacia are considerable, especially if it is shown that healing could be influenced by drugs or by the alteration of joint mechanics.

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