TRIAMCINOLONE HEXACETONIDE PROTECTS AGAINST FIBRILLATION AND OSTEOPHYTE FORMATION FOLLOWING CHEMICALLY INDUCED ARTICULAR CARTILAGE DAMAGE

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Although corticosteroids have been shown to cause articular cartilage degeneration, recent studies of experimentally induced osteoarthritis indicate that under certain conditions they may protect against cartilage damage and osteophyte formation. The present study examines the in vivo effect of triamcinolone hexacetonide on the degeneration of articular cartilage which occurs following intraarticular injection of sodium iodoacetate. Three weeks after a single injection of iodoacetate into the knees of guinea pigs, ipsilateral femoral condylar cartilage exhibited fibrillation, loss of staining with Safranin O, depletion of chondrocytes, and prominent osteophytes. In striking contrast, when triamcinolone hexacetonide was injected into the ipsilateral knee 24 hours after the intraarticular injection of iodoacetate, fibrillation was noted in only 1 of 6 samples, osteophytes were much less prominent, pericellular staining with Safranin O persisted, and cell loss was less extensive. Knees of animals which received only one-tenth as much intraarticular triamcinolone hexacetonide after the iodoacetate injection also exhibited marked reduction in size and extent of osteophytes. However, the degree of fibrillation, loss of Safranin O staining, and chondrocyte depletion was similar to that observed in animals injected with iodoacetate but not treated with intraarticular steroid. No apparent morphologic or histochemical changes were observed after intraarticular injection of the steroid preparation alone. Thus, triamcinolone hexacetonide produced a marked, dose-dependent protective effect in this model of chemically induced articular cartilage damage.

While administration of corticosteroids may result in degeneration of articular cartilage (1–4), intraarticular corticosteroid injections are commonly used in the treatment of osteoarthritis (OA) in humans (5,6) and have been shown to protect against some of the degenerative cartilage changes in experimental animal models of OA (4,7). Butler et al (8) reported that a single injection of triamcinolone hexacetonide (TH) into the ipsilateral knee of rabbits which had been subjected to partial lateral meniscectomy and transection of the sesamoid and collateral fibular ligaments reduced chondrocyte cloning, loss of cells, osteophyte formation, and fibrillation. Similarly, Goldberg et al (4) found that weekly intraarticular injections of triamcinolone acetate, which has a much shorter duration of action than TH, reduced osteophyte formation in rabbit knees after partial medial meniscectomy.

We have shown recently that intraarticular injection of sodium iodoacetate (IA) in guinea pig knees causes progressive degeneration of articular cartilage, with fibrillation, chondrocyte depletion, diminished staining of the articular cartilage with Safranin O (indicating a loss of matrix proteoglycans), and formation of prominent osteophytes (9). In light of the

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Table 1. Grading of severity of joint abnormalities

Abnormality	Grade				
	0	+1	+2	+3	+4
Defects in articular surface	None	Focal, extending to the transitional zone	Moderate, covering up to 50% of articular surface and extending to radial zone	Widespread, covering more than 50% of articular surface and extending into radial zone	Total loss of uncalcified zone
Osteophytes	None	Early cartilage metaplasia, no exophytic bulge	Small exophytic bulge	Moderate exophytic bulge	Large exophytic bulge
Loss of Safranin O staining	None	Focal, confined to transitional zone	Moderate, extending into radial zone	Marked, extending to tidemark	Complete, including uncalcified cartilage
Chondrocyte depletion	None	Slight	Moderate	Marked	Virtually complete

previous data suggesting that corticosteroids may protect against mechanically induced OA, the present study was designed to determine if TH could modify the cartilage damage caused by IA.

MATERIALS AND METHODS

Animals. Adult male albino guinea pigs (32–40 weeks old; mean weight 570 gm) were housed individually in 18″ × 18″ × 18″ stainless steel wire-bottom cages and fed Guinea Pig Chow 5025 (Ralston Purina, Richmond, IN) (ascorbic acid content 1.0 mg/gm) ad libitum (10). Food intake was monitored daily.

The guinea pigs were randomly divided into 7 experimental groups. Group 1 consisted of 6 animals which received a single injection of IA (0.3 mg/kg) into the left knee. Group 2 comprised 6 animals whose left knees were injected with IA, as above. These animals also received a single injection of TH (0.40 mg/kg) into the ipsilateral knee 24 hours later. Group 3 included 6 animals which did not receive intraarticular IA, but received a single intraarticular injection of TH (0.40 mg/kg). Group 4 was composed of 5 animals whose left knees were injected with IA, followed in 24 hours by a single intraarticular injection of TH at one-tenth the concentration used in group 2 (i.e., 0.04 mg/kg). Group 5 consisted of 5 animals which did not receive IA but were given a single intraarticular injection of the lower concentration of TH (0.04 mg/kg). Group 6 included 5 animals which were given a single intraarticular injection of 1% carboxymethyl cellulose sodium (CMC), which was used as the vehicle for the TH. The CMC was formulated as follows: polysorbate 80 NF, 0.40% weight/volume; sorbitol solution USP, 50% w/v; benzyl alcohol, 0.9% w/v; water in a sufficient quantity, 100% volume. Group 7 comprised 10 untreated animals.

The weight of each guinea pig was recorded at the beginning of the experiment and weekly thereafter. Animals in groups 1–6 were killed by intraperitoneal injection of T-61 euthanasia solution (Taylor Pharmacal, Decatur, IL) 3 weeks after the beginning of the study; group 7 animals were killed at the outset of the study. Both knees of each animal were examined daily to assess mobility and swelling.

Drug administration. Prior to each intraarticular injection, animals were anesthetized by an intramuscular injection of ketamine hydrochloride (50 mg/kg). After the left knee was shaved and was washed with 70% isopropyl alcohol, the injection was performed under aseptic conditions by passing a 26-gauge needle attached to a tuberculin syringe through the joint capsule, lateral to the patellar ligament. In groups 1, 2, and 4, a sterile solution of 0.3 mg of IA in 0.1 ml of sterile saline was injected.

TH, which was obtained from the manufacturer as a suspension (Aristospan, 20 mg/ml in 1.0% CMC; Lederle Laboratories, Pearl River, NY), was diluted with sterile saline so that an intraarticular injection of 0.1 ml provided a dose of 0.40 mg/kg (groups 2 and 3) or 0.04 mg/kg (groups 4 and 5). The volume of CMC injected into the knees of group 6 animals was the same as that used for the intraarticular injections in the other groups, i.e., 0.1 ml.

Tissue analysis. When the animals were killed, both knees were immediately opened and examined grossly. The distal femora were removed with a bone rongeur and, with the parapatellar synovial membrane, were fixed for 1–3 weeks in 10% buffered formalin, after which the tissues were embedded in paraffin. Prior to embedding, the condyles were decalcified in Decalcifier I (Surgical Medical Industries, Chicago, IL) for 7–10 days. Microscopic sections (8 μm) of the central weight-bearing regions of the femoral condyles were stained with Safranin O and fast green to demonstrate matrix proteoglycans (PGs) (11), or with hematoxylin and eosin. Estimates of cell density were made using sections stained with hematoxylin and eosin. Samples of synovium were stained only with hematoxylin and eosin. Sections from both knees of experimental animals and from the untreated animals (group 7) were stained concurrently, to control for variations in uptake of the stain.

Representative microscopic sections from each animal in each group were scored (0 to +4) with respect to the degree of: defects in the articular surface, osteophytes, loss of staining with Safranin O, and chondrocyte depletion (Table 1). Mean grades for each experimental group were derived by summing the scores of individual samples and dividing by the number of animals in the group. Ranks of individual parameters were analyzed by the Wilcoxon rank sum method (12).

RESULTS

The daily chow intake of each animal ranged from 35–70 gm and thus supplied a nonscorbutic dietary level of ascorbic acid (13). Initial body weight was maintained throughout the study in all animals in groups 1–6.

Intraarticular injection of IA, TH, or CMC resulted in slight swelling of the knee joint which, in each case, subsided within 24 hours. Thereafter, none of the animals exhibited joint swelling or synovial effusion. Neither gross instability nor knee stiffness was observed in any animal.

Controls. *Gross observations.* Femoral articular cartilage from the knees of all control animals (group 7), from the right (untreated) knees of animals in groups 1–6, and from the left knees of animals which were injected only with the CMC vehicle (group 6) was translucent and pink, with a smooth, grossly intact surface.

Articular cartilage histology and histochemistry. Articular cartilage from all of the control knees was smooth and showed no disruption of surface integrity (Figure 1A and Table 2). Safranin O staining revealed differential staining properties of the matrix, i.e., the orange-red staining of the calcified zone was less intense than that of the overlying uncalcified cartilage. Infrequently, focal areas of reduced staining of interterritorial (IT) matrix were observed. With the

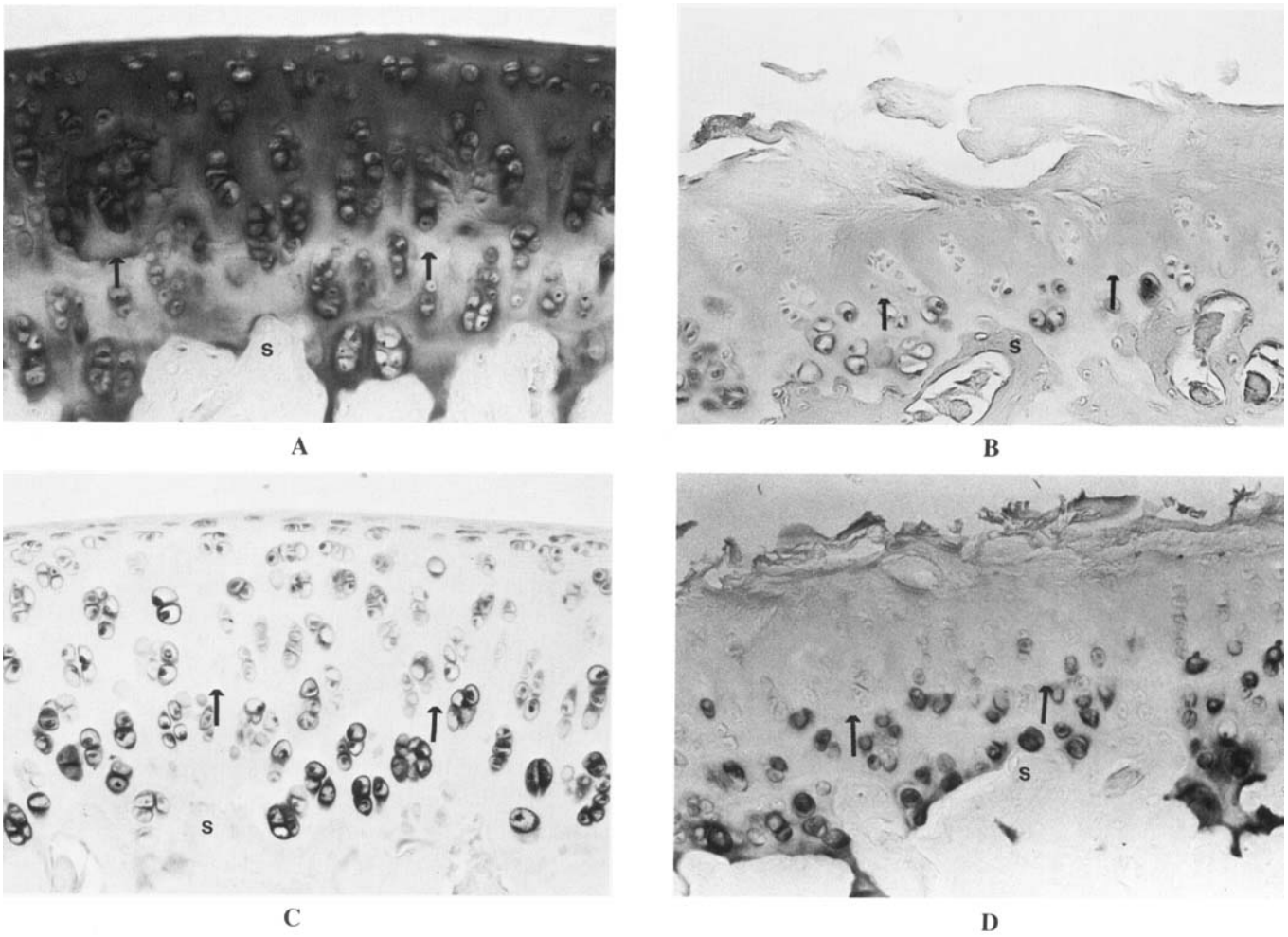

Figure 1. Articular cartilage of guinea pigs, taken from the central region of the medial femoral condyle, stained with Safranin O–fast green. **A**, Control (group 7). **Arrows** indicate tidemark; **S** = subchondral bone. **B**, Three weeks after intraarticular injection of iodoacetate (IA) (group 1). Note surface fibrillation, depletion of chondrocytes, and absence of interterritorial and pericellular staining with Safranin O throughout the uncalcified cartilage. **C**, Intraarticular injection of IA followed by a single injection of triamcinolone hexacetonide (TH) (0.40 mg/kg) (group 2). Note the intact surface and persistence of pericellular staining with Safranin O, despite the absence of interterritorial staining. **D**, Intraarticular injection of IA followed by a single injection of TH (0.04 mg/kg) (group 4). Note surface fibrillation, chondrocyte loss, absence of pericellular and interterritorial staining. (Original magnification × 50.)

Table 2. Changes in guinea pig knees following intraarticular injection of iodoacetate, and effects of an injection of triamcinolone hexacetonide into the ipsilateral knee 24 hours later*

Experimental group	Number of animals	Intraarticular iodoacetate	Intraarticular triamcinolone hexacetonide	Fibrillation, mean grade (range)	Loss of Safranin O staining, mean grade (range)		Osteophytes, mean grade (range)	Chondrocyte depletion, mean grade (range)
					IT	PC		
1	6	Yes	No	1.0 (0–2)	3.0 (3)	1.7 (0–4)	3.2 (2–4)	2.7 (2–4)
2	6	Yes	0.40 mg/kg	0.2 (0–1)†	2.8 (2–3)‡	0.3 (0–2)†	1.7 (0–3)§	1.3 (1–3)†
3	6	No	0.40 mg/kg	0	0	0	0	0
4	5	Yes	0.04 mg/kg	1.2 (0–4)†	3.0 (3)‡	2.0 (0–3)‡	2.4 (2–4)‡	3.0 (2–4)‡
5	5	No	0.04 mg/kg	0	0	0	0	0
6	5	No	CMC vehicle only	0	0	0	0	0
7	10	No	No	0	0	0	0	0

* IT = interterritorial matrix; PC = pericellular matrix; CMC = carboxymethyl cellulose sodium.
† $P < 0.05$ versus group 1.
‡ Not significantly different from group 1 ($P > 0.05$).
§ $P < 0.01$ versus group 1.

fast green counterstain, the most superficial zone of the cartilage and the subchondral bone stained pale green.

Osteophytes. No osteophytes were noted in either knee of the animals in groups 6 or 7, or in the uninjected (right) knees of animals in groups 1–5 (Table 2). The normal medial joint margin in the guinea pig knee was characterized by a gradual tapering of the articular cartilage of the femoral condyle, which blended into the periosteum and was joined by a reflection of the synovial membrane, creating a deep synovial recess (Figure 2A). The intercondylar groove was similarly marked by a gradual thinning of articular cartilage and by the origins of the cruciate ligaments, which were covered by a layer of synovium.

Effects of intraarticular IA injection. *Gross observations.* In marked contrast to the controls, femoral articular cartilage from the injected knees of every animal in group 1 had lost its normal pink translucency and was diffusely white and opaque.

Articular cartilage histology and histochemistry. Defects in the integrity of the articular surface were noted in 5 of the 6 injected knees in group 1 animals (Table 2). Focal disruption, which extended through the transitional zone, was present on the medial condyle in 3 joints (Figure 1B) and on the lateral condyle in a fourth. Horizontal fissuring in the radial zone, beneath an intact articular surface, was noted on the medial condyle of 1 injected knee. In the other samples, fibrillation was much more widespread. It extended into the radial zone of the medial condyle and was accompanied by focal surface disruption of the lateral condyle. Only 1 injected knee of an animal in group 1 was free of horizontal cartilage fissuring or surface defects.

The medial condyle of every injected knee in group 1 animals showed marked loss of IT staining. Loss of pericellular (PC) staining was much more variable; 3 injected knees showed a moderate loss, and 1 showed a marked loss of PC staining, whereas 2 samples were normal in this respect (Table 2).

Extensive loss of chondrocytes and lacunae was noted in uncalcified cartilage of the medial condyle of every injected knee of the animals in group 1. In general, lateral condyles were slightly less affected than medial condyles with respect to both the reduction in Safranin O staining and cell loss. Furthermore, in every case the calcified zone showed no evidence of chondrocyte depletion or histochemical alteration, and the tidemark was intact.

Osteophytes. In every injected knee of group 1 animals, exophytic cartilaginous buds were present at the medial joint margin (Figure 2B and Table 2). In 2 cases they were present also at the lateral joint margin. These osteophytes consisted of spicules of remodeling bone, covered by a large cap of hyaline cartilage which stained intensely with Safranin O. Frequently, a small zone of fibrous tissue that did not stain with Safranin O was noted near the junction of the periosteum and the synovial reflection. In addition, small- to medium-sized osteophytes were seen on the medial aspect of the intercondylar groove in all 6 injected knees in group 1 animals, and small osteophytes were noted on the lateral aspect of the groove in 5 of the 6 injected knees.

Protective effects of intraarticular injection of TH after injection of IA. *Gross observations.* The femoral articular cartilage from every animal which received intraarticular TH after intraarticular IA (groups 2 and 3) was diffusely white and opaque. It

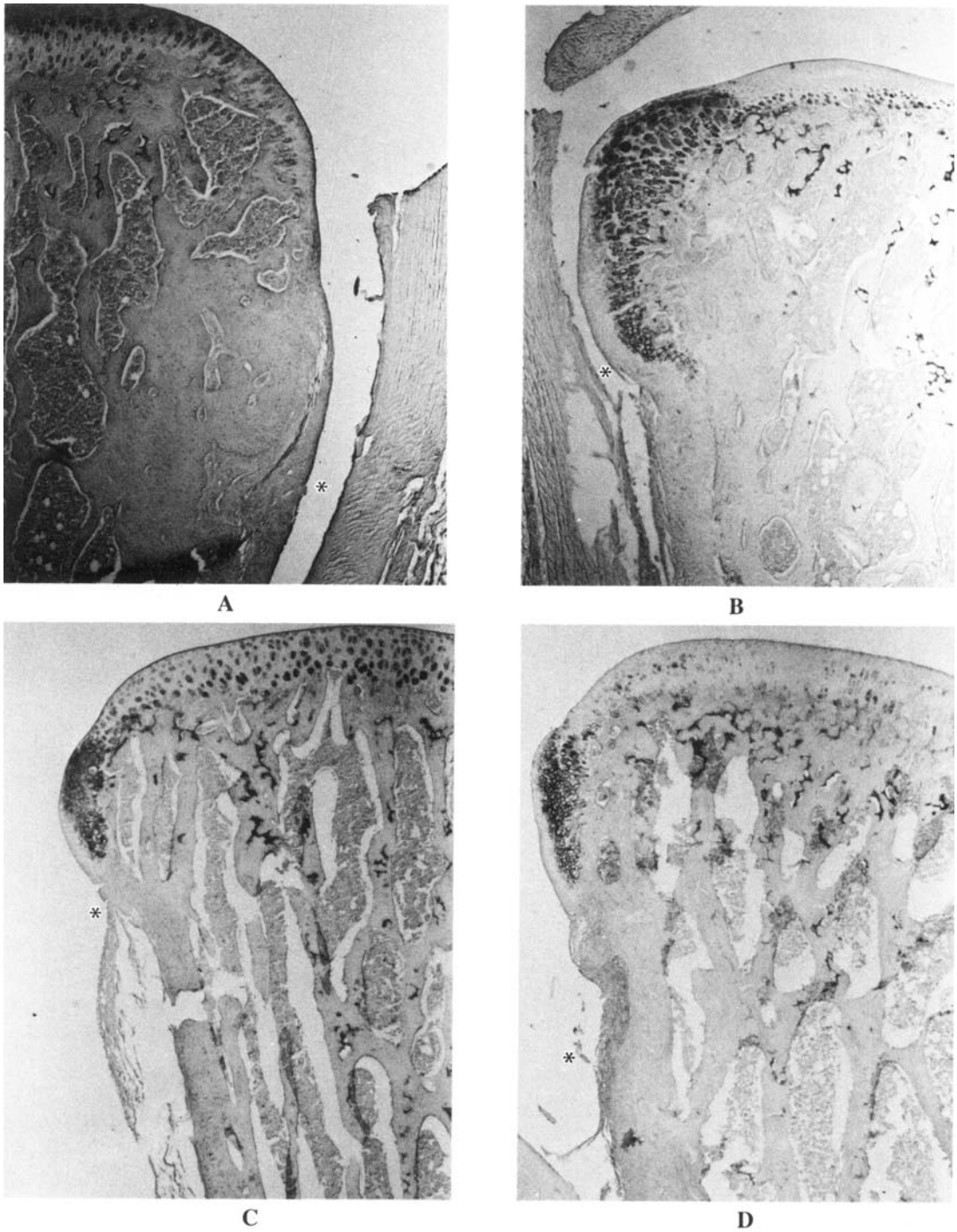

Figure 2. Medial joint margin of guinea pigs, stained with Safranin O–fast green. **A**, Control (group 7). * = synovial recess. **B**, Three weeks after a single intraarticular injection of iodoacetate (IA) (group 1). Prominent osteophyte developing at the medial joint margin. The cartilage matrix of the osteophyte stains deeply with Safranin O. Note absence of stain in the articular cartilage, which contains a horizontal cleft in the radial zone. **C**, Intraarticular injection of IA followed by a single injection of triamcinolone hexacetonide (TH) (0.40 mg/kg) (group 2). The osteophyte is considerably smaller than that developing in animals which did not receive TH after IA injection (compare with **B**). **D**, Intraarticular injection of IA followed by a single injection of TH (0.04 mg/kg) (group 4). Osteophyte size is reduced in comparison with group 1 animals, and is similar to that seen with the higher dose of TH (compare with **C**). (Original magnification × 10.)

was grossly indistinguishable from cartilage of the injected knees of group 1 animals.

Articular cartilage histology and histochemistry. In marked contrast to group 1 animals, the surfaces of medial femoral condyles and of all but 1 of the lateral femoral condyles of the injected knees in group 2 animals remained smooth and intact (Figure 1C and Table 2). On the central portion of the lateral condyle of 1 animal, however, a surface defect, which was 0.25 mm wide and extended to the tidemark, was noted. The protective effects of TH with respect to surface integrity appeared to be dose-related, since fibrillation was noted in 3 of the 5 animals which received only 0.04 mg/kg of TH after IA injection (Figure 1D). These changes were judged to be slightly more severe than those in group 1 animals.

Uncalcified cartilage from the medial condyles of 5 of the 6 injected knees of group 2 animals showed marked diffuse loss of IT staining with Safranin O, while 1 knee showed only a moderate reduction in staining, confined to the central weight-bearing region (Figure 1C and Table 2). PC staining was altered to a lesser extent than IT staining in group 2 animals. Thus, only 1 injected joint showed reduction in PC staining, while the remaining 5 were normal.

In group 4 animals, which received a lower dose of intraarticular TH, loss of IT Safranin O staining was similar to that in group 2. However, loss of PC staining was more apparent (Figure 1D).

A slight-to-moderate loss of chondrocytes was observed in uncalcified cartilage from every injected knee of group 2 animals. This cell loss was less marked than that in group 1. However, the extensive loss of cells noted in group 1 was also seen in medial condylar cartilage of the injected knees of every animal in group 4, which received the lower dose of TH (mean grade 3.0). As noted in group 1 animals, chondrocyte depletion and loss of Safranin O staining in groups 2 and 4 were less apparent in lateral condyles than in medial condyles.

Osteophytes. In comparison with group 1 animals, osteophyte formation was much less marked in animals from group 2 (mean grades 3.2 and 1.7, respectively). One of the injected knees of a group 2 animal exhibited no evidence of osteophytes, while 3 had small osteophytes and 1 had a medium-sized osteophyte at the medial joint margin (Figure 2C). In addition, a single small osteophyte at the medial aspect of the intercondylar groove was present in 1 knee, and early cartilage metaplasia was noted at the medial joint margin or in the intercondylar groove in 4 knees. No osteophytic changes were seen at the lateral joint margin in group 2 animals.

The size of osteophytes, and their extent, were diminished also in group 4 animals (Figure 2D), but the lower dose of TH was clearly less effective than the higher dose in inhibiting osteophytes (mean grades 2.4 and 1.7, respectively).

Effects of intraarticular TH injection in animals not injected with IA. Articular cartilage from the injected knees of animals which received a single injection of TH (0.40 or 0.04 mg/kg), but did not receive an intraarticular IA injection, was grossly normal. The articular surface was smooth and intact, and the matrix revealed normal Safranin O staining. No osteophytes were present.

Histologic analysis of synovial membranes. The synovial membrane from both knees of all animals in groups 1–7 appeared grossly and histologically normal. It consisted of an intima 1–6 cells thick and a subintima of loosely arranged collagen fibers and adipose tissue. Occasional villi protruded into the joint cavity. Neither inflammatory cell infiltration nor lining cell proliferation was observed in any specimen.

DISCUSSION

The present data confirm our previous observation (14) that a single intraarticular injection of 0.3 mg of iodoacetate invariably produces articular cartilage degeneration in the guinea pig knee. Thus, samples from animals in group 1 exhibited a marked loss of matrix proteoglycans and chondrocytes and had prominent osteophytes and disruption of the articular surface.

Additionally, the present data indicate that a single injection of TH, 0.40 mg/kg, into the ipsilateral knee 24 hours after the IA injection prevented articular surface defects in 5 of the 6 animals in group 2, reduced the loss of chondrocytes, preserved Safranin O staining of pericellular PGs, reduced the size of osteophytes, and confined their spread. Since all experimental animals in the study were killed at 3 weeks, whether the protective effects of TH would also have been demonstrable at longer intervals after IA injection is unknown. Notably, intraarticular injection of one-tenth as much TH also diminished IA-induced osteophyte formation and resulted in partial preservation of pericellular Safranin O staining, but did not alter chondrocyte depletion, fibrillation, or loss of interterritorial staining.

Glucocorticoids may induce the synthesis of enzyme inhibitors (15–18), interfere with synthesis or

secretion of catabolin-like factors (19), stabilize lysosomal membranes (20,21), and stabilize the collagen meshwork (22,23). It should be noted that the effects of corticosteroids on cartilage vary with concentration. Thus, Hill (20) reported that 10^{-4} to $10^{-3}M$ cortisol reduced in vitro incorporation of ^{3}H-thymidine, ^{3}H-leucine, and $^{35}SO_4$ by calf costochondral cartilage, while lower concentrations had no effect. Dexamethasone (10^{-7} to $10^{-5}M$) and hydrocortisone (10^{-6} to $10^{-4}M$) stimulated in vitro synthesis of an inhibitor of phospholipase A_2 in guinea pigs, thus reducing prostaglandin production (16). Prednisolone (10^{-6} to $10^{-4}M$) has been shown to inhibit the in vitro production of catabolin (19).

In the present in vivo study of chemically induced cartilage injury, the higher dose of TH employed (which corresponded to a TH concentration of $10^{-3}M$ suspended with vehicle) was clearly protective, whereas the lower dose ($10^{-4}M$) had little effect on cell loss, fibrillation, or loss of matrix staining with Safranin O, although it did reduce osteophyte formation. It is apparent, however, that the concentration of TH present at various intraarticular sites under such conditions is uncertain.

In vivo corticosteroid administration has been reported to be beneficial also in experimental models of mechanically induced OA (4,7,8). Thus, weekly intraarticular injection of triamcinolone acetonide ($10^{-2}M$) markedly reduced the frequency and size of femoral and tibial osteophytes and prevented fibrillation, but did not reduce loss of cartilage proteoglycans, in rabbit knees after partial meniscectomy (4). The weight of the rabbits used in that study was not stated, but assuming that the rabbits weighed 2.5 kg each, the amount of triamcinolone injected (3 mg) would have been equivalent to 1.2 mg/kg.

Colombo et al (7) reported that daily oral administration of triamcinolone (0.1 mg/kg) prevented the loss of chondrocytes and matrix proteoglycans, reduced the prevalence of articular surface disruption, and markedly reduced the frequency and size of osteophytes following partial lateral meniscectomy and transection of the sesamoid and collateral fibular ligaments in rabbits. A single intraarticular injection of TH (0.25 mg/kg, i.e., a slightly lower concentration than that used in the present study) also reduced cell loss and osteophyte formation, and diminished fibrillation in the same rabbit model of OA (8).

In patients with osteoarthritis, intraarticular steroid injection may provide symptomatic relief (24,25). Other data, however, have shown similar improvement following injection of procaine, isotonic saline, or the vehicle alone (26,27). Furthermore, it is well recognized that multiple injections of corticosteroids in humans (1–3) or experimental animals (4,28) may result in a "corticosteroid arthropathy," with fibrillation, chondrocyte degeneration, loss of matrix PGs, and cyst formation. However, neither Butler et al (8) nor Colombo et al (7) reported changes in lapine knee cartilage after a single intraarticular injection of TH. In the present study, the cartilage from joints of guinea pigs which received a single intraarticular injection of TH, at either concentration tested, was normal in every respect.

We have previously shown that benoxaprofen, when administered orally to guinea pigs after intraarticular injection of IA, reduces the loss of PGs and chondrocytes and prevents fibrillation and osteophyte formation (29). Although the basis for the protective effect of benoxaprofen in this model is not known, this long-acting propionic acid derivative stimulates cartilage PG synthesis in vitro and may thus facilitate repair of IA-induced cartilage damage (30).

The mechanism by which TH protected against cartilage damage and osteophyte formation in animals in the present study is unknown. Suppression of osteophyte formation may have been due to the acute inhibition of protein synthesis in cartilage that is caused by adrenal corticosteroids (20,31). The effects are not likely to be due simply to the antiinflammatory properties of TH. In the present study, none of the IA-injected joints, regardless of whether they had been injected subsequently with TH, showed evidence of synovitis. Previous work has shown that only a slight inflammatory cell infiltrate is seen 24 hours after intraarticular IA injection in guinea pigs (32). These changes subside rapidly, so that by 1 week after the injection, no inflammatory infiltrate remains and only mild focal hypercellularity of the lining cell layer is noted.

Although we did not measure levels of hydrolytic enzymes in the cartilage, it is likely that injection of IA, a broad metabolic poison (33), resulted in the release into the matrix of large quantities of hydrolytic enzymes from the chondrocytes. It is possible that TH inhibited their secretion or activity, thus reducing the chondrocytic chondrolysis which occurs following intraarticular injection of IA. It is of interest that the lower dose of TH used in this study was less protective than the higher dose since, in both cases, sufficient corticosteroid should have been available to inhibit synovial catabolin production. This would suggest that catabolin may not play a significant role in the breakdown of cartilage in this model.

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