Agents and Actions, vol. 18, 3/4 (1986)

0065-4299/86/040384-10$3.50

Pharmacological studies of antigen-induced arthritis in BALB/c mice I. Characterization of the arthritis and the effects of steroidal and non-steroidal anti-inflammatory agents

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Abstract

Chronic monoarticular allergic arthritis was induced in BALB/c mice using methylated BSA as antigen and Freund's complete adjuvant, together with Bordetella pertussis as a secondary adjuvant. The optimum conditions for induction of chronic persistent arthritis and the histological characteristics of the arthritic lesion are described.

Both the synovitis and erosive progression of the arthritis could be suppressed by daily treatment with prednisolone (1–10 mg/kg) or dexamethasone (0.5–2.5 mg/kg) for 4 weeks commencing 2 weeks after the induction of arthritis. In contrast, daily treatment with the non-steroidal anti-inflammatory agents ibuprofen (50–100 mg/kg), flurbiprofen (1–9 mg/kg) or indomethacin (0.1–3 mg/kg) had no significant effect on either the synovitis or erosions as judged histologically. Synovial fluid differential leukocyte counts were altered by treatment with ibuprofen and indomethacin but not by flurbiprofen or the corticosteroids.

The suppressive effect of the corticosteroids was not due to either suppression of antibody synthesis or alteration of the number of leukocytes in the peripheral circulation.

Introduction

The antigen-induced monoarticular model of arthritis in rabbits described by Dumonde and Glynn [1] bears strong resemblance to rheumatoid arthritis with regard to the pathological changes occurring in both the synovium and cartilage [2]. Furthermore, pharmacological studies have shown that this model responds to antirheumatic agents in a manner similar to the clinical disease [3].

Chronic monoarticular arthritis can also be induced in mice by procedures comparable to those used for rabbits [4]. This mouse model resembles its rabbit equivalent in several respects. In both situations, the synovial histology is characterized by hypertrophy and hyperplasia of the synovial lining cells with infiltration of the synovial subintima by lymphocytes, plasma cells and macrophages, forming pannus which produces marked erosive changes in the articular cartilage and subchondral bone [4]. Other similarities between the two models include a dependence on T-cell function [5, 6], retention of the inducing antigen in hypovascular structures within the arthritic joint [7], decreased proteoglycan synthesis in articular cartilage in arthritic joints [8] and exacerbation of the arthritis after systemic administration of antigen [9, 10]. However, as yet detailed pharmacological studies on antigen-induced arthritis in mice are lacking.

In this paper, we describe our initial investigations into the induction of arthritis, its progression and the actions of steroidal and non-steroidal anti-inflammatory agents. The actions of second-line antirheumatic agents in this model are described in the accompanying paper [11].

Materials and methods

Induction of arthritis

Arthritis was induced in mice using procedures similar to those reported by BRACKERTZ et al. [4]. Inbred category 4 female BALB/c mice were supplied by BANTIN and KINGMAN. The mice were fed a pelleted diet and water ad libitum.

Mice 10 weeks of age were sensitized by subcutaneous injection, into the flank, of 100 μl of an emulsion comprising a solution of methylated bovine serum albumin (Met-BSA; Sigma) in sterile saline emulsified with an equal volume of Freund's complete adjuvant (FCA; Difco) to which had been added Mycobacterium tuberculosis (Weybridge). A simultaneous intraperitoneal injection of Bordetella pertussis (Wellcome Pertussis Vaccine B.P.) was also administered. Seven days later, an identical set of injections was given. Fourteen days after the second immunization, 10 μl of a solution of Met-BSA in sterile saline was injected into one knee joint using a Hamilton syringe with a 26 g × 3/8″ needle.

In certain experiments, the concentrations of all

materials used to induce arthritis were varied. For the majority of experiments, 100 μg Met-BSA was used as a standard sensitizing dose, 50 μg M. tuberculosis was added to the FCA (giving a total of 75 μg M. tuberculosis per injection) and 2×10^9 B. pertussis organisms were injected ip. 100 μg Met-BSA was used routinely for intra-articular challenge.

Histology

Animals were killed by CO_2 asphyxiation and both hind legs removed. Femurs and tibia were cut midway along their length and the knee joints trimmed free of skin and musculature. The joints were placed in perforated plastic holders and fixed in 10% formol saline for at least 48 h. They were then decalcified in 5% formic acid for 72 h with constant agitation (replacing the formic acid after the first 24 h), washed in water, dehydrated in alcohol and embedded in paraffin wax. The joints were sectioned in the sagittal plane at 5 μm and stained with either haematoxylin/eosin or Van Gieson's stain. Each joint was sectioned at 3 levels.

Assessment of arthritis

The severity of arthritis was assessed histologically. All sections were coded prior to assessment to eliminate observer bias. Each section was scored by three independent observers. Synovitis and pannus formation was graded on a 0–5 scale according to the degree of synovial lining cell hypertrophy and hyperplasia, infiltration of the synovium by lymphocytes, plasma cells, macrophages, fibroblasts and polymorphonuclear leukocytes, and the degree of pannus formation. This is illustrated below.

Score	Lining cell hypertrophy/hyperplasia	Cellular infiltration	Pannus
0	−	−	−
1	+	±	±
2	+	+	+
3	+	++	++
4	+	+++	++
5	+	+++	+++

Erosion of cartilage and bone was also graded on a 0–5 scale, the score reflecting the proportion of articular surface eroded as well as the depth of the erosions, as follows.

Score	Cartilage (area eroded)	Bone
0	−	−
1	0–25%	−
2	25–50%	−
3	Approx. 50%	+
4	50–75%	++
5	75–100%	+++

The total arthritic score was taken as the sum of the synovitis/pannus and erosions scores.

Differential cell counts were performed on some sections. Four fields, each containing 100 cells, were counted for each animal.

Measurement of antibody levels

Blood for serum antibody measurements was collected immediately post-mortem by cardiac puncture. Serum antibodies to Met-BSA were measured by haemagglutination analysis using sheep erythrocytes coated with BSA using 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (ECDI; Sigma) as described by Mishell [12]. Washed packed erythrocytes (0.5 ml) were mixed with 15 ml BSA solution (80 mg/ml in phosphate buffered saline and 2.5 ml freshly prepared ECDI solution (100 mg/ml in phosphate buffered saline) added rapidly with mixing. The reaction was allowed to continue for 1 h at 4°C with continual mixing, after which the cells were washed three times and resuspended in phosphate buffered saline.

Measurement of peripheral blood leukocyte counts

Blood was collected into EDTA immediately post mortem by cardiac puncture. Total leukocyte counts were determined on a Coulter counter and differential leukocyte counts were determined manually.

Drug treatment

Dexamethasone and indomethacin were obtained from Sigma. Flurbiprofen, ibuprofen and prednisolone were prepared in-house. Drugs were administered daily orally in solution or in suspension by gastric intubation. Drug treatment commenced 14 days after intra-articular injection and continued for 28 days, after which the animals were killed and the joints removed for histology.

Results

1. Characterization of the arthritis

Intra-articular injection of antigen into sensitized mice produced a severe chronic arthritis in the injected joint. No arthritis was observed in the contralateral knee joint in any of the animals. The progression of the synovitis and erosive changes was followed for 6 weeks after intra-articular injection (Fig. 1). After one week, there was an intense synovitis characterized by dense infiltration of the synovium and synovial fluid by inflammatory cells (both mononuclear and polymorphonuclear) from the blood. This subsided over the following two weeks to a relatively static level of chronic

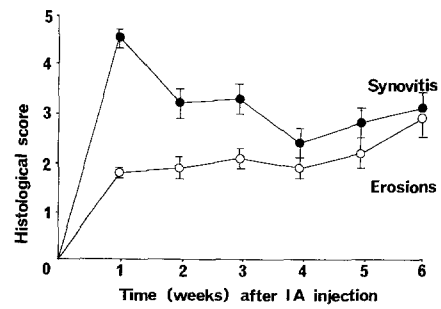

Figure 1
Progression of synovitis (●) and erosions (○) in BALB/c mice with experimental monoarticular arthritis. Each point represents the mean ± S.E.M. of 15 animals. Synovitis and erosions were each scored on a 0–5 scale.

synovitis. Erosion of the cartilage was evident 1 week after intra-articular injection and progressed steadily, affecting a greater area of the articular surface and progressing deeper into the subchondral bone, over the following five weeks. Erosions at week 6 were significantly different ($p < 0.05$) from those at weeks 1, 2 and 4 (Fig. 1). In a separate experiment, intense synovitis was observed two days after intra-articular injection and progression of the arthritis (both synovitis and erosions) was still evident 8 weeks after intra-articular injection. Differential counting of the cells in the synovial fluid revealed only minor changes in the relative proportions of the different cell types between days 2 and 42 after intra-articular injection (Table 1). The only significant change was a gradual increase in lymphocyte count.

The histological characteristics of the chronic synovitis are shown in Fig. 2. The synovitis was characterized by hypertrophy and to a lesser extent, hyperplasia of the synovial cells (Fig. 2b). The synovial subintima was densely infiltrated with both polymorphonuclear (PMN) and mononuclear cells. The proportion of these cell types in the different areas of the arthritic joint is summarized in Table 2. Although the synovium contained predominantly mononuclear cells (macrophages, lymphocytes, plasma cells, fibroblasts) there were considerable numbers of PMN leukocytes present immediately

Table 1
Differential cell counts in the synovial fluid of BALB/c mice at various times after induction of experimental arthritis.

	Cell count (percentage)		
	Monocytes	Lymphocytes	PMN Leukocytes
Day 2	19 ± 4	4 ± 1	77 ± 4
Day 7	21 ± 5	5 ± 3	74 ± 4
Day 42	17 ± 3	8 ± 3*	75 ± 4

Each value represents the mean ± SD of 6 animals.
* Significantly different ($p < 0.005$) from Day 2 value according to the Mann-Whitney U test.

Table 2
Differential cell counts in various regions of the arthritic joint

Region of joint	Cell count (percentage)	
	PMN leukocytes	Mononuclear cells
Synovial fluid	75 ± 4	25 ± 4
Synovial subintima I*	36 ± 13	64 ± 13
Synovial subintima II*	14 ± 7	86 ± 7
Pannus	5 ± 5	95 ± 5

* These areas are defined in Fig. 2.
Each value represents the mean ± SD of 6 animals.

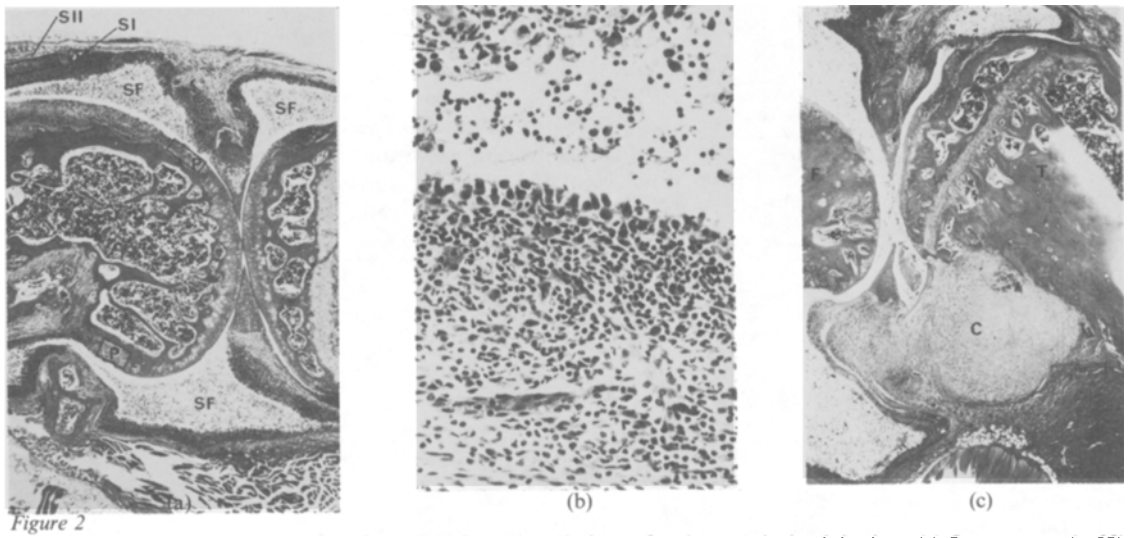

Figure 2
Photomicrographs of arthritic joints from BALB/c mice 42 days after intra-articular injection. (a) Low power (× 32) micrograph showing moderate-severe arthritis, illustrating the regions of the joint used for differential cell counting (SF: synovial fluid, SI: synovial subintima I, SII: synovial subintima II, P: pannus). Van Gieson's stain. (b) High power (× 300) micrograph showing hypertrophy of synovial lining cells, dense cellular infiltration (both mononuclear and polymorphonuclear) immediately beneath the synovial membrane, and less dense cellular infiltration in the deeper layers. Stain: Haematoxylin and eosin. (c) Micrograph (× 30) showing chondrophyte (C) formation on the posterior face of the tibia (T) associated with subluxation of the femur (F). Stain: Haematoxylin and eosin.

beneath the synovial membrane itself. As shown in Table 2, there seemed to be a gradient of PMN leukocytes with the highest concentration in the synovial fluid and the lowest concentration at the leading edge of the synovial pannus, where there were very few PMN leukocytes to be seen. Erosion of cartilage and subchondral bone was quite extensive. The erosions appeared to result primarily from the action of the pannus i.e. there was little cartilage destruction in areas of the articular surface which were in contact with the synovial fluid in the absence of synovium. In some severely involved joints, subluxation of the femur occurred, presumably as a result of damage to the cruciate ligaments. This was invariably associated with the production of a large osteo/chondrophyte on the posterior face of the tibia (Fig. 2c). Occasionally, osteophytes were observed in other areas of the joint such as the femoral condyles.

In a considerable proportion of animals, inflammatory changes in the periarticular tissues were observed. These included (a) thickening of the joint capsule due to fibroblast proliferation, deposition of collagen and infiltration by mononuclear cells (b) proliferation of fibroblasts in the ligamentum patellae with cellular infiltration occurring on its outer surface (c) infiltration of inflammatory cells, predominantly mononuclear but also some PMN leukocytes, into areas of muscle immediately adjacent to the joint and (d) localized erosion of the diaphysis of the tibia and femur.

The optimum concentration of all reagents used to induce the arthritis was determined (Fig. 3). Initially, the dose of Met-BSA used to sensitize the animals was varied, keeping the adjuvants and intra-articular challenge conditions fixed (FCA supplemented with 100 μg M. tuberculosis; 2×10^9 B. pertussis organisms; 100 μg Met-BSA intra-articular challenge). Under these conditions, 100 μg was found to be the optimum dose of Met-BSA for sensitization (Fig. 3a). Using this concentration of antigen together with the same adjuvant conditions, the intra-articular challenge dose was varied (Fig. 3b). Again, the best results were achieved with 100 μg Met-BSA, although no higher doses were examined. Finally, the amounts of Mycobacterium and B. pertussis were varied whilst the sensitization and challenge doses of Met-BSA were kept constant at 100 μg (Fig. 3c). The severity of the arthritis decreased markedly when

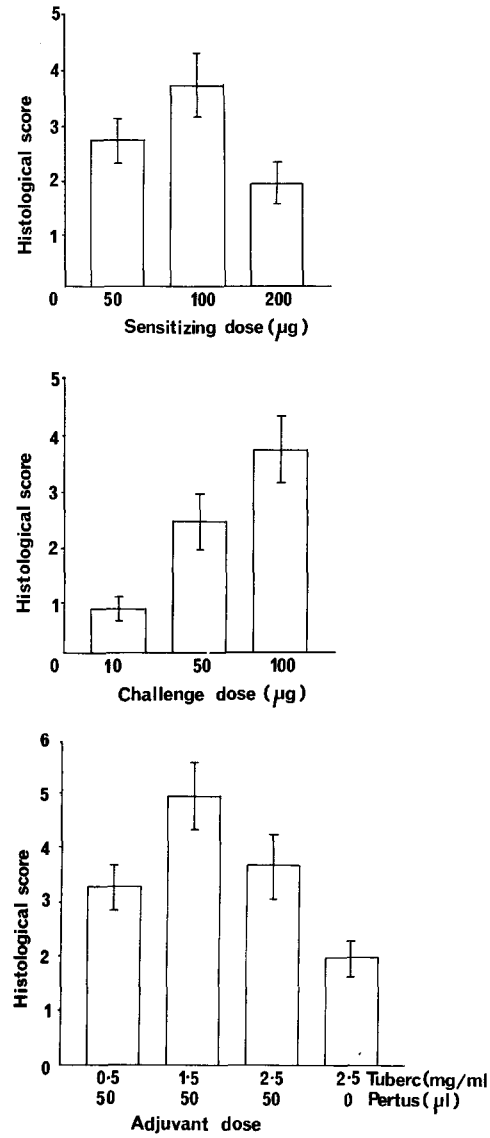

Figure 3
Effects of varying (a) the sensitizing dose of Met-BSA, (b) the intra-articular challenge dose of Met-BSA, and (c) the doses of microbial adjuvants, on the induction of experimental monoarticular arthritis in BALB/c mice. For experimental details see text. Each bar represents the mean ± SEM of 15 animals.

B. pertussis was omitted. Maximal arthritic severity was achieved when the FCA (which already contained 25 μg Mycobacterium) was supplemented with 50 μg M. tuberculosis. Increasing the amount of M. tuberculosis resulted in suppression of the arthritis.

Table 3
Differential cell counts in the synovial fluid of BALB/c mice with experimental monoarticular arthritis after daily treatment with anti-inflammatory agents for 4 weeks

Drug	Dose (mg/kg)	Cell count (percentage)		
		Monocytes	Lymphocytes	PMN Leukocytes
Control	0	18 ± 4	7 ± 2	75 ± 5
Prednisolone	1	16 ± 4	5 ± 3	79 ± 4
	5	18 ± 5	4 ± 2	78 ± 5
Ibuprofen	50	26 ± 7	3 ± 2**	71 ± 7
	100	25 ± 6	4 ± 1*	71 ± 6
Flurbiprofen	3	20 ± 4	5 ± 2	75 ± 5
	9	18 ± 7	4 ± 2	78 ± 8
Indomethacin	0.1	24 ± 4	9 ± 4	67 ± 6
	1	36 ± 3***	6 ± 4	58 ± 6***

Drug treatment commenced 2 weeks after intra-articular injection.
Each value represents the mean ± SD of 6–10 animals.
* $p < 0.025$ relative to untreated arthritic animals,
** $p < 0.001$ according to the Mann Whitney U test
*** $p < 0.0001$

2. Effects of corticosteroid treatment

BALB/c mice with established arthritis were treated daily with either prednisolone or dexamethasone for 4 weeks, commencing 2 weeks after intra-articular injection. The results are summarized in Fig. 4. Dose-dependent reductions in both the synovitis and erosions scores were seen with both prednisolone and dexamethasone, achieving statistical significance in both cases. The steroids appeared to reduce the cellular content of the synovial fluid, but this could not be quantitated reliably. However, differential cell counting of synovial fluid leukocytes indicated that treatment with prednisolone had no significant effect on this parameter (Table 3).

In a further study, treatment with prednisolone commenced either on the day of intra-articular injection or 7 days later and continued for 4 weeks. The degree of suppression of disease activity obtained under these conditions was similar to that shown in Fig. 4. The effects of prednisolone on antibody levels in the arthritic mice was also investigated. Serum samples were obtained immediately post-mortem and the concentration of circulating antibodies to BSA determined by haemagglutination analysis. Treatment with prednisolone for a period of 6 weeks, at a dose (1 mg/kg) which produced profound suppression of the arthritis, had no effect on the serum antibody concentration (Table 4). In a separate experiment, the effect of prednisolone treatment on the peripheral blood leukocyte count was determined. Treatment for 4 weeks with a dose of 1 mg/kg commencing two weeks after intra-articular injection had no effect on the leukocyte count.

3. Effects of treatment with non-steroidal anti-inflammatory agents

Relatively high doses of NSAIA's were employed in order to determine whether or not this type of drug could affect the progress of this experimental model of arthritis. Treatment commenced 2 weeks after intra-articular injection and was continued for 4 weeks. None of the NSAIA's investigated produced any statistically significant change in either the synovitis or erosions scores (Fig. 5). Evidence of gross toxicity was observed with indomethacin at 3 mg/kg.

Ibuprofen and indomethacin produced an increase in the synovial fluid monocyte count (Table 3) with a corresponding decrease in PMN leukocytes which reached statistical significance only at the highest dose of indomethacin examined. Flurbiprofen had no effect on the synovial fluid differential cell count. There was evidence of reduction in synovial fluid lymphocyte count with some of the drugs examined but this reached statistical significance only with ibuprofen. There appeared to be some suppression of total synovial fluid cell count with all three NSAIA's, although this could not be quantitated accurately.

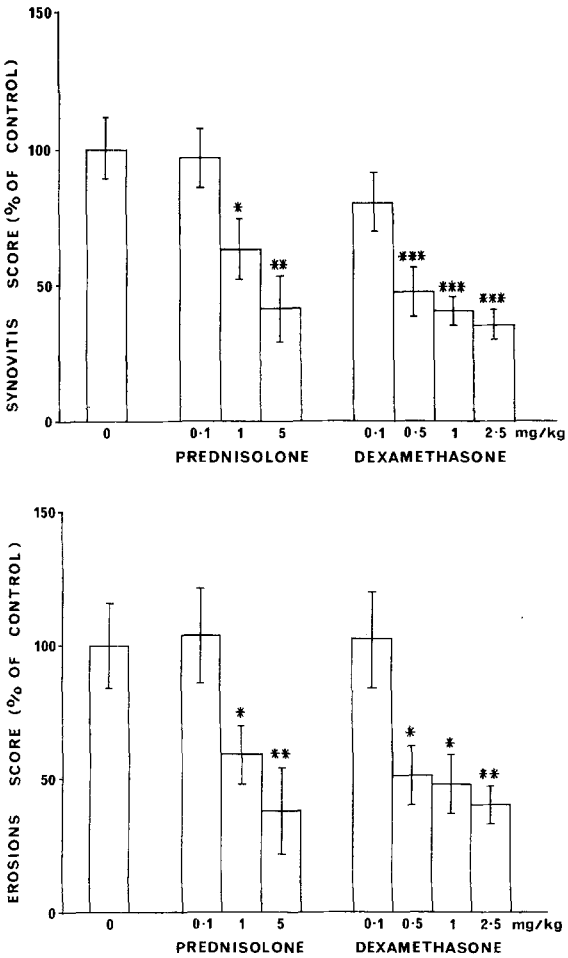

Figure 4
The effect of daily treatment with prednisolone and dexamethasone on (a) synovitis and (b) erosions in BALB/c mice with experimental monoarticular arthritis. Animals were treated orally for 4 weeks commencing 2 weeks after intra-articular injection. Each bar represents the mean ± SEM of 15 animals. * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$ (Mann-Whitney U test).

Table 4
Anti-BSA antibodies in the serum of BALB/c mice with chronic monoarticular arthritis treated with prednisolone.

Prednisolone dose (mg/kg)	Log_2Haemagglutination Titre (mean ± SEM)	Arthritic Score (mean ± SEM)
0	6.6 ± 0.5	5.8 ± 0.7
0.5	6.8 ± 0.4	4.9 ± 0.9
1.0	6.4 ± 0.5	3.0 ± 0.5*

Mice were dosed daily for 6 weeks commencing 2 weeks after induction of arthritis.
* Significantly different ($p < 0.01$) from untreated arthritic animals, according to the Mann Whitney U test.

Discussion

In common with other workers [8], we have shown that using procedures comparable to those described by BRACKERTZ et al. [4], we can induce a chronic monoarticular arthritis in mice. Variations in the conditions used to sensitize the mice revealed that suppression (as evidenced by a reduced level of arthritic severity) could be produced if excessive doses of both the Met-BSA antigen and M. tuberculosis in the Freund's adjuvant were used. In accord with the observations of BRACKERTZ et al. [4], severe arthritis could not be induced in the absence of B. pertussis. As to be expected from previous studies in rabbits [13], the consistency and severity of the arthritis was dependent on the amount of antigen injected into the knee joint, 10 μg being insufficient to produce significant arthritis.

Antigen-induced arthritis in BALB/c mice progressed very rapidly with quite marked erosive changes occurring 7–14 days after intra-articular injection and chronic arthritis at day 42 being characterized by severe erosive pannus producing loss of 50% or more of the articular cartilage in most animals. This feature of the model is particularly important in view of the subsequent pharmacological studies. In line with previous studies in rabbits [14], it was felt that the conditions employed for investigating the effects of drugs in this mouse model of arthritis should resemble, as closely as possible, those employed in man. As a result, a dosing schedule commencing 14 days after intra-articular injection was chosen i.e. drug administration commenced at a time after erosive disease had become established. It could be argued that in an aggressive erosive model such as this, irreversible changes could have occurred by day 14. However, preliminary experiments revealed that corticosteroids administered for 4 weeks commencing 14 days after intra-articular injection could produce marked suppression of the disease and hence this schedule was chosen for the studies reported here. The drugs were administered once per day since this has been shown to be adequate in rodent models of chronic inflammation known to respond to steroids and NSAIA's [15, 16].

In contrast to antigen-induced monoarticular arthritis in rabbits, chronic antigen-induced arthritis in BALB/c mice was characterized by a relatively high incidence (36%) of PMN

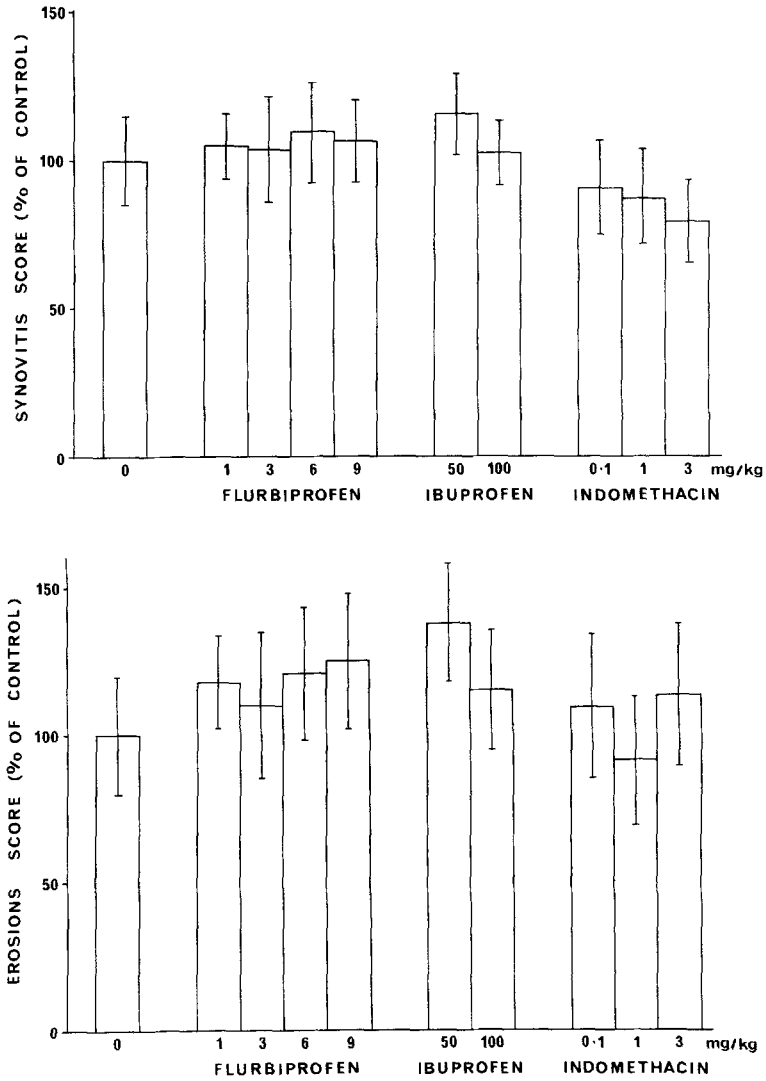

Figure 5
The effect of daily treatment with flurbiprofen, ibuprofen and indomethacin on (a) synovitis and (b) erosions in BALB/c mice with experimental monoarticular arthritis. Animals were treated orally for 4 weeks commencing 2 weeks after intra-articular injection. Each bar represents the mean ± SEM of 15 animals. None of the changes were statistically significant at the 5% level according to the Mann-Whitney U test.

leukocytes in the synovial subintima, particularly in the area immediately beneath the synovial membrane itself. Whether or not this implies a greater role for PMN leukocytes in the pathogenesis of arthritis in mice than in rabbits is an open question. However, the pannus which appeared to be the major source of erosive damage, contained 95% mononuclear cells with no PMN leukocytes visible at the pannus/cartilage interface. Furthermore, there was little cartilage destruction in regions of the articular surface in direct contact with the synovial fluid which was very rich in PMN leukocytes. Therefore, it was concluded that the mononuclear cells are primarily responsible for the articular cartilage destruction and that the influx of large numbers of PMN leukocytes into the joint is a response to the rapid generation of large quantities of cartilage matrix debris. Hence the appearance of PMN leukocytes in

the synovial subintima may reflect the movement of these cells from the synovial capillaries into the synovial fluid.

Using multiple intra-articular injections in an antigen-induced model of monoarticular synovitis in rabbits, GOLDLUST et al. [17] demonstrated the presence of large numbers of PMN leukocytes in synovial tissue under certain conditions. Furthermore, their data indicated that the most severe joint destruction occurred in the presence of large PMN exudates in the joint whether or not PMNs were prevalent in the synovial tissue at the time of death. However, a causal relationship between PMN and joint destruction could not be drawn from their data; and, since these animals were killed soon after their last intra-articular challenge injection, the presence of PMN in the synovial tissue and fluid in this instance may reflect the acute response to the challenge injection which is unrelated to the underlying chronic destructive process.

KRUIJSEN et al. [18] reported a 80–90% incidence of mononuclear cells in the synovium in antigen-induced arthritis in C57B1 mice. The corresponding lower incidence of PMN leukocytes in the synovium in this strain relative to our findings with BALB/c mice may reflect a subtle difference between the two strains in the pathological features of the arthritis. However, other pathological features such as the synovial fluid changes, rate of erosive progression, occurrence and nature of periarticular changes, and cellular and matrix changes in the cartilage, appear to be very similar.

The principal aim of this investigation was to ascertain whether or not this model behaved in a similar manner to rheumatoid arthritis with regard to the effects of steroidal and non-steroidal anti-inflammatory drugs on the progress of the arthritis. Preliminary experiments revealed that, due to the size of the mouse knee joint and the surrounding musculature, measurement of joint swelling or gross pathological changes was not practicable; therefore, histological assessment of the severity of the arthritis was taken as the sole criterion for drug efficacy. It has been shown recently [19] that joint inflammation in the experimental arthritic mice can be measured by ^{99m}Tc accumulation and that this correlates with histological score 7 days after induction of the arthritis. However, such a correlation may not persist indefinitely and since we were primarily interested in the degenerative changes occurring over a period of 6 weeks, histological criteria were considered as being the best method for assessing these changes.

The anti-inflammatory steroids prednisolone and dexamethasone both produced dose-responsive suppression of the synovitis and erosions. For a 4 week dosing schedule, the minimum daily dose of prednisolone producing suppression was 1 mg/kg. These results compare favourably with results of studies with prednisolone and dexamethasone in antigen-induced arthritis in rabbits [14, 20–23] as well as those of the original MRC trial which showed that treatment with prednisolone at a dose of 20 mg/day for two years reduced the radiological progression of rheumatoid arthritis [24]. However, the mouse model does appear to be slightly less sensitive to steroids than both the rabbit model and the clinical disease.

In contrast to the rabbit studies [14, 22], prednisolone treatment of mice failed to produce any suppression of circulating antibody levels or leukocyte numbers at doses which caused significant suppression of the arthritis. Delayed hypersensitivity tests were not performed in these mice since such tests may have affected the progression of the arthritis. However, other workers have shown that prednisolone and dexamethasone can inhibit the elicitation of delayed hypersensitivity responses to Met-BSA in mice [25, 26]. In these instances, higher doses of the steroids were administered over a much shorter period of time (4 days) making comparison with the mouse arthritis results difficult. Nevertheless, studies with the rabbit model of arthritis [14] showed that suppression of the arthritis by prednisolone correlated closely with reduction in cell-mediated immune responsiveness. Therefore, it is possible that suppression of the arthritis in BALB/c mice may have been accompanied by a reduction in cell-mediated immune responsiveness. Such a conclusion is in accord with the T-cell dependence of this model of arthritis demonstrated by BRACKERTZ et al. [5, 6]. Studies to investigate this possibility are currently in progress.

In contrast to the steroids, the three NSAIA's investigated had no significant effect on the synovitis or erosions, a result which is in complete agreement with studies by other workers using the comparable model in rabbits [21, 22] but in contrast to rat adjuvant arthritis

[15, 16]. Although ibuprofen and indomethacin appeared to alter the differential cell count in the synovial fluid, this appeared to be unrelated to events within the synovium and cartilage and reinforces our opinion that the cells within the synovial fluid do not play a major role in the cartilage and bone destruction. In this regard, BLACKHAM and co-workers [21, 27] showed that indomethacin and naproxen could reduce the total synovial fluid cell count and joint swelling in the rabbit arthritis model without exerting any significant effect on the macroscopic or histopathological indices of joint damage. In view of the lack of effect of NSAIA's on the histopathology when administered from day 14 after intra-articular injection, further experiments are being performed at present to see whether or not treatment from the day of intra-articular injection has any effect. However, in the rabbit monoarticular arthritis model, NSAIA's had no significant effect when administered in this way [22] and hence it seems unlikely that the mouse model should behave differently.

In conclusion, we have shown that the antigen-induced monoarticular arthritis model, originally described by BRACKERTZ et al. [4, 5, 6], responds to drug treatment in a manner comparable to both antigen-induced arthritis in rabbits and rheumatoid arthritis i.e. the erosive progression of the disease can be suppressed by anti-inflammatory steroids, albeit at relatively high doses, but not by NSAIA's. The effects of slow-acting disease-modifying antirheumatic drugs on the model are described in the following paper.

Acknowledgments

We are grateful to Dr. M. C. Lancaster and the staff of the Pathology Department of The Boots Company PLC, Research Department, for the preparation of the histological sections.

Received 26 May 1985; accepted 24 October 1985

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