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Treatment of Antigen-Induced Arthritis in Rabbits by the Intra-articular Injection of Methylprednisolone, ^{90}Y or Chlorambucil

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Abstract—Rabbits with a bilateral antigen-induced arthritis were injected intra-articularly (i.a.) in one joint with methylprednisolone (1 mg), ^{90}Y (18·5 MBq) or chlorambucil (1 mg) as a single dose. The severity of arthritis was determined by measuring joint swelling and skin surface temperature, macroscopic and histological changes in the joint being assessed 8 weeks after induction of arthritis when the rabbits were killed. Methylprednisolone injected at the time of antigen challenge or 3 weeks later caused a reduction in joint swelling and temperature ($P<0·05$) for 1 to 6 weeks after injection. ^{90}Y had an initial pro-inflammatory effect lasting several days, but later caused a modest reduction in joint swelling for up to 4 weeks ($P<0·05$). Eight weeks after induction of arthritis, neither methylprednisolone nor ^{90}Y-treated joints showed any significant reduction in erosion or histopathology compared with control arthritic joints. Chlorambucil injected 1 week after antigen challenge caused a rapid reduction in joint swelling which was maintained for the duration of the study. Joint surface temperature was reduced to a lesser extent. Eight weeks after induction of arthritis, chlorambucil-treated joints showed a decrease ($P<0·05$) in all of the parameters of disease pathology assessed. Treatment with chlorambucil intra-articularly was clearly more effective than with methylprednisolone or ^{90}Y at the doses employed and deserves further study as a potential treatment for chronic synovitis.

The rationale for treating arthritic joints with locally administered drugs is that high concentrations of drug can be attained in the joint cavity, whilst having minimal systemic effects. Corticosteroids are by far the most commonly used drugs for intra-articular (i.a.) injection and can be very effective in the short-term suppression of disease activity in selected joints. Corticosteroids suppress inflammation and pain and improve joint mobility, although the beneficial effects are relatively transient, lasting 1 to 6 weeks, even with the use of microcrystalline slow release preparations (Bird et al 1979; Gray & Gottlieb 1983). Although corticosteroids are unequalled in suppressing short-term inflammatory reactions, controlled trials over 2 years or more have failed to demonstrate that corticosteroids significantly diminish destruction of the articular cartilage, indeed the reverse may be the case (Chandler et al 1959; Ishikawa 1981; Bertouch et al 1983). There is, therefore, an urgent need for other forms of local treatment for arthritic joints which will be of long-term benefit. One treatment which has been practised for many years with varying degrees of enthusiasm is surgical synovectomy. Complete ablation of the diseased synovium is technically difficult and subsequent regrowth can occur, the regenerating synovial tissue often having similar inflammatory characteristics. Open surgical synovectomy also requires a considerable period of rehabilitation, but recently developed arthroscopic micro-surgical techniques which cause much less trauma are attracting increasing interest (see Gschwend 1989).

Chemical synovectomy is an alternative to surgery in which the diseased synovium is destroyed by injecting cytotoxic agents into the joint cavity. A wide variety of agents has been employed for this purpose, including osmic acid (Nissila et al 1978), nitrogen mustard (Henderson & Nathan 1969), thiotepa (Ellison & Flatt 1971), and methotrexate (Hall & Head 1975). One problem with using cytotoxic agents is that they may be cleared rapidly from the injected joint and exert systemic effects. This risk can be reduced by formulating the agent in microparticles or liposomes, which have the additional advantage of being preferentially taken up by phagocytic cells in the diseased joint (Bard et al 1983; Ratcliffe et al 1984). Alternatively, a synovectomy can be effected by injecting a radionucleotide into arthritic joints to irradiate and destroy the diseased synovium. Irradiation synovectomy was first performed using colloidal ^{198}Au (Ansell et al 1963), but ^{90}Y is now the radionucleotide most commonly used because of its more penetrating β-radiation (Gumpel 1978; Menkes 1979).

The objective of this study was to compare the efficacy of irradiation and chemical synovectomy in treating a chronic bilateral arthritis in rabbits. ^{90}Y was used to induce irradiation synovectomy and the alkylating agent chlorambucil used to effect a chemical synovectomy. For comparison, some rabbits were treated with intra-articular methylprednisolone.

Materials and Methods

Materials

Drugs and other materials were obtained as follows: Freund's complete adjuvant (Difco, Detroit), ovalbumin (Sigma, Poole), ^{90}Y silicate (Amersham International, Amersham), chlorambucil (Wellcome, Beckenham), methylprednisolone acetate (Upjohn, Crawley) and promethazine

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hydrochloride (Fisons, Loughborough). All doses for drugs are expressed as the base.

Rabbits were inbred of the Old English strain, weighing 1·4–1·6 kg at the time of antigen sensitization and 1·9–2·1 kg when the arthritis was treated.

Antigen-induced arthritis

A bilateral arthritis was induced in the knee joints of rabbits as previously described (Foong & Green 1993). Briefly, ovalbumin 20 mg mL^{-1} in sterile saline was emulsified with an equal volume of Freund's complete adjuvant, the rabbits being sensitized by injecting a total of 1 mL of the emulsion subcutaneously at five sites. The sensitization procedure was repeated three weeks later and after a further two weeks a bilateral arthritis was induced by injecting 5 mg ovalbumin in saline into both knee joints. Thirty minutes before ovalbumin challenge, rabbits were pretreated with promethazine 5 mg kg^{-1} intraperitoneally to mitigate some of the effects of acute anaphylaxis.

Assessment of arthritis

The development of arthritis was monitored at regular intervals by measuring changes in knee joint diameter and skin surface temperature over the joint as previously described (Foong & Green 1993). Immediately before the injection of the challenging dose of antigen, the diameter of the knee joints was 18·2±0·2 mm and the skin surface temperature 33·9±0·2°C (n=33). One week after injection of antigen, the joint diameter of untreated knees had increased to 23·3±0·4 mm and the surface temperature to 37·5±0·2°C (n=33).

When the rabbits were killed, the knee joints were opened and their morphological appearance graded on a scale of 0 to 4 for each of the following parameters: Synovial fluid: very small volume, slight discolouration 1; small volume with discoloration 2; discolouration with some tissue debris 3; large volume with discolouration and tissue debris 4. Synovium: slight hyperplasia and vascularization 1; as 1 with occasional petechiae 2; hyperplasia with petechiae and some discolouration 3; hyperplasia with many petechiae and discolouration 4. Cartilage and bone: cartilage erosion 1; cartilage erosion with limited bone erosion of femoral condyles 2; extensive erosion of femoral condyles 3; erosion also affecting the intercondylar fossa and patella 4.

Histological sections of the joints were prepared and stained as previously described (Foong & Green 1993). The histology of the sections was assessed blind, being graded on a scale of 0–5 as follows: normal synovium with a few plasma cells and lymphocytes 1; moderate synovial hyperplasia with plasma cells and lymphocytes 2; increased hyperplasia and cellular infiltrate with vasculitis 3; cellular infiltration of whole synovium, pannus formation with abnormal chondrocyte distribution and cartilage erosion 4; dense cellular infiltrate with erosion of cartilage and bone 5.

Administration of drugs

Drugs were normally injected intra-articularly in 0·5 mL 0·9% NaCl (saline). Chlorambucil was first dissolved in ethanol, the final solution for injection containing 20% ethanol in saline. Contralateral control arthritic joints were injected with an equal volume of vehicle.

Statistics

Results are expressed as mean±s.e.m., statistical significance being determined using paired Student's *t*-test, significance being accepted at $P<0·05$.

Results

Treatment with methylprednisolone

Methylprednisolone (1 mg) injected intra-articularly at the time of antigen challenge reduced joint swelling within 24 h, a significant beneficial effect persisting for 6 weeks after injection. Surface temperature of the treated joint was suppressed to a lesser extent (Fig. 1). Two rabbits which were injected intra-articularly with methylprednisolone at the time of antigen challenge and killed 5 weeks later showed only mild synovial hyperplasia, occasional petechiae and minimal erosion of articular cartilage in the treated joint. Microscopically the synovium showed only a sparse scattering of plasma cells and lymphocytes, although the blood vessels showed marked congestion and haemorrhage. In rabbits injected with methylprednisolone at the time of antigen challenge and killed 8 weeks later, macroscopic examination of the treated joints showed a small but significant reduction in pathological changes in the synovium, but assessments for erosion and joint histopathology did not differ significantly from control arthritic joints (Table 1).

Treatment of an established arthritis of 3 weeks duration with methylprednisolone (1 mg, i.a.) caused a small but

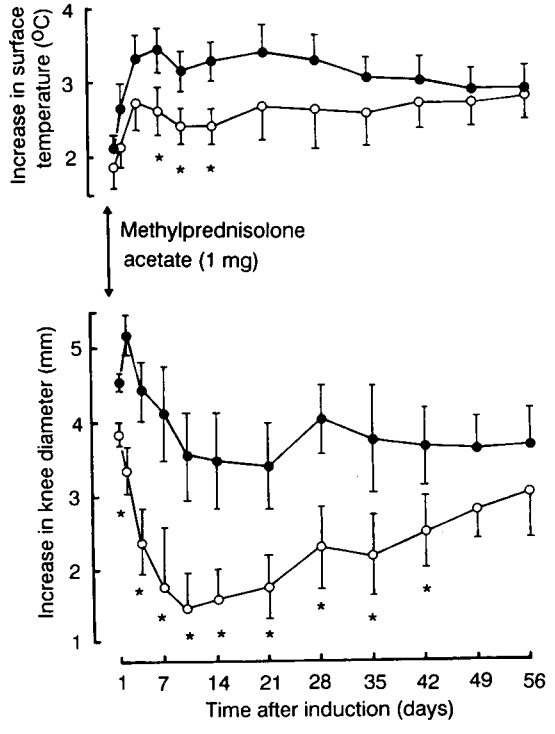

FIG. 1. Effect of methylprednisolone (1 mg, i.a.) (○) on joint diameter and surface temperature of arthritic joints when injected at the time of antigen challenge. Saline (●) was injected into the contralateral arthritic joint. Values indicate mean±s.e.m., n=6. *$P<0·05$ compared with control joint.

Table 1. Morphological and histological assessment of arthritis in control arthritic joints and arthritic joints injected with methylprednisolone, ^{90}Y or chlorambucil.

Treatment and time of injection after induction of arthritis		Macroscopic assessment: Synovial fluid	Synovium	Cartilage and bone erosion	Histological assessment
Methylprednisolone 1 mg (6)	Control	2·8±0·2	3·0±0·3	3·3±0·2	4·1±0·2
Day 0	Treated	2·8±0·2	2·4±0·2*	2·9±0·2	3·8±0·2
Methylprednisolone 1 mg (4)	Control	3·7±0·3	3·0±0·3	3·5±0·3	4·4±0·2
Day 21	Treated	2·7±0·2*	2·3±0·3*	3·0±0·3	3·9±0·3
^{90}Y 18·5 MBq (4)	Control	3·2±0·0	3·5±0·3	3·0±0·0	4·7±0·3
Day 7	Treated	2·7±0·2*	3·0±0·3	3·0±0·3	4·5±0·3
^{90}Y 18·5 MBq (4)	Control	3·5±0·3	3·7±0·2	3·3±0·2	4·2±0·2
Day 21	Treated	3·3±0·2	3·3±0·2	3·7±0·2	4·2±0·4
Chlorambucil 0·1 mg (4)	Control	3·3±0·3	3·5±0·3	3·4±0·3	4·3±0·3
Day 7	Treated	3·5±0·4	3·0±0·1	3·1±0·1	4·0±0·2
Chlorambucil 1 mg (5)	Control	3·5±0·4	3·3±0·3	3·3±0·3	4·4±0·2
Day 7	Treated	1·9±0·1*	2·1±0·2*	2·1±0·2*	3·6±0·3*

A bilateral arthritis was induced in rabbits and methylprednisolone, ^{90}Y or chlorambucil was injected into one joint at various times after induction. When the rabbits were killed, 8 weeks after induction of arthritis the morphological (graded 0 to 4) and histological (graded 0 to 5) appearance of the joints was scored at 0·5 intervals. Values indicate means±s.e.m. Figures in parentheses indicate the number of rabbits in each group. *$P<0·05$ when compared with contralateral control arthritic joints.

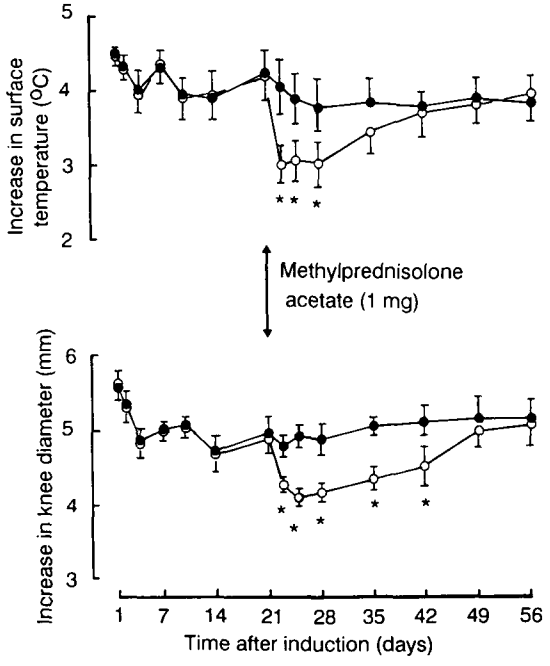

FIG. 2. Effect of methylprednisolone (1 mg, i.a.) (○) on joint diameter and surface temperature of arthritic joints when injected 21 days after antigen challenge. Saline (●) was injected into the contralateral arthritic joint. Values indicate mean±s.e.m., n=4. *$P<0·05$ compared with control joint.

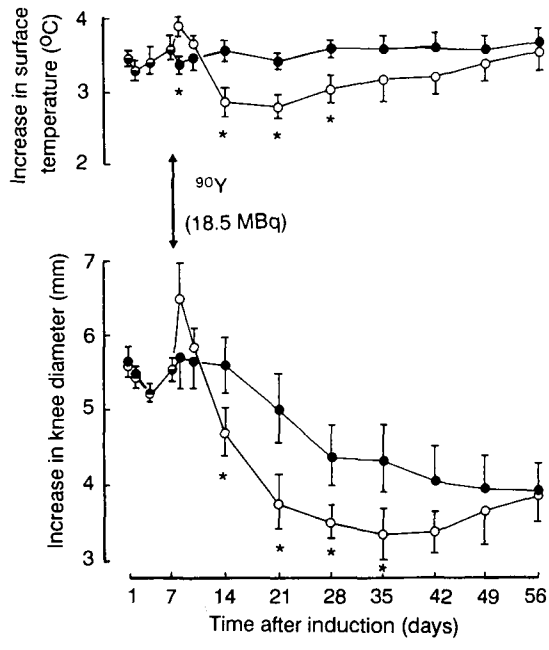

FIG. 3. Effect of ^{90}Y (18·5 MBq, i.a.) (○) on joint diameter and surface temperature of arthritic joint when injected 7 days after antigen challenge. Saline (●) was injected into the contralateral arthritic joint. Values indicate mean±s.e.m., n=4. *$P<0·05$ compared with control joint.

significant reduction in both joint swelling and surface temperature. The effect on joint swelling was greatest, persisting for up to 3 weeks after injection of methylprednisolone (Fig. 2). Examination of the opened joints 5 weeks after injection of methylprednisolone showed a reduction in the inflammatory assessment for the synovium and synovial fluid, with no change in erosion or histopathology scores for the treated joints (Table 1).

Treatment with ^{90}Y

In preliminary studies in 3 rabbits, ^{90}Y (9·25 MBq) injected intra-articularly 7 days after antigen challenge appeared to have no significant beneficial effect on joint swelling or temperature. The amount of ^{90}Y injected was therefore increased to 18·5 MBq in subsequent studies. ^{90}Y (18·5 MBq) injected intra-articularly 7 days after antigen challenge had an initial pro-inflammatory effect, causing an increase in joint swelling and surface temperature of the treated joint for 3 days after injection (Fig. 3). However, 7 days after

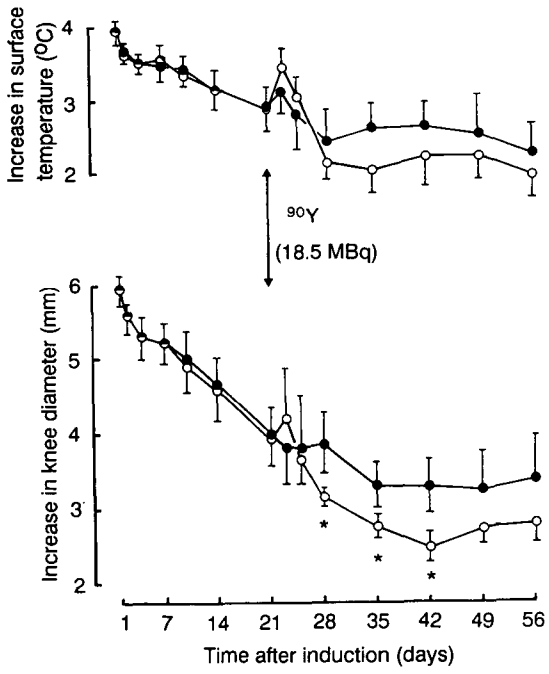

FIG. 4. Effect of ^{90}Y (18·5 MBq, i.a.) (○) on joint diameter and surface temperature of arthritic joints when injected 21 days after antigen challenge. Saline (●) was injected into the contralateral arthritic joint. Values indicate mean ± s.e.m., n = 4. * $P < 0.05$ compared with control joint.

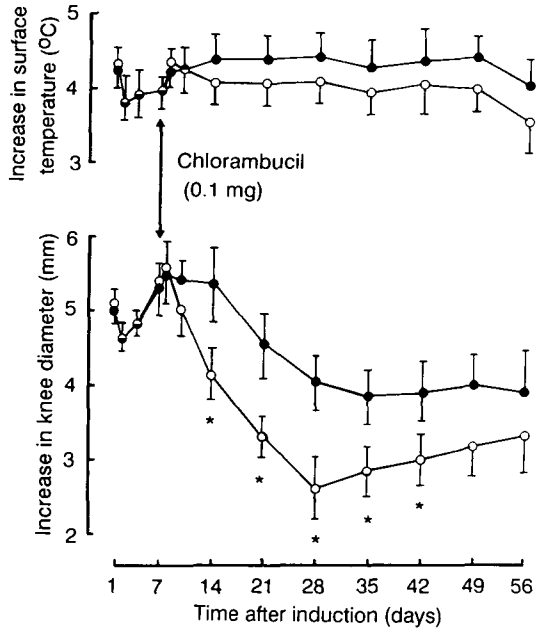

FIG. 5. Effect of chlorambucil (0·1 mg, i.a.) (○) on joint diameter and surface temperature of arthritic joints when injected 7 days after antigen challenge. Saline (●) was injected into the contralateral arthritic joint. Values indicate mean ± s.e.m., n = 4.

injection, swelling and surface temperature of the treated joint was significantly less than the contralateral control arthritic joint, the beneficial effect persisting for approximately 4 weeks. When the rabbits were killed, 8 weeks after induction of arthritis, joint swelling and surface temperature of joints injected with ^{90}Y were not significantly different from control arthritic joints. The opened joints showed the synovial fluid to be slightly reduced in volume and pathological appearance in those that had been treated, but there were no other significant morphological or histological differences between ^{90}Y-treated and control arthritic joints. Both showed marked synovial hyperplasia, lymphocyte infiltration and pannus formation with erosion of cartilage and bone (Table 1). ^{90}Y injected intra-articularly 21 days after induction of arthritis was less effective in suppressing inflammatory changes than when injected 7 days after antigen challenge, causing only a significant reduction in joint swelling 7 to 21 days after treatment (Fig. 4). There were no significant morphological or histological differences between ^{90}Y-treated and control arthritic joints when examined 8 weeks after induction of arthritis (Table 1).

Treatment with chlorambucil

Chlorambucil (0·1 mg, i.a.) 7 days after antigen challenge caused a significant reduction in joint swelling 7 to 35 days after injection ($P < 0.05$, n = 4) but had no significant effect on joint temperature (Fig. 5). Morphological and histological examination of the joints 8 weeks after induction of arthritis showed no significant beneficial effects in the chlorambucil-treated joints (Table 1). However, increasing the amount of chlorambucil injected to 1 mg, substantially reduced the severity of arthritis in the injected joint. Thus, chlorambucil (1 mg, i.a.) 7 days after antigen challenge again caused no initial irritation but significantly reduced both joint swelling and skin surface temperature within 3 days of injection. Swelling in the chlorambucil-treated joint was reduced by approximately 30% for the duration of the study, but the effect on joint temperature was less and transitory (data not shown). Morphological and histological examination of chlorambucil-treated joints 8 weeks after induction of arthritis showed a significant reduction in severity for all of the parameters of inflammation measured, including synovial proliferation and erosion of cartilage and bone.

Discussion

Antigen-induced arthritis in rabbits provides one of the best models of rheumatoid arthritis available. Following sensitization, injection of a challenging dose of antigen into a joint results in production of immune complexes which become deposited on the articular tissues. An Arthus reaction develops within hours of the challenging injection, large numbers of polymorphonuclear leucocytes infiltrate the synovium with vasodilatation and plasma extravasation into the joint cavity. The acute inflammation is replaced by a chronic synovitis characterized by mononuclear cell infiltration which appears to be dependent upon a cell-mediated immune response. There is gross synovial hyperplasia with germinal centres of lymphocytes synthesizing specific antibody against the immunizing antigen (Glynn 1968; Zvaifler 1973). Subsequently, synovial pannus overgrows the articular cartilage, eroding the cartilage and bone as occurs in

rheumatoid arthritis. Moreover, the responsiveness of this animal model to antirheumatic and anti-inflammatory drugs is similar to that of the clinical disease (see Hunneyball 1984; Crossley et al 1987).

Methylprednisolone is a sparingly-soluble corticosteroid and therefore can be expected to exert a relatively prolonged anti-inflammatory effect in injected joints. In the antigen-induced arthritic rabbit, intra-articular methylprednisolone suppressed both joint swelling and temperature, whether injected 1 or 3 weeks after induction of arthritis. The effects on joint swelling were most pronounced, significant inhibition remaining for up to 6 weeks after injection. In rabbits killed 5 or 7 weeks after injection of methylprednisolone, examination of the opened joints showed a modest reduction in inflammatory scores for the treated joints, but erosion of articular cartilage and histological changes were not suppressed. This is in broad agreement with previous reports of the effects of corticosteroids in antigen-induced arthritis. Blackham (1978) showed that when systemic treatment with prednisolone was discontinued, after 5 weeks joint swelling and synovial pathology was not significantly different from controls. Similar results were obtained by Davis (1971) and correlates with clinical experience obtained with these drugs (see Gray & Gottlieb 1983). Corticosteroids have been implicated in arthropathy of the rheumatoid knee (Chandler et al 1959) and animal studies have shown that intra-articular corticosteroids cause both biochemical and structural changes in the articular meniscus and cartilage, resulting in subchondral cysts, fissuring and cartilage loss (Hunneyball 1981; Ishikawa 1981). Corticosteroids are therefore not suitable for the long-term management of recurrent synovitis.

Synovectomy, whether achieved surgically or by injection of cytotoxic chemicals or radionucleotides, is becoming increasingly recognized for the treatment of chronic synovitis (see Gschwend 1989). Recent advances in arthroscopy have greatly reduced operative and post-operative morbidity associated with surgical synovectomy. Even so, chemical- or irradiation-induced synovectomy has a clear advantage in requiring only a single injection, involving minimal hospitalization and rehabilitation. The long-term prognosis for arthritic joints, whether treated by open surgical or radionucleotide-induced synovectomy appears to be similar, 50 to 80% of treated joints showing clinical improvement over two years or more (Gschwend 1989; Smiley & Wasilewski 1990). However, chemical- or irradiation-induced synovectomy is not appropriate in all cases, for example where there is involvement of the tendon sheath (Smiley & Wasilewski 1990). Moreover, there is the potential hazard of serious side-effects resulting from the leakage of injected cytotoxic or radionucleotide from the treated joint.

Several clinical studies indicate that ^{90}Y is particularly effective in controlling recurrent synovitis in the knee (Gschwend 1989), although treatment failures are common (Yates et al 1977; Combe et al 1989). In the current study, ^{90}Y (18·5 MBq) injected into antigen-induced arthritic rabbits had an initial pro-inflammatory effect, but later caused a modest reduction in joint swelling and surface temperature which was only sustained for a few weeks. Macroscopic and histological examination of the joints 8 weeks after induction of arthritis showed that inflammatory and degenerative changes had not been inhibited in the treated joints. This contrasts with a more favourable response to ^{90}Y in a histological study of antigen-induced arthritis in rabbits reported by Meier-Ruge et al (1976), who used a smaller dose of ^{90}Y, 40 to 80% of the dose used here, but still observed secondary irradiation damage to the cartilage. ^{90}Y has also been reported to cause damage to the articular cartilage in arthritic rats and in rheumatoid arthritis (Kerschbaumer et al 1979). In retrospect it is possible that radiation produced by ^{90}Y is too penetrating for treating arthritis in a joint the size of the rabbit knee. ^{90}Y emits β-radiation with an average penetration in soft tissue of 3·6 mm (Kerschbaumer et al 1979), making it more suitable for use in large joints. Isotopes producing less penetrating radiation, such as ^{189}Er or ^{165}Dy are recommended for treating finger and interphalangeal joints (Gschwend 1989), these being comparable in size with the rabbit knee joint.

Chlorambucil is an alkylating agent and was selected for intra-articular injection in this study since, unlike cyclophosphamide, it does not require metabolic activation. Chlorambucil has similar efficacy to cyclophosphamide in the systemic therapy of connective tissue disease, but is not widely used for this purpose except in France (Amor & Mery 1980; Luqmani et al 1990). To our knowledge chlorambucil has not previously been reported to have been injected into joints. However, in this study chlorambucil (1 mg) injected into rabbit joints in which arthritis had been induced 7 days previously caused an approximate 30% reduction in joint swelling, which was rapid in onset and maintained for the duration of the study. Chlorambucil also suppressed pathological changes in the treated joints, including erosion of cartilage and bone. The beneficial effect of intra-articular chlorambucil was greater than with methylprednisolone or ^{90}Y, and substantially greater than we have previously reported for intra-articular methotrexate in antigen-induced arthritis (Foong & Green 1993). Indeed, methotrexate only suppressed arthritis if injected intra-articularly at the time of antigen challenge, having no effect on an established arthritis of 7 days duration. However, the efficacy of methotrexate in suppressing arthritis was increased approximately 10-fold if the drug was entrapped in liposomes. The increased efficacy of liposomal methotrexate was due, at least in part, to greatly enhanced retention of drug in the injected joint (Foong & Green 1988). Liposomal entrapment has also been shown to enhance the suppressive effects of corticosteroids or daunorubicin injected into arthritic joints (Page Thomas & Phillips 1979). It would therefore, be of interest to evaluate the efficacy of chlorambucil formulated in liposomes for intra-articular injection. The lipid solubility of chlorambucil should enable it to be entrapped in the liposomal phospholipid bilayers with a high degree of stability. Since liposomes are preferentially taken up by phagocytic cells in the inflamed joint, liposomal entrapment might be expected to enhance the suppressive effect of chlorambucil on the disease process, as well as reducing drug clearance from the injected joint, minimizing potential adverse systemic effects.

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