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A limited arthritic model for chronic pain studies in the rat

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Summary Freund's adjuvant induced polyarthritis in rats has been used extensively to study pain processes of long duration. There are limitations of this model for chronic studies of pain/arthritis since the severe systemic changes provoke ethical concerns and also affect behaviour, physiology and biochemistry. Attempts to limit adjuvant-induced arthritis by plantar injection of the inoculum have been made. In this model, however, the process evolved to produce widespread polyarthritis if followed for the 6-plus-weeks necessary for chronic studies. Therefore, although it offers the researcher a reliable limited model of inflammation and nociception at the outset, for longer studies it may have all the disadvantages of the polyarthritic rat. The purpose of the present study was to produce a limited arthritic process in rats, stable over 6 weeks and suitable for behavioural and neurochemical studies of various chronic pain treatment methods.

Injection (0.05 ml) of complete adjuvant containing 300 μg *Mycobacterium butyricum* in the tibio-tarsal joint produces a predictable monoarthritis, stable clinically and behaviourly from weeks 2 through 6 post injection. As revealed by clinical observations and X-ray examinations, the arthritis produced was limited anatomically, pronounced, prolonged and stable. A marked increase in sensitivity to paw pressure was seen in the affected limb. Animals gained weight and remained active, indicating little systemic disturbance as opposed to polyarthritic rats. We propose this limited model of arthritis as a suitable alternative to the polyarthritic rat for prolonged studies.

Key words: Monoarthritic rat; Freund's adjuvant; Chronic pain

Introduction

Polyarthritic rats have been used extensively to study pain processes of long duration and to evaluate the potential analgesic or anti-inflammatory effects of drugs (see Besson and Guilbaud 1988). In previous experiments, we used the polyarthritic rat for pharmacological studies needing a model which had continuing nociception over several weeks (Godefroy et al. 1984; Butler et al. 1985; Godefroy et al. 1986). These studies attempted to mimic a chronic pain treatment in man – tricyclic antidepressant therapy – which requires a minimum of 2 weeks and often 4 or more to produce clinical effects (Butler 1984; Monks 1989). This time frame for a therapeutic response was mirrored in the polyarthritic rat as effects of treatment appeared at 3 weeks but were not statistically significant until after 4 weeks of therapy with a stable dose of tricyclic antidepressant (Butler et al. 1985).

In addition to having a relatively stable nociceptive process to treat, it is necessary to allow time for pathophysiologic changes to take place in the model before initiating a treatment to be studied. There is a growing literature showing plastic changes in the nervous system at many levels in response to continued nociceptive input (Devor and Wall 1978; Menétrey and Besson 1982; Guilbaud et al. 1985; Dubner et al. 1988; Guilbaud 1988; Schnaible and Schmidt 1988) for review see (Dubner 1991). In an article addressing animal models for pain research, Casey and Dubner (1989) cite several authors in emphasizing the possible importance of these changes in the development of chronic pain states in man. These introductory studies are beginning to give us clues as to possible mechanisms producing

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chronic pain and clues as to why the physiology of and treatments for chronic pain differ from acute pain. Much further work needs to be done, not only to investigate the pathophysiology of this still poorly understood problem, but also to explain why existing empiric treatments are successful and to develop new treatment strategies.

Before continuing such studies, we felt obliged to reconsider the polyarthritic model in terms of the ethical issues concerning the use of animal models of chronic pain addressed by several authors (Wall 1976; Casey 1986; Coderre and Wall 1987). We also had strong concerns about the obvious widespread systemic disease in response to injection of complete Freund's adjuvant (Pearson and Wood 1959; Glen et al. 1965; Mathur et al. 1977; De Castro Costa et al. 1981; Colpaert et al. 1982; Rainsford 1982; Calvino et al. 1987a). Our concern was that some of the behavioural or neurochemical modifications ascribed to nociception could be non-specific effects related, for instance, to systemic metabolic (Godefroy et al. 1987) or neurological (Reiber et al. 1984) changes induced by the disease. We felt that a more limited pain stimulus of long duration, a minimum of 6 weeks for the above stated reasons, would allow a better evaluation of behavioural and physical changes produced by chronic treatment as in our previous experiment performed in polyarthritic rats.

Alternatives to the polyarthritic rat model do exist but we found them wanting for our particular needs for several reasons. Many research teams have turned to unilateral plantar injection of Freund's adjuvant (Larsen and Arnt 1985; Iadarola et al. 1988; Millan et al. 1988) originally described as a model of monoarthritis. In this model, however, the process evolved to produce widespread polyarthritis if followed for the 6-plus weeks necessary for our proposed studies. Therefore, although it offers the researcher a reliable limited model of inflammation and nociception at the outset, for longer studies it may have all the disadvantages of the polyarthritic model.

The ankle joint urate arthritic models proposed by Otsuki et al. (1986) and Coderre and Wall (1987) seem to be too limited in terms of the duration of a stable nociceptive input for our purposes. This is borne out by Coderre and Wall's finding that behavioural changes and heightened responses to an acute pain stimulus totally disappeared after 1 week, clearly far short of the 6-plus-week target we were looking for.

Of more interest to us was the protocol used by Grubb et al. (1988) who injected Freund's adjuvant into the periarticular tissues of the ankle joints of rats. We used this as the basis for a series of studies which have produced a reliable, reproducible, monoarthritic model, stable clinically over several weeks and with a minimum of systemic effects by our measurements. Our primary purpose was to add more behavioural data and a more complete physical description to the information in their article, but we felt that the Grubb model should be modified because the injections were peri-articular. Since we wished to produce a prolonged process with primarily intra-articular changes, we chose to inject complete adjuvant intra-articularly. Preliminary studies were performed with a commercially prepared Freund's complete adjuvant (Sigma F4258) and with various concentrations of a complete adjuvant prepared in our laboratory to obtain an optimum response. A preliminary report of these studies has appeared elsewhere (Butler et al. 1990). The present paper reports on the investigation of the final model using measurements of behaviour, physical signs of arthritis (including radiographic signs) and response to an acute pain stimulus. Our aim was to define the parameters which distinguish it as a reliable model of physically circumscribed, prolonged nociception for chronic investigations.

Methods

Sprague-Dawley male rats from the Centre d'Elevage Charles Rivers, France, arriving at a weight of 150–175 g were used throughout these studies. They were housed 6 to a cage with sawdust bedding, given food and water ad libitum and kept in an animal house at a constant temperature of 22°C with a 12 h alternating light–dark cycle. All observations were performed by one of the authors to avoid inter-observer differences. The studies were not done in a blinded manner as there were obvious physical differences between groups which would nullify any attempts to blind the observer.

Induction of monoarthritis

For the formal studies of the final model the complete adjuvant was prepared as follows: 60 mg of killed *Mycobacterium butyricum* (Difco laboratories) were added to a mixture of paraffin oil (6 ml), NaCl 0.9% (4 ml), Tween 80 (1 ml), mixed thoroughly and then autoclaved for 20 min at 120°C to rupture the cell walls of the mycobacteria. This preparation was refrigerated, but warmed and thoroughly mixed prior to injection to prepare each set of animals.

Three groups of 12 rats were used: the first consisting of rats in which the left tibio-tarsal joint was injected with vehicle alone; the second consisting of rats in which a similar injection was made with 0.05 ml of complete adjuvant prepared from killed, denatured *Mycobacterium butyricum*; the third consisting of rats injected through the plantar fascia with 0.05 ml of the same complete adjuvant.

Injection of the left ankle joint was performed under brief halothane/N_2O/O_2 anesthesia as follows: the tarsial area of the hind paw was grasped and the fossa distal and medial to the 'lateral malleolus' of the fibula was palpated. A 26-gauge needle was introduced into the capsule of the tibio-tarsal joint percutaneously by directing it cephalad, mesiad and superiorly from the midpoint of the 'inframalleolar fossa,' until a distinct loss of resistance was felt – approximately 4 mm – and complete adjuvant or vehicle injected. With a true intracapsular injection, a firm resistence to injection was characteristically felt after the injection of 0.05 ml of fluid.

Baseline (pre-induction) behavioural and clinical observations were made prior to injection of vehicle or complete adjuvant, and then at 2, 4 and 6 weeks.

TABLE I

EVALUATION SCALES OF NUMERICAL MOBILITY, STANCE AND STIFFNESS SCORES

Evaluation scale	Score
Numerical mobility score	
The rat lies down only	0
The rat crawls only	1
The rat walks with difficulty	2
The rat walks and runs with difficulty	3
The rat walks and runs normally	4
Numerical stance score	
The rat stands on three paws only	0
The rat stands with the arthritic paw touching floor, toes curled under	1
The rat stands bearing some weight on the arthritic limb	2
The rat stands bearing weight equally on all four limbs	3
Numerical joint stiffness score	
Restriction of full range of flexion	1
Restriction of full range of extension (max. score 2 for each paw)	1

Clinical observations

The clinical observations included weight, circumference measurements of the tibio-tarsal or ankle joints bilaterally, a mobility score, a stance score and a joint stiffness score as described in Table I.

Radiographic evaluation was performed on the basis of whole body radiographs and coned down views of rear limbs.

Behavioural observations

For behavioural observations, rats were put singly into a 50×50×40 cm clear plastic cage, faintly illuminated, located in a dark and quiet room. All observations took place between 8.00 and 12.00 h and 6 rats were observed each day to accommodate this schedule.

The behavioural parameters included exploring, grooming, scratching recorded as number of seconds each was performed by each rat in 30 min and rearing recorded as number of times performed in 30 min. Scratching was evaluated as described by De Castro Costa et al. (1981). Exploring activity encompassed time spent moving about the cage plus active investigation of the environment while stationary (such activities as sniffing of the cage corners and rearing). Rearing activity indicates that the rat stands with the weight supported on the hind limbs only.

Responses to painful stimuli

(a) The Randall–Selitto apparatus was used to obtain a threshold for struggle by applying a graded weight to the hind foot and recording the weight at which the rat forcefully removed the foot from the plinth. Two readings were taken at each session for each hind paw and these values were then averaged for calculations.

(b) Vocalizations to flexion and extension of the ankle within its limits of range of motion were recorded; two manipulations in each direction of each ankle were used at each session and the total number of vocalizations for each paw was recorded.

Statistical analyses

Statistical analyses were carried out using the Wilcoxon matched-pair signed rank test and variance analysis. When P values were greater than 0.05, differences were not considered to be significant.

Results

Rats were divided in three groups as described in Methods. For the subsequent presentation group A will refer to those rats injected intra-articularly with the vehicle; group B will refer to those rats injected intra-articularly with the complete adjuvant prepared in our laboratory, and group C will refer to those rats injected into the plantar region with the complete adjuvant prepared in our laboratory.

Clinical observations

No incidence of arthritis was observed in group A. Clear monoarthritis was seen in group B. Only 1 rat in this group exhibited evidence of mild polyarthritis. In contrast, clear evidence of polyarthritis was observed in 6 of 12 rats in group C.

The polyarthritis observed in the plantar injected group was characterized by the occurrence of arthritis in the contralateral limb and in the tail (see below). One of the rats in this plantar injected group died at 5 weeks post injection. The mild evidence of arthritis in the tail without occurrence of arthritis in the contralateral limb observed in one rat of the group B at 4 weeks disappeared at 6 weeks.

X-ray examinations of rats were made at 6 weeks. They showed no signs of arthritic changes in rats of group A (Fig. 1). Radiographs of rats of group B showed ipsilateral joint destruction and bony proliferation largely confined to the region of the tibio-tarsal joint with no other changes (Fig. 2). Radiographs of rats of group C, i.e., those injected into the plantar region (Fig. 3), showed (i) ipsilateral soft tissue swelling in the foot region in all rats in this group; (ii) extensive ipsilateral joint destruction and bony proliferation of the metatarsal, tarsal and ankle regions in all rats in this group; and (iii) similar contralateral metatarsal, tarsal and ankle changes plus changes in the bony and soft tissue architecture of the tail in the 6 rats of group C with polyarthritis. In this group of rats injected into the plantar region, measurements of the other clinical or behavioural criteria were made only in rats with arthritis only in the injected hind paw (6 of 12 rats).

Weight gain was progressive in all groups (Table II), with a high degree of significance at each weekly measurement, but the rat weight gain was slightly slowed in groups B and C at 2 weeks and 4 weeks. At 6 weeks, however, no differences between the three groups were observed.

With regard to increase in ankle circumference (Table II), on the injected side all groups showed a statistically significant enlargement when compared to pre-incubation period at 2, 4 and 6 weeks. Enlargement of the contralateral side in group A, however, was parallel and equivalent to that of the non-injected side (pre-induction: 2.71 ± 0.02; 6 weeks: 3.01 ± 0.03 cm) showing

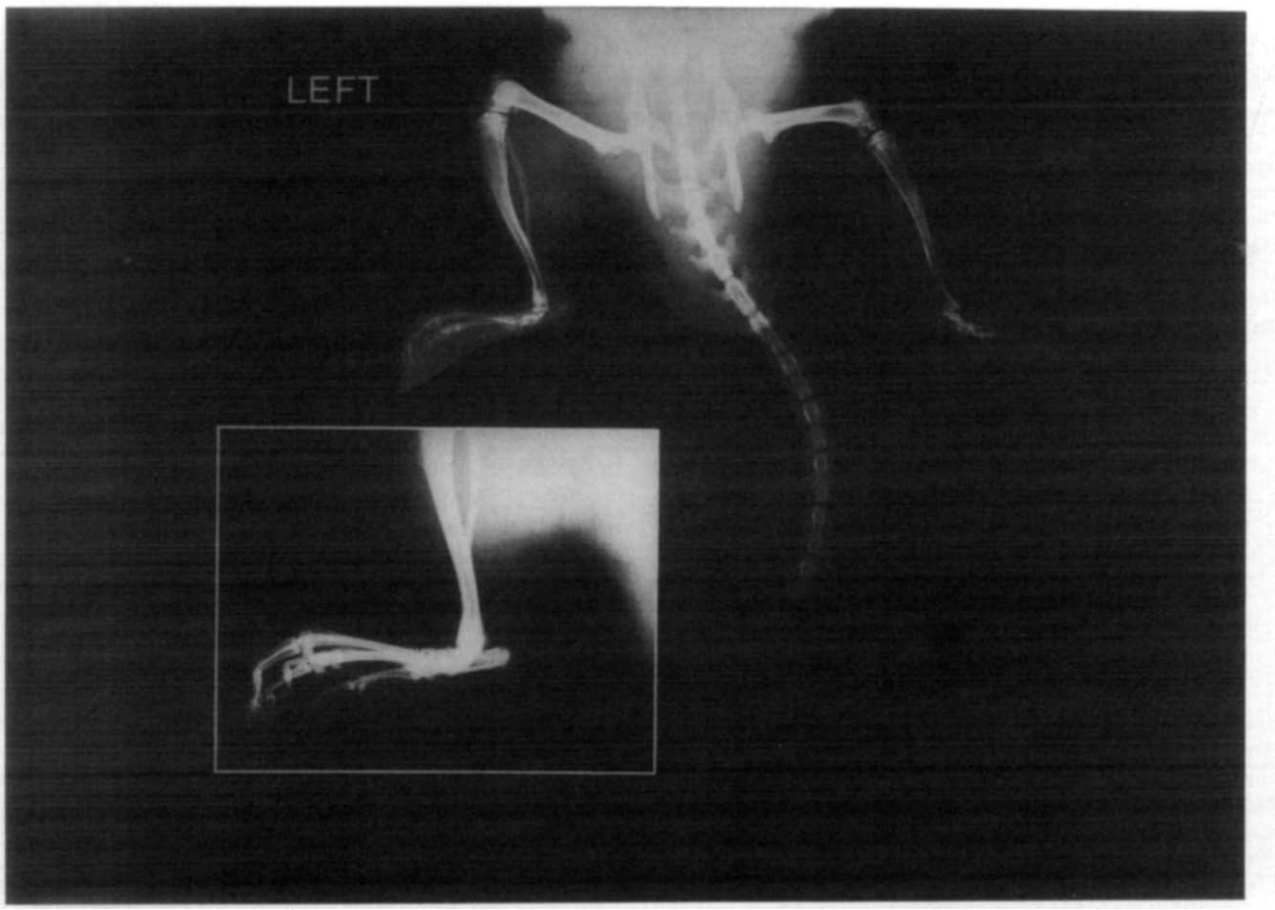

Fig. 1. Individual example of whole body radiograph and coned down view of rear limb of rat 6 weeks after intra-articular injection (left ankle) of vehicle (group A). See Methods.

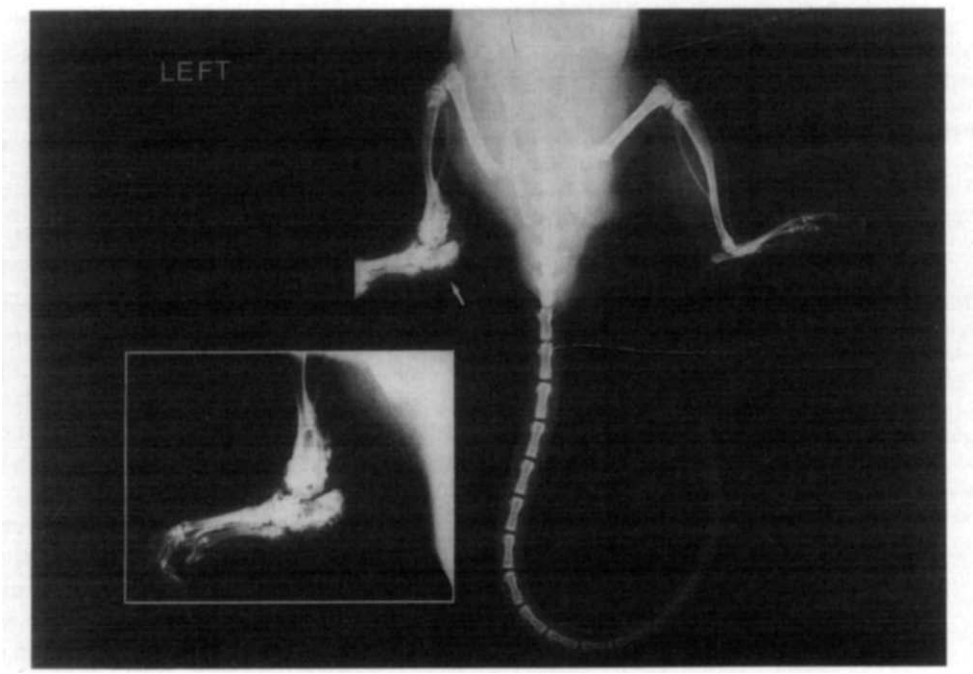

Fig. 2. Individual example of whole body radiograph and coned down view of rear limb of rat 6 weeks after intra-articular injection (left ankle) of complete Freund's adjuvant (group B). See Methods.

that this increase is mainly related to growth. Groups B and C had much more marked increases of ankle circumferences on the injected limb than ankle circumferences in group A. The differences between groups B and C compared to group A were significant at 4 and 6 weeks. No difference was observed between the ankle circumference in the contralateral side in group B and the ankle circumference in group A (group B, 6 weeks: 3.10 ± 0.04 cm). In the polyarthritic rats of group C an increase in the ankle circumference was observed in the contralateral side.

Both the mobility and stance scores remained at baseline values for group A for all of the study. They were reduced from 2 through 6 weeks in groups B and C but there was no difference between these last two groups (Table II).

No joint stiffness was evident in group A at any point in the study. Joint stiffness was observed in groups B and C (except in group C at 2 weeks) at each post-inoculation period (Table II) in the injected side. No joint stiffness was evident in the contralateral side in the rats of group B, whereas in group C joint stiffness was observed in the polyarthritic rats of the group.

Behavioural observations

Exploring activity tended to decrease in all groups over time, but this decrease was only significant in group C at 4 weeks and 6 weeks (Fig. 4).

The incidence of rearing was decreased in groups B and C, this being significant at 2, 4 and 6 weeks. No inter-group differences were found (Fig. 4). It is important to underline that *in these two groups rearing was very often done on one hind limb only, that being the non-arthritic limb*. Usually, these rats display 'guarding' behaviour and do not place weight on the injected limb even when walking.

Grooming did not show any significant changes over time or between groups during the study. No exacerbation of scratching behaviour was observed in groups B and C.

Response to painful stimuli

Randall–Selitto test. As shown in Fig. 5, no changes from baseline (pre-induction) for the struggle response to paw pressure were found in either limb for group A. Group B showed a significant decrease in weight tolerated when compared to baseline values on the *affected limb* at 4 and 6 weeks. No change was seen at 2 weeks,

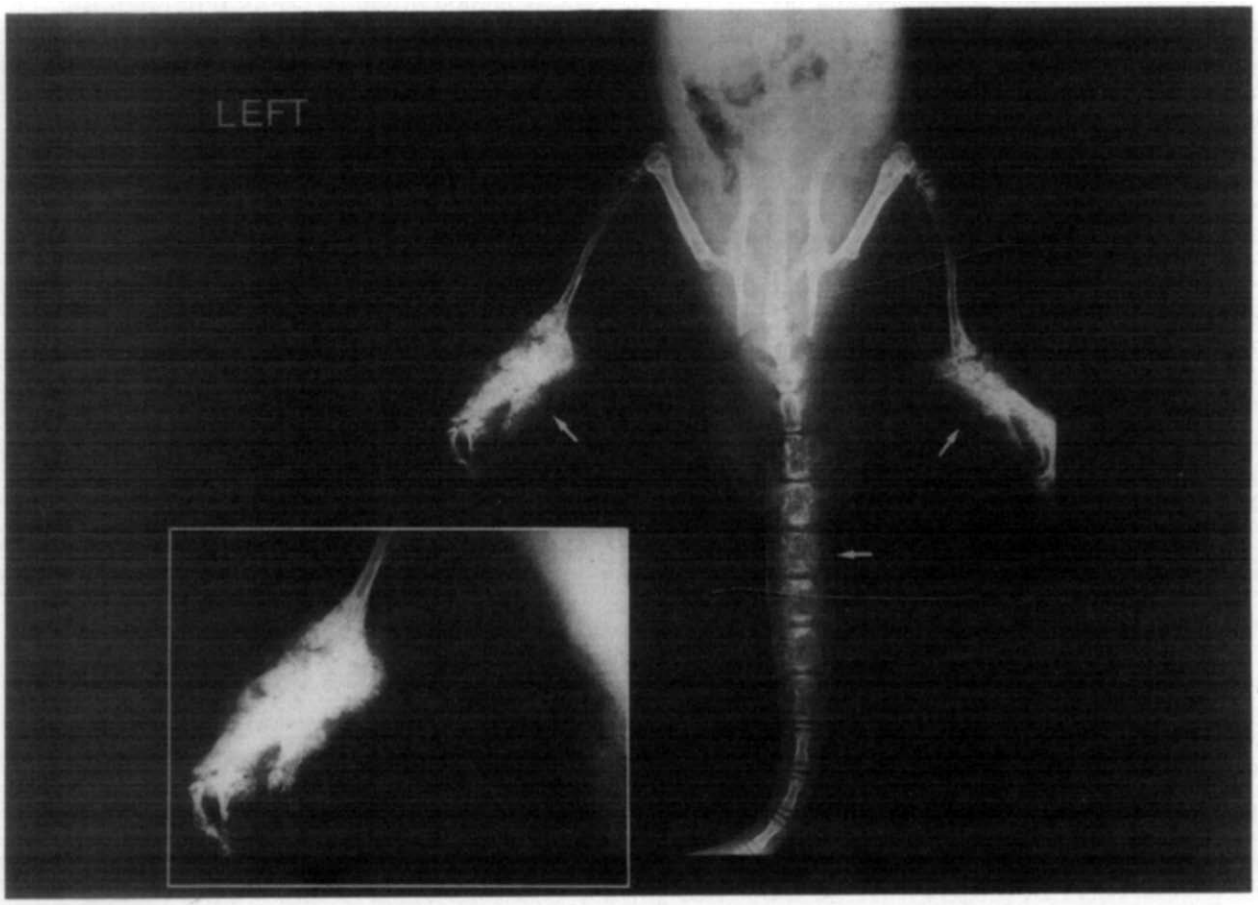

Fig. 3. Individual example of whole body radiograph and coned down view of rear limb of rat 6 weeks after intra-plantar injection (left foot) of complete Freund's adjuvant (group C). See Methods.

however. In group C, a significant reduction of weight tolerated was seen only at 4 weeks.

On the contralateral side, the *non-affected limb*, no changes were observed in groups A and C (it must be noted that in the subpopulation of polyarthritic rats of group C, which has not been included in this evaluation, a decrease in this threshold for struggle was observed). In group B, those with intra-articular injection of complete adjuvant, a significant increase in weight tolerated was seen at 2 and 4 weeks (Fig. 5).

Vocalization response to ankle flexion and extension. The response was positive in groups B and C only. A minimal response in the two groups was present at week 2 and a marked response at week 4 in the affected limb but no differences between groups was observed. At week 6, no response was present in group C whereas group B still had a weakly positive response. No positive response was observed in the contralateral limb in rat of group B whereas a positive response was observed in the contralateral side in the polyarthritic rats of group C at weeks 2 and 4.

Discussion

First, a brief comment is presented on the results of our preliminary studies (Butler et al. 1990) in order to explain the present protocol. Our pilot studies compared the effects of injection of 0.15 ml of a commercially prepared complete Freund's adjuvant (Sigma F 4258) containing 1.0 mg/ml *Mycobacterium tuberculosis* into the plantar surface of the hind paw versus the same quantity injected peri/intra-articularly at the tibio-tarsal joint. The plantar injections produced only a local soft tissue response as discussed by Iadarola et al. (1988); the peri/intra-articular injections produced local swelling with mild joint stiffness but neither produced sustained changes in behaviour nor a significant change from baseline of the response to the Randall–Selitto test past 2 weeks. Since the complete adjuvant prepared in the laboratory appeared to be more potent than the commercial preparation for the induction of polyarthritis (B. Calvino, personal communication), we looked at the dose/response curve of this locally prepared complete adjuvant and found that the peri/intra-articular injection of 0.15 ml of a suspension containing 1.8 mg *Mycobacterium butyricum*/1 ml vehicle produced sustained physical and behavioural changes. However, there was a 30% incidence of polyarthritis in this model which we felt unacceptable for our future studies.

The search for a more 'pure' model was focussed on the reduction of the incidence of polyarthritis but also on limiting soft tissue effects as much as possible. We

TABLE II

CLINICAL OBSERVATIONS IN RATS WITH ADJUVANT-INDUCED MONOARTHRITIS

Rats were injected with 0.05 ml complete Freund's adjuvant (containing 300 μg killed *Mycobacterium butyricum*) either in the left tibio-tarsal joint (group B) or in the left foot pad (group C). Control animals (group A) were injected with 0.05 ml vehicle (incomplete adjuvant) in the left tibio-tarsal joint (see Methods). Measurements were performed before inoculation (pre-induction period) and at 2, 4 and 6 weeks post inoculation.

	Pre-induction	2 weeks	4 weeks	6 weeks
Weight (g)				
Vehicle/joint	195 ±2	278 ±5 ***	399 ± 9 ***	368 ±13 ***
Adjuvant/joint	207 ±4	244 ±5 **	317 ±13 ***	368 ±13 ***
Adjuvant/pad	195 ±4	255 ±9 **	286 ±12 ***	347 ±17 **
Circumference injected joint (cm)				
Vehicle/joint	2.7 ± 0.02	2.8 ±0.03 *	2.9 ± 0.03 **	3.0 ± 0.04 **
Adjuvant/joint	2.7 ± 0.03	3.5 ±0.06 +++	4.6 ± 0.15 +++	4.8 ± 0.24 +++
Adjuvant/pad	2.7 ± 0.03	3.1 ±0.09 +	4.4 ± 0.22 +++	4.3 ± 0.26 ++
Mobility score				
Vehicle/joint	4	4	4	4
Adjuvant/joint	4	3.0 ±0.19 ++	2.4 ± 0.18 +++	2.6 ± 0.26 ++
Adjuvant/pad	4	3.4 ±0.18 +	2.5 ± 0.19 +++	3.0 ± 0.00 +++
Stance score				
Vehicle/joint	3	3	3	3
Adjuvant/joint	3	1.88 ±0.23 ++	1.00 ± 0.43 ++	1.38 ± 0.26 ++
Adjuvant/pad	3	2.13 ±0.30 +	0.88 ± 0.13 +++	1.71 ± 0.18 +++
Stiffness score				
Vehicle/joint	0	0	0	0
Adjuvant/joint	0	1.13 ± 0.13	1.88 ± 0.13	1.88 ± 0.13
Adjuvant/pad	0	0.13 ± 0.13	1.25 ± 0.31	1.43 ± 0.30

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ compared with pre-induction period.

\+ $P < 0.05$; ++ $P < 0.01$; +++ $P < 0.001$ compared with vehicle-injected joint.

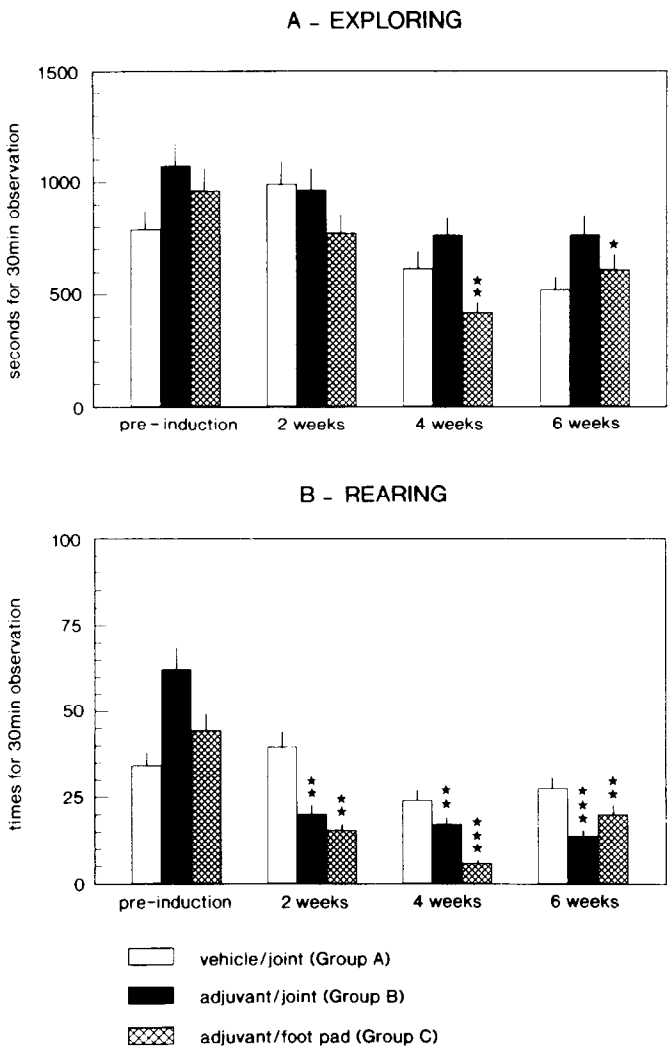

Fig. 4. Modification of exploring and rearing in rats with adjuvant-induced monoarthritis. Rats were injected with 0.05 ml complete adjuvant (containing 300 μg killed *Mycobacterium butyricum*) either in the left tibio-tarsal joint (group B) or in the left foot pad (group C). Control animals (group A) were injected with 0.05 ml vehicle in the left tibio-tarsal joint (see Methods). In group C, only the rats exhibiting monoarthritis (n = 6) were used (see Clinical observations in Results). Observations were performed before inoculation (pre-induction period) and at 2, 4 and 6 weeks post inoculation. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ compared with pre-induction period.

reasoned that injection of the total dose of adjuvant into the joint capsule might well succeed in satisfying both aims and, therefore, decided on the protocol outlined above. Since we found, in agreement with other authors (Otsuki et al. 1986) that the capsule of the tibio-tarsal joint of our rats had a volume limited to 0.05 ml, we needed to increase the concentration of the complete adjuvant to deliver the chosen dose in total mg of *Mycobacterium* in this volume. This explains the rise in concentration from 1.8 mg *Mycobacterium*/1 ml in the preliminary studies (Butler et al. 1990) to 5.45 mg *Mycobacterium*/1 ml in the final model.

The most striking characteristic of this model of monoarthritis is the attitude of the affected limb which is held flexed at the ankle, knee and hip throughout the 6-plus weeks we observed these animals. This is so striking that attempts were made following sacrifice to straighten the deformities above the level of the injected joints but these efforts were without success. Obviously, shortening of soft tissues about the knee and hip joints had occurred. This 'guarding' behaviour and the subsequent changes offer another area of study as similar changes are present in many chronic pain

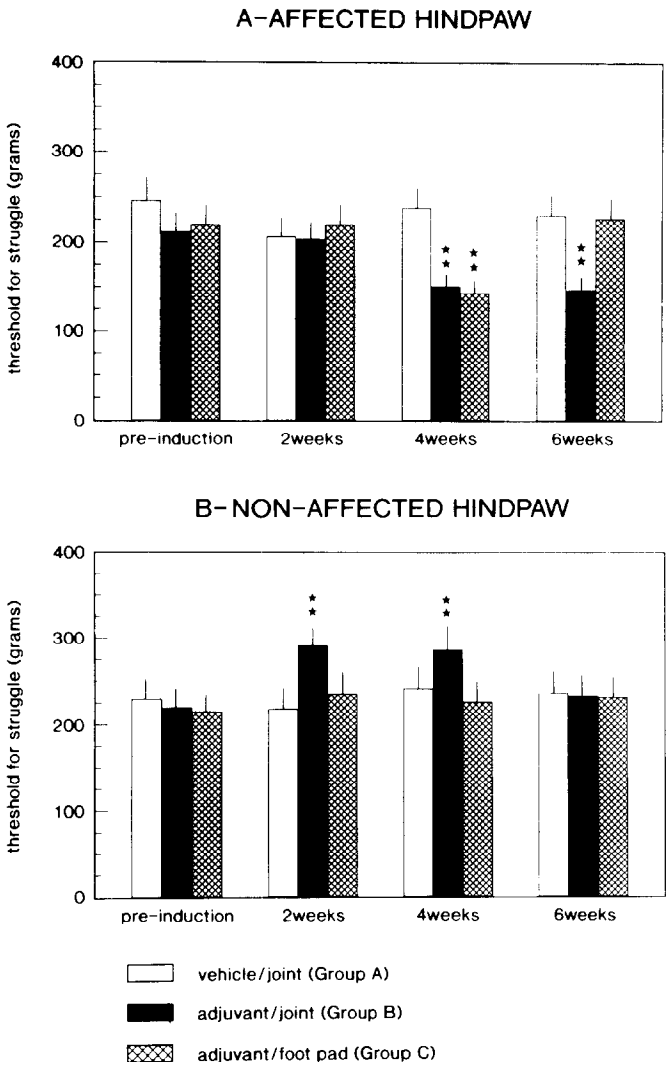

Fig. 5. Modification of the threshold for struggle in response to graded foot pressure (Randall–Selitto apparatus) in rats with adjuvant-induced monoarthritis. Rats were injected with 0.05 ml complete adjuvant (containing 300 μg killed *Mycobacterium butyricum*) either in the left tibio-tarsal joint (group B) or in the left foot pad (group C). Control animals (group A) were injected with 0.05 ml vehicle in the left tibio-tarsal joint (see Methods). In group C, only the rats exhibiting monoarthritis (n = 6) were used (see Clinical observations in Results). Measurements of the threshold were performed before inoculation (pre-induction period) and at 2, 4 and 6 weeks post inoculation. ** $P < 0.01$ compared with pre-induction period.

patients. Despite the focal arthritis and guarding behaviour that it provoked, these animals do not display signs of the many systemic changes described in the polyarthritic rats. The radiological evidence for limited joint involvement, i.e., confinement of bony changes primarily to the tibio-tarsal joints in our model, may explain the minimal systemic involvement. It would seem that injection of the complete adjuvant into the joint capsule limits systemic uptake and the subsequent widespread polyarthritis seen with the intraplantar injection of the same dose. It must be reported that there was a variability in the incidence of a polyarthritic response after intra-articular injections, however. Generally, the incidence was approximately 1/12 or 1/10 but, for some subsequent pilot work, the incidence of polyarthritis rose to 3/10 when problems occurred in the animal house – overheating for several hours and a malfunction of the light cycling mechanism so that the animals were subjected to constant light over a weekend. The polyarthritis incidence for other studies subsequently dropped to 1/12 using the same batch of adjuvant administered by the same operator which underlines the importance of a constant environment in the production of the model and for animal research in general. Particularly, this observation agrees with the well documented effect of stress on the development of arthritis (Levine et al. 1988).

In the present model of monoarthritis, the arthritis itself is very stable in terms of physical signs, although the response to paw pressure does not follow the same time course. The increased sensitivity on the affected side does not appear until 3 weeks following injection but is stable through the sixth week. We did not follow it further in the evolution of the clinical state but it may well continue longer. In contrast, the decreased sensitivity to paw pressure on the contralateral side was relatively short lived, lasting only from the second to the fourth week. The alteration in response to an acute pain stimulus in the non-affected limb probably reflects involvement of inhibitory controls caused by the obvious long-standing nociceptive input from the contralateral arthritic limb. This latter hypothesis agrees with the demonstration of the occurrence of inhibitory mechanisms involving pathways arising from supraspinal structures in polyarthritic rats (Calvino et al. 1987b) as well as in urate crystal monoarthritic rats (Coderre and Wall 1988).

In conclusion, we present a regional limited form of stable arthritis for long-term studies of inflammation and nociception and the secondary affects of prolonged noxious sensory input. The rats are obviously quite active by our behavioural measures but also appear lively, interested in their environment and never display the irritability typical of the polyarthritic model. More importantly to the researcher, at no time did irritability lead to attempt to bite the manipulator as is frequent with polyarthritic rats. Weight which has been used by others as an indication of general health in various arthritic models (Calvino et al. 1987a; Coderre and Wall 1987) increases normally in our model. Although no biochemical studies have been done to date, there is little evidence for widespread systemic changes which challenge the validity of studies performed with the polyarthritic rat. There always will be ethical concerns over chronic studies involving nociception but we feel this model has limited the behavioural and activity changes to a minimum to answer many of the ethical problems of other long-term models. It would appear to offer the chance to test the effects of plasticity in production of 'chronic pain.' The prolonged and stable nature of the arthritic process makes it appropriate for studies of chronic treatments used in pain therapy, those which would outlast the changes produced in other more limited proposed models of pain. We suggest it as a substitute for the polyarthritic rat for chronic studies.

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