Non-Steroidal Anti-Inflammatory Drugs in the Therapy of Canine Osteoarthritis

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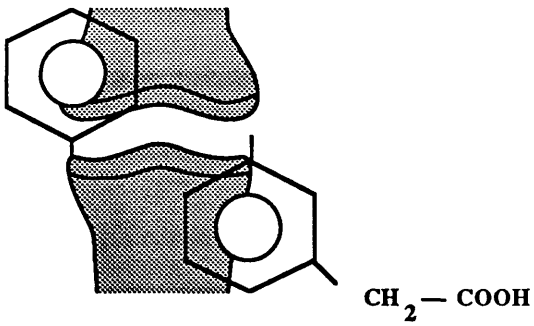

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General Summary

This thesis is in two parts. In the first three chapters the pathogenesis of osteoarthritis is discussed with particular reference to the mediators and enzymes involved. Current knowledge of medical treatment with analgesics, non-steroidal anti-inflammatory drugs (NSAIDs) and disease modifying drugs is presented. Chapters 4 and 5 detail experimental work on the NSAID carprofen and the steroid-NSAID combination PLT® Tablets.

Canine osteoarthritis usually occurs secondary to primary joint incongruity or instabilty but it may occur as a primary entity in older animals. Over the last two decades some of the ultrastructural pathogenic mechanisms of osteoarthritis have become clearer. Whatever the initiating cause of articular cartilage degeneration, there appear to be common mediator and enzyme pathways which induce biochemical and gross changes in articular cartilage and synovium. The chondrocyte reacts to alterations in pressure and forces within articular cartilage. The synovium liberates a number of mediators which affect chondrocyte metabolism. Free proteoglycan fragments in the synovial fluid induce synovial production of the cytokine interleukin-1. An increasingly important rôle is being ascribed to interleukins, and a number of other cytokines, growth factors and chondrocyte stress proteins may also be involved. There is evidence of humoral immune response to 'hidden' autoantigen in articular cartilage which is liberated as the cartilage is damaged.

The degradation of the matrix appears to be due to enzymatic destruction of proteoglycan by neutral metalloproteinases which are produced in increased quantities by chondrocytes in osteoarthritic cartilage. A reduction in specific tissue inhibitors of metalloproteinases (TIMP) may make available increased amounts of free active metalloproteinases. Proteoglycan loss exposes the collagen network to enzymatic damage and also reduces the elasticity and resilience of articular cartilage such that mechanical damage of collagen is possible. Loss of matrix may reduce the barrier to mediators in the synovial fluid. The net result is cartilage fibrillation and erosion.

The treatment of osteoarthritis involves the avoidance or elimination of factors which promote joint damage such as joint instability, obesity, or inappropriate exercise. Analgesics are used to control the symptoms of pain and stiffness. The opiates are not recommended for long term use because of their central depressent effects. NSAIDs, which have analgesic and anti-inflammatory activity, have demonstrated better efficacy in osteoarthritis than pure analgesics such as paracetamol.

The activity of NSAIDs is primarily due to the inhibition of the synthesis of prostanoids, some of which are beleived to mediate or modulate synovial inflammation and pain. The inhibition of prostaglandin synthesis by NSAIDs can be potentially damaging since it is responsible for toxic effects, particularly in gastrointestinal and renal tissue. The NSAIDs have different pharmacokinetics in different species and dose rates cannot be extrapolated between species. A number of drugs have been used in the dog. Some of the drugs used in man are much more toxic in dogs and should not be used. The drugs presently available are discussed in Chapter 3.

The NSAIDs only offer symptomatic treatment and do not inhibit disease progression. Some NSAIDs promote degenerative changes in osteoarthritic cartilage *in vitro* and *in vivo*. More recently, interest has been shown in 'disease modifying drugs'. Although higher doses of corticosteroids cause osteoarthritic changes in joints, low doses have demonstrated inhibitory effects on articular cartilage degradation. Glycosaminoglycan polysulphated esters, hyaluronate and glucosamine have demonstrated chondroprotective properties *in vitro* and *in vivo*. These drugs and agents which affect cytokines or mimic growth factors may be important in the therapy of canine osteoarthritis in the future. However, NSAIDs are the most widely used drugs in the medical therapy of osteoarthritis to date and will probably remain important therapeutic agents.

One of the newer NSAIDs, carprofen, a propionic acid derivative has been demonstrated to be better tolerated in the dog than many other NSAIDs. Daily oral administration of carprofen at over 5 times the recommended daily dose for over 12 months has been well tolerated by experimental dogs. Pharmacokinetics were studied in beagles after a single oral dose at a rate of 4 mg/kg bodyweight. A fourteen day tolerance study at 9 mg/kg bodyweight/day was performed to assess the clinical, haematological and biochemical effects of carprofen at a supratherapeutic dose. A clinical trial on the efficacy of carprofen in the therapy of osteoarthritis in dogs was carried out with the cooperation of practicing veterinarians. Although a blinded cross-over trial with radiological corroboration of the clinical diagnosis would have been the prefered experimental method, it was not considered practical since no funds were available for the remuneration of participating veterinarians. Instead, it was only possible to perform an unblinded trial using two groups of limited comparability, and using phenylbutazone treated dogs as positive controls. The experimental evidence suggested that carprofen was at least as efficacious as phenylbutazone in the therapy of osteoarthritis and may be a useful drug in the chronic therapy of osteoarthritis at 2-4 mg/kg/day as a single dose or divided into two doses.

PLT ® Tablets are a development of Predno-Leucotropin ® Tablets which have been used in the therapy of musculoskeletal disorders for 22 years. PLT Tablets contain the NSAID cinchophen and a low dose of the steroid prednisolone but, unlike Predno-Leucotropin Tablets, they do not contain hexamine. The combination may have synergistic activity since the two drugs have anti-inflammatory activity at different levels of the arachidonic acid conversion pathway. The prednisolone dose rate is similar to that demonstrated to have chondroprotective properties in early experimental osteoarthritis. A clinical trial on the efficacy of PLT Tablets was carried out since there are no reports in the veterinary literature on the efficacy of cinchophen, or of cinchophen and prednisolone in combination. Trial design resembled that for the carprofen clinical efficacy trial and had the same drawbacks. PLT Tablets appeared to be at least as efficacious as phenylbutazone in the therapy of osteoarthritis in the dog and were efficacious at dose rates below the manufacturers recommendations.

Abbreviations

kg	kilogram
mg	milligram
µg	microgram
l	litre
ml	millilitre
M	molar
mM	millimolar
pKa	pH at which a salt is 50% ionised
S.D.	Standard Deviation from the mean
SEM	Standard error from the mean
s.i.d.	one daily administration
b.i.d.	two daily administrations
t.i.d.	three daily administrations
q.i.d.	four daily administrations
ED50	Effective dose 50%: dose rate causing desired effect in 50% of the population
LD50	Lethal dose 50%: dose rate causing death in 50% of the population
IC50	Inhibitory concentration 50%: concentration of drug which inhibits activity of effected system [eg. enzyme conversion] by 50%
MED	Minimum effect dose: minimum dosage of drug have significant effect
AUC	Total area under the curve of drug concentration plotted against time
UV	Ultraviolet
HPLC	High Pressure / High Performance Liquid Chromatography
OA	Osteoarthritis
CNS	Central nervous system
PMN	Polymorphonuclear leucocyte
PG	Prostaglandin
PGI_2	Prostacyclin
TBX	Thromboxane
LT	Leukotriene
SRS-A	Slow reacting substance of anaphylaxis
PAF	Platelet Activating Factor
ROS	Reactive oxygen species
IL	Interleukin
TNF	Tumour necrosis factor
IFN	Interferon
OAF	Osteoclast activating factor

IGF	Insulin growth factor
GAG	Glycosaminoglycan
Ig	Immunoglobulin
NMP	Neutral metalloproteinase
TIMP	Tissue inhibitors of metalloproteinases
ATP	Adenosine triphosphate
PLA	Phospholipase
NSAID	Non-Steroidal Anti-Inflammatory Drug
DMD	Disease Modifying Drug
SAID	Steroidal Anti-Inflammatory Drug
EC-ASA	Enteric Coated Aspirin
GAGPS	Glycosaminoglycan Polysulphated Ester
^{3}H-GAGPS	Tritiated GAGPS
HA	Hyaluronate / Hyaluronic Acid
DMSO	Dimethylsulphoxide
Cu	Copper
Zn	Zinc
Na_2HPO_4	Sodium hydrogen phosphate
CRP	C-reactive protein
Li	Lithium
K	Potassium
®	Registered trademark
∞	alpha

Chapter 1

An Overview of the Aetiology and Pathogenesis of Osteoarthritis

An Overview of The Aetiology and Pathogenesis of Osteoarthritis

1.1 Introduction

Canine osteoarthritis has been recognised for many years. Osteoarthritis is also a very common disease in man. Osteoarthritic changes are present in 35% of knees of people aged 30, and are almost universal in people over 70 (Roberts and Burch, 1966). In man, clinical osteoarthritis is two or three times as prevalent as rheumatoid arthritis (DiPascale, 1986). Osteoarthritis affects all mammals except sloths and bats; this includes aquatic, non-weightbearing mammals such as whales, dolphins and porpoises.

1.2 Nomenclature

At least fifty-four different names have been used for the pathological process which is called osteoarthritis in this thesis (Tarnopolsky, 1950). The term "*degenerative joint disease* " implies that the process is catabolic, but much of the pathophysiological process in osteoarthritis is anabolic, synthetic, and reparative. In the UK and Europe the pathological process is often called osteoarthrosis. This term is often used to describe subclinical or preclinical osteoarthritic changes, or changes not associated with inflammation. Many authors are not happy with the term osteoarthritis since it implies an inflammatory component whereas inflammation is not detectable in all osteoarthritic joints. However, osteoarthritis is the terminology widely used and accepted in human and veterinary literature and is therefore the term used in this thesis.

1.3 Aetiology of Osteoarthritis

Although osteoarthritis is very common, many aspects of the aetiology and pathogenesis are poorly understood. Osteoarthritis is now widely considered to be not a single entity but a pattern of reactions to injury of the articular and periarticular tissues (eg.Arnoczky and Marshall, 1981; Berry and Paulus, 1983; McCarty, 1989). It would perhaps be better to regard the subclinical (but radiographic and anatomical) changes which are common in so many older people, and in many older animals (Tirgari and Vaughan, 1975), as normal processes of repair, remodelling and adjustment in response to joint insult (Bland, 1986). Where clinical signs develop then the term osteoarthritis can be applied and regarded as a failure of normal subclinical joint repair and readjustment.

Historically, osteoarthritis has been divided into primary and secondary types. Primary osteoarthritis could also be termed idiopathic since the factor or factors which have caused a clinical problem are unclear. Secondary osteoarthritis develops as a response to an identifiable causative factor such as acute or chronic trauma, articular fractures, infection, aseptic necrosis and so on. In man, secondary osteoarthritis is being increasingly recognised with a concurrent reduction in cases that are designated as primary osteoarthritis (Stulberg and others, 1975; Berry and Paulus, 1983; Hough and Sokoloff, 1989). Primary canine osteoarthritis has been documented. In one study, 20% of dogs at necropsy, selected at random, had osteoarthritic changes in one or more joints. In 61% there was no identifiable predisposing cause (Tirgari and Vaughan, 1975). Some investigators have stated that primary osteoarthritis of the shoulder is common in dogs (Ljünggren and Olsson, 1975; Tirgari and Vaughan, 1975). Primary osteoarthritis of the elbow also occurs but is less common (Ljunggren and Olsson, 1975). However, many cases of primary osteoarthritis may be secondary to a cause which has become obscured by the osteoarthritic process.

Secondary osteoarthritis is apparently much more common in the dog (Clayton-Jones, 1985). Joints most often affected in canine osteoarthritis are weightbearing synovial joints: the hip, the elbow, the stifle and the shoulder. In contrast to human osteoarthritis, interphalangeal joints are rarely affected in the dog. Primary causes are often identifiable in the young dog such as hip dysplasia, or osteochondritis. In the older dog rupture of the anterior cruciate ligament of the stifle is a common cause of stifle osteoarthritis. In many older dogs the primary cause cannot be determined from the history or at necropsy. In many cases, the dog will only show lameness in latter life but the initiating cause may have been present much earlier. The joints most often affected in the older dog are those in which developmental problems such as osteochondritis lesions are common (Arnoczky and Marshall, 1981).

The aetiology of osteoarthritis is still uncertain. There is evidence of a genetic contribution in man. A defect in cartilage metabolism has been suggested. However, the genetic component may be related to differences in the conformation and infrastructure of joints, long bones and in soft tissue structures which predispose to osteoarthritic change as in hereditary hip dysplasia in the dog. Some hormonal imbalances affect the osteoarthritic process. In man, acromegaly, a syndrome caused by excess growth hormone production, induces osteoarthritis earlier and with a higher incidence. Diabetes mellitus appears to predispose to osteoarthritis. Conversely, osteoporosis due to a fall in oestrogen concentrations decreases the incidence of osteoarthritis, possibly because the subchondral bone is softened or because of direct hormonal effects (Hough and Sokoloff, 1989; Moskowitz, 1989).

Chemical theories include primary synovitis, possibly due to immune complex formation, and the secondary stimulation of degradative enzymes in cartilage by synovial factors. Synovitis is not a consistent finding in osteoarthritic joints (Mankin, 1985; Hough and Sokoloff, 1989). It has been proposed that the primary defect in osteoarthritis is in the synovium and in products of the synovium.Studies of early hip dysplasia in dogs suggested that lesions in articular cartilage are preceded by synovitis and synovial effusion (Lust and Summers, 1981). Laver-Ruelich and Silberman (1985) demonstrated that the surface of articular cartilage is negatively charged and that with age the charge density was decreased. A possible relationship with the onset of osteoarthritic changes was proposed.

The favoured theories remain those based on a mechanical initiation. Recent developments in the knowledge of lubrication and fluid mechanics make previously widely accepted views on the importance of synovial viscosity in maintaining low friction at the cartilage-cartilage interface untenable (McCutchen, 1978; Davis and others, 1979). Pressure application to cartilage causes the surface to "weep". Less tightly bound water molecules are forced out of the cartilage matrix. Some of the water content appears to be tightly bound to the matrix proteoglycan (Mankin, 1985). The surface of cartilage is protected in a "low-shear environment" by undulations and microscopic dimples in the cartilage surface which trap synovial fluid. A specific glycoprotein, "*Lubricin* ", adheres to the cartilage and makes it more slippery (Swann, 1978). No deficiency in the boundary-lubricating ability of synovial fluid has been demonstrated in osteoarthritis (Davis and others, 1978). Although hyaluronic acid appears to have no rôle in cartilage-cartilage interface lubrication, it is an effective lubricant of the periarticular soft tissue and is probably the primary lubricant of synovium (Davis and others, 1979; Mankin, 1985).

Joint incongruity or instability, or changes in the stiffness of the subchondral bone may initiate osteoarthritis. There is evidence that bony changes and repeated impact loading are important (Felson and others, 1988). Articular cartilage is much thinner than the length of bone available for impact absorption. In experimental and clinical lesions, microfractures and sclerosis in the subchondral trabecular bone have been seen to precede measurable changes in the cartilage (Roy and Ghadially, 1966; Hough and Sokoloff, 1989). Cartilage has been found to be mechanically more liable to damage by impact loading than by shearing forces (Radin and others, 1973). Sustained pressure on cartilage causes a suppression of chondrocyte activity (Crellin and Southwick, 1964). In man, some investigators have found a relationship between the increase in body mass associated with obesity and the incidence of osteoarthritis of the knee. They proposed possible alterations in subchondral bone density as a causative mechanism (Davis and others, 1988).

1.4 Pathogenesis of Osteoarthritis

Whatever the initiating cause, and there may be a combination of factors, the changes in the osteoarthritic joint appear to follow a "final common pathway". Knowledge of some of the various pathways of damage and repair in the osteoarthritic joint has increased substantially in the last two decades. However, the relative importance of different mechanisms and interactions between them, and the factors which affect the progression of the disease and severity of clinical signs associated with osteoarthritis are still poorly understood.

The gross changes, which include joint capsule thickening, synovitis, bony remodelling, bony end plate sclerosis, osteophyte formation, cartilage softening, fibrillation, fissuring and erosion, are paralleled by biochemical changes. The water content of osteoarthritic articular cartilage increases, probably due to a decrease in proteoglycan content and in proteoglycan aggregation. There appears to be damage to proteoglycan and hyaluronate. The number of living chondrocytes does not decrease until a late stage in the disease process (Sokoloff, 1969; Mankin, 1985; Hough and Sokoloff, 1989).

Although it is still possible that most cartilage destruction proceeds mechanically (Freeman, 1979; Maroudas, 1980), there is a large amount of evidence that, in primary *and* secondary osteoarthritis, biochemical and mediator effects are very important in the disease pathogenesis. Many experimental studies have shown the enhancement or inhibition of osteoarthritic changes by various mediators and especially the cytokines and various growth factors (see 2.5-2.6). Articular cartilage degradative enzyme activity has been reported to be correlated with synovial inflammation and synovial inflammation and effusion may precede cartilage changes (Lust and Summers, 1981). Good correlation has been reported between the disease activity and the active metalloproteinase content of articular cartilage in secondary osteoarthritis (see 2.11). Some disease modifying drugs have demonstrated marked chondroprotective effects in models of secondary osteoarthritis (see 3.7) which suggests that mechanical effects per se are not the direct mechanism of cartilage destruction.

1.4.1 Rôle of the Synovium

Inflammation is associated with up to three-quarters of all cases of osteoarthritis in man (Dieppe, 1984). Synovitis is probably important in the pathogenesis of osteoarthritis and in the clinical signs of pain and stiffness. Some authors have proposed synovial initiation of the osteoarthritic process and there is evidence that synovial changes precede changes in cartilage in secondary osteoarthritis (Dingle, 1979; Lust and Summers, 1981). The synovium has been shown to liberate a number of mediators including interleukin-1 and other cytokines which have effects on the chondrocyte and the synovial and fibrous capsule and bony tissues (see 2.5). Osteophytes formed at the joint periphery are metaplastic synovial cells and indicate an active inflammatory process and synovitis (Mankin, 1985).

1.4.2 Rôle of the Chondrocyte

In recent years, the increasingly important rôle of the chondrocyte has been recognised. As in other connective tissues, physical and mechanical forces and biochemical changes appear to result in a complex pattern of chondrocyte responses which react to return the articular cartilage system to normal function. In effect the chondrocyte in association with the synovium, the joint capsule, the subchondral bone and muscular and ligamentous structures responds to repeated joint trauma or insult or to normal or changing loading forces to retain a homeostatic state (Mankin, 1985; Howell, 1989; Hough and Sokoloff, 1989).

The complex double-diffusion pathway for the nutrition of the chondrocytes from the synovium via the synovial fluid means that chondrocytes rely predominantly upon anaerobic glycolytic metabolism (Sokoloff, 1969; Mankin, 1985; Hough and Sokoloff, 1989). Chondrocytes are extremely resistant to low oxygen tension. In response to a reduction in the supply of glucose, chondrocytes respond by switching to oxidative (aerobic) metabolism and this is associated with degradation of the surrounding intercellular substance. Disturbances in nutrition may involve:

-changes in the synovial blood flow or changes in synovial blood vessel structure
-structural changes in synovial tissues, especially fibrosis
-changes in synovial fluid quantity and quality
-biochemical and ultrastructural changes in the articular cartilage matrix
-subchondral stiffening; cartilage and subchondral deformation under loading are reduced and thus a nutrient pumping effect is also reduced (Hough and Sokoloff, 1989).

The chondrocyte is sensitive to changes in biochemical environment and the disruption of the supply of nutrients may cause changes in the synthesis of matrix components by the chondrocytes. *In vitro*, mechanical stimulation of chondrocyte culture increases sulphated glycosaminoglycan ten-fold in the media, and fifty-fold adherent to the cell membranes (Sokoloff, 1980). It is now known that chondrocytes are extremely active. The glycosaminoglycan content of cartilage is in a continuous cycle of removal and replenishment. Collagen is also synthesised and degraded although turnover is much slower (Mankin, 1985).

1.4.3 Rôle of Matrix Components:

Glycosaminoglycans are linear polysaccharide chains which, in articular cartilage, consist of three types of dimeric unit: chondroitin-4 sulphate, chondroitin-6 sulphate and keratan sulphate synthesised by the chondrocyte. Some of the factors affecting the synthesis of glycosaminoglycan are given in TABLE 1 (right).

TABLE 1: Factors affecting synthesis of glycosaminoglycans and proteoglycans

-osteoarthritis	-ascorbic acid
-laceration injury	-vitamin E
-hydrostatic pressure	-pH
	-calcium concentration
-temperature	-lipopolysaccharides
-[substrate]	-hyaluronate
-cortisol	-salicylate
-cytokines	-other NSAIDs
-prostaglandins	
-growth hormone	

Proteoglycans are formed when approximately 100 chondroitin sulphate and 60 keratan sulphate chains are bound to a core protein (Molecular weight = 200000). Interchain binding of the glycosaminoglycans appears to occur for all glycosaminoglycans except hyaluronate, which lacks a SO_4 group, and keratan sulphate, which lacks a carboxyl group. Up to 100 proteoglycan molecules consisting of glycosaminoglycan side chains around a core protein aggregate with hyaluronate (Mankin, 1981; Mankin, 1985; Hough and Sokoloff, 1989). There is very specific binding between hyaluronate and hyaluronate-binding region of the proteoglycan core proteins which suggests a "lock and key" mechanism rather than electrostatic interaction (Lindahl and Höök, 1978). Proteoglycan aggregates are extremely large ($\geq 2x10^8$ daltons). The arrangement is represented diagrammatically in FIG 1. Glycosaminoglycans bind to collagen by electrostatic interaction at physiological pH. There are two collagen binding sites in the proteoglycan molecule: one in the core protein, one in the polysaccharide chains (Toole, 1976). The size and distribution profiles of proteoglycan aggregates is dependent upon the quality and quantity of link protein, proteoglycan subunits and hyaluronic acid, and probably to the biochemical properties of normal and osteoarthritic cartilage (Buckwater and others, 1986; Manicourt and others, 1986; Pita and others, 1986).

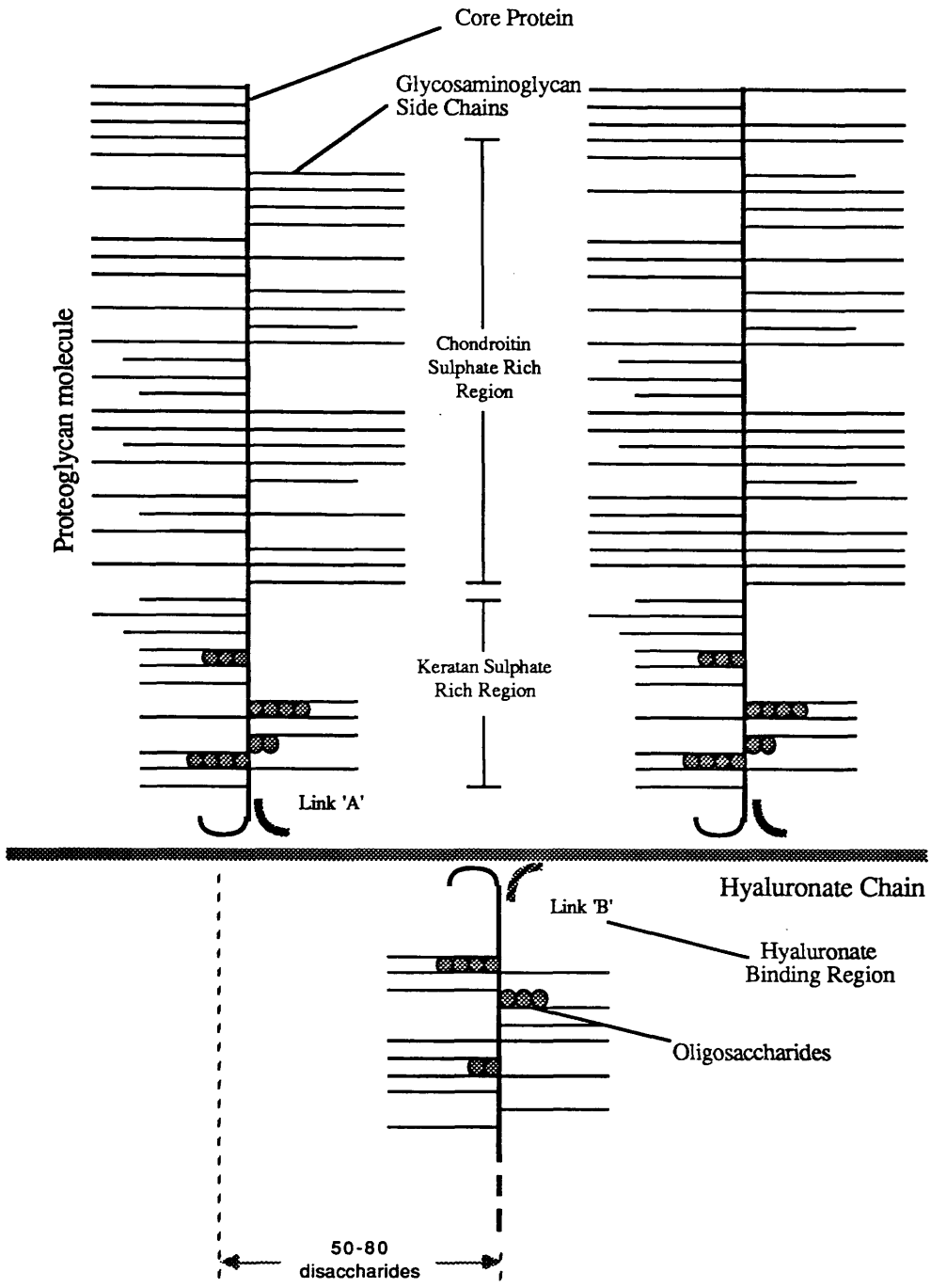


Fig 1: Diagrammatic representation of the proteoglycan aggregate structure. The structure is based on proteoglycan molecules with molecular weights of about 2 million daltons which are bound by two types of link protein to a hyaluronate molecule. The proteoglycan is made up of a core protein to which are attached glycosaminoglycan (GAG) side chains. In the area close to the hyaluronate binding region keratan sulphate GAG and associated oligosaccharides are most common whilst larger chondroitin sulphate GAG chains predominate in the distal region.

Collagen is formed into an organised lattice which is structured to resist compressive and shear forces. In a resting state the collagen network is quite random when histologically examined but under mechanical stress the network becomes ordered (Broom, 1984; Broom, 1986). Glycosaminoglycans are highly electronegative and the proteoglycan 'gel' traps water. The collagen arcade is normally sealed and the proteoglycan is forced to exist in a semi-hydrated state. Collagen retains the form of the articular cartilage, resisting the osmotic forces generated by proteoglycans which tend to swell the cartilage and which are responsible for the elasticity of normal cartilage (Mankin, 1981; Mankin, 1985; Hough and Sokoloff, 1989).

With damage to the collagen arcade, remaining proteoglycan will imbibe water and expand, increasing the exposure of proteoglycan and collagen to enzymatic degradation and resulting in a decrease in the elasticity and impact load dispersion capacity of the articular cartilage, which predisposes to further cell and matrix damage. Unmasking of the middle layers of cartilage may be an important pathophysiological event in osteoarthritis (Broom, 1984; Broom, 1986). Degenerative, traumatic or enzymatic damage to the collagen network will cause common structural transformations. The normal collagen cross-linkages are broken and the collagen assumes a soft, parallel configuration (Chrisman and others, 1981; Radin, 1983; Howell, 1986). It has been suggested that proteoglycans protect interconnecting regions of the collagen network from enzymatic disruption and removal of the proteoglycans exposes the linkages of the collagen network to more direct attack from collagenases (Broom, 1988).

The nature of the connection between the collagen fibrils is still uncertain. The collagen fibrils may link directly or there may be a third matrix component which acts as a link. Collagen Type II predominates in cartilage, but there are also small quantities of minor collagens Types V, VI, IX, and XI which make up approximately 3% of the total collagen content. Collagen Type IX has non-helical regions which give the molecule flexibility and is concentrated close to intersections of the fibril network. It has been proposed that Collagen Type IX could act as the interfibril linkage molecule (Broom, 1988).

The total proteoglycan content of cartilage is decreased in osteoarthritis. The ratio of keratan sulphate and chondroitin 6-sulphate to chondroitin 4-sulphate decreases. The length of the proteoglycan subunit core protein is shortened in either the chondroitin sulphate or hyaluronic acid binding region. Glycosaminoglycan chains are reduced in length and hyaluronic acid polymer size and content decrease (Moskowitz and others, 1979; Howell, 1989; Moskowitz, 1989).

The capacity to form aggregates with proteoglycan subunits becomes variable. The concentration of non-proteoglycan and non-collagen proteins is increased. Degraded proteoglycans rapidly diffuse into the synovial fluid or are further degraded by chondrocytes. Undamaged proteoglycan subunits may reaggregate (Moskowitz and others, 1979; Howell, 1989; Moskowitz, 1989). Released proteoglycan fragments have demonstrated the potential to cause synovitis and may be an important mediator of osteoarthritis pathogenesis (see 2.8).

In natural and experimental osteoarthritis, proteoglycan loss usually precedes cartilage erosion (Howell and others, 1986). The mechanism may involve defects in chondrocyte repair responses, direct mechanical damage and enzymatic degradation (Lowther and others, 1981). Candidates for the enzymes involved include neutral metalloproteinases and serine proteases. Several experiments have suggested that serine proteases activate latent metalloproteinases (Woessner, 1977; Woessner, 1982; Sapolsky and Howell, 1982; see 2.11).

The matrix configuration and charge affect the rate of diffusion of many substances through the matrix. The diffusion of larger molecules is particularly sensitive to the concentration of proteoglycan (Mankin, 1985). This may be important in the regulation of access of various chondrocyte-function mediators to the chondrocyte. The matrix seems to inhibit chondrocyte mitosis since the loss of matrix barrier in cartilage erosions is associated with clusters of chondrocyte clones (Mankin, 1981; Mankin, 1985; Hough and Sokoloff, 1989).

1.5 Repair of Cartilage

There is substantial evidence that articular cartilage repair occurs and that the cartilage damage in osteoarthritis is potentially reversible (Bland, 1986). Osteoarthritic articular cartilage is *more* active than normal. In osteoarthritis, the microenvironment of the chondrocyte changes. Mitosis is stimulated and clone clusters form (Solokoff, 1969; Sokoloff, 1980; Hough and Sokoloff, 1989). In chondrocyte cell culture, mature cells divide, grow and synthesise phenotypic glycosaminoglycans and collagen. It appears that ordinarily, the matrix of cartilage switches off the cell replication mechanism and that mitosis can occur when the chondrocytes are released from the matrix (Green, 1971; Sokoloff, 1980). Proliferating cells in osteoarthritis not only incorporate Thymidine as a marker of DNA synthesis (Havdrup and Telhag, 1980; Hirotani and Ito, 1975) but also increase sulphate uptake (Meachin and Collins, 1962).

In osteoarthritic articular cartilage, chondrocytes become very anabolic, increasing production and secretion of glycosaminoglycans and increasing collagen synthesis. The collagen that is produced is now believed to be Type II and the repair tissue can therefore be considered hyaline type cartilage (Mankin, 1985; Hough and Sokoloff, 1989). Earlier authors considered tissue produced in experimental cartilage damage and repair not to be primary normal hyaline cartilage (Sokoloff, 1974). The rate at which articular cartilage repair can occur *in vivo* is undoubtedly slow, but it may be significant over a long period (Mankin, 1981; Bland, 1986). An additional reparative pathway exists in the pluripotential granulation tissue which is present in subchondral bone marrow and which may become exposed in severe osteoarthritis (Harrison, 1953; Gay and others, 1976; Cheung and others, 1980).

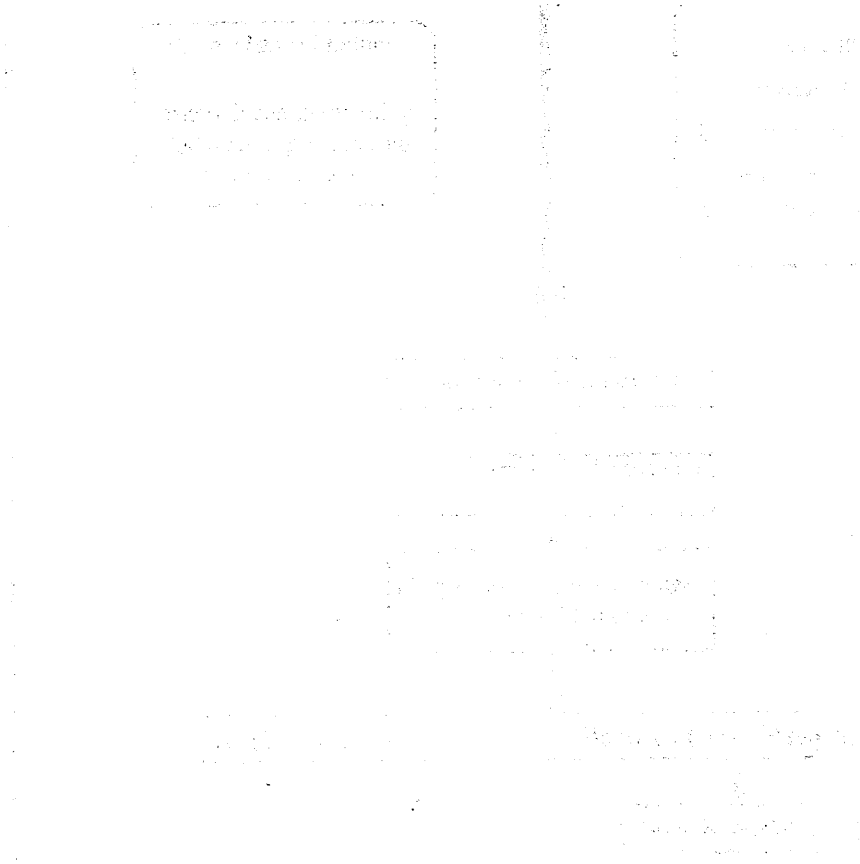
In man, it is recognised that there can be extensive damage to articular cartilage in a joint without any symptoms. It also appears that osteoarthritis may not be progressive in older people. Some cases of advanced and very painful osteoarthritis can become painless, or the pain may be intermittent. Spontaneous remission has been reported. In hip osteoarthritis in man, marked clinical improvement and radiographic recovery of joint space occurred in many cases in one study (Forman and others, 1983; Bland, 1986).

It has been suggested that pharmaceutical or physical stimuli might encourage the regeneration of cartilage which is functionally normal (Salter and others, 1980; Burkhardt and Ghosh, 1986). Continuous passive motion [the repeated flexion and extension of a joint without load by exogenous mechanical means] has been found to be a powerful stimulus for cartilage regeneration and healing. Full thickness defects in rabbit articular cartilage healed very slowly if the joint was immobilised. If ambulation was permitted then healing was more rapid, but the repair was with fibrocartilage and not hyaline cartilage. Also, in this group the joints became osteoarthritic within six months. In a group treated with continuous passive motion, hyaline cartilage regenerated and the cartilage was normal six months later (Salter and others, 1980).

1.6 Summary

The almost ubiquitous nature of radiographic and anatomical changes in older people and the symptomless nature of many cases in man and animals suggests that some of these changes are a normal reparative response to joint damage. There are no clinical signs and there is essentially full joint function. If, however, damage exceeds repair or if clinical effects are mediated for instance by secondary synovial inflammation, then clinical osteoarthritis supervenes. The clinician is interested in the factor or factors which tip the balance and the potential for modification or reversal of these factors and the osteoarthritic process.

Osteoarthritis is now believed to be a common reaction to different joint insults or traumas. The concept of a "final common pathway" is widely accepted (FIG 2). Previous theories based on simple "wear and tear" mechanical mechanisms have proved to be untenable with new knowledge on the dynamic nature of articular cartilage and other joint structures. It now appears that ultra-structural mechanisms and biochemical changes play a major rôle in the regulation of cartilage repair and in the pathogenesis of osteoarthritis. The precise interactions and relative importance of these mechanisms is still unclear but important advances in our knowledge of the subject have been made in recent years. Secondary osteoarthritis in the dog is likely to be initiated by biomechanical overloading. It now appears that this induces changes in the chondrocyte or matrix microenvironment which mediate alterations in the synthesis and enzymatic degradation of matrix proteoglycan . Possible mediators of cartilage and synovial changes are discussed in the next chapter.



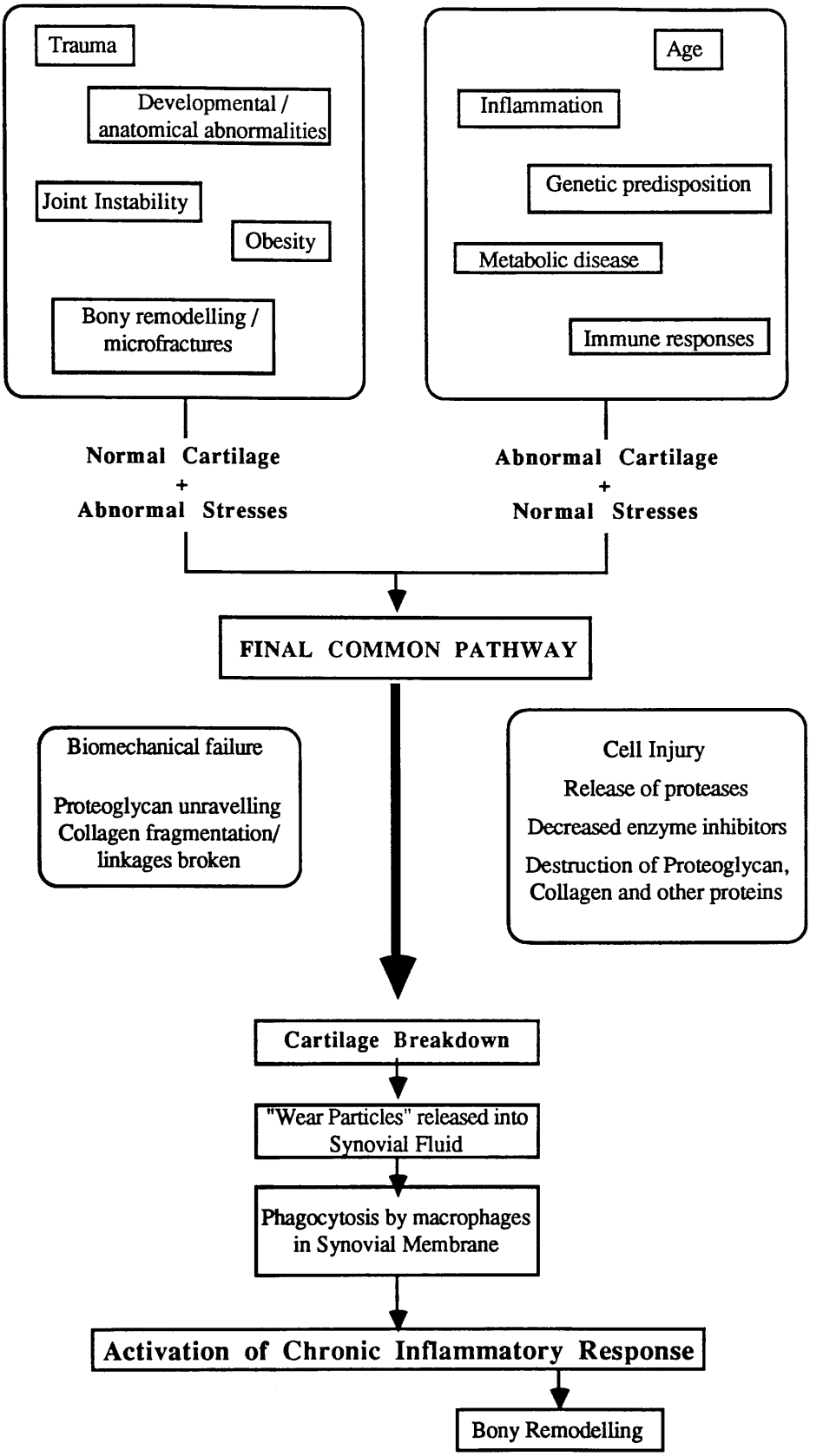


FIG 2: The basic pathogenesis of osteoarthritis and the concept of a "Final Common Pathway"

Chapter 2

Rôle of Mediators in the Pathogenesis and Clinical Signs of Osteoarthritis

2

Rôle of Mediators in the Pathogenesis and Clinical Signs of Osteoarthritis

2.1 Introduction

It has been suggested that chondrocytes are unlikely to receive and respond to humoral messages because of the double diffusion barrier which exists between the synovium and the chondrocyte [capillary -> synovium -> synovial fluid -> articular cartilage matrix -> chondrocyte] and because of the selectivity of diffusion into the highly electronegative proteoglycan matrix. Instead, it is likely that chondrocytes are sensitive to alterations in physical forces, for instance pressure and shear forces. However, it does appear that many synovium-derived factors including various growth factors and cytokines can influence chondrocyte activity (Dingle, 1978; 1979; 1981; Mankin, 1985).

The collagenolytic activity of synovial and cartilage tissues increases in osteoarthritis. The collagenolytic activity of cartilage is proportional to the degree of inflammation of the synovial membrane and not to the collagenolytic activity in the synovium (Pelletier and others, 1985). This suggests that stimulatory mediators may, but collagenolytic factors probably do not, diffuse from the synovium to the articular cartilage and modulate tissue breakdown. It has been reported that in canine hip dysplasia synovitis and effusion precede cartilage damage and bony remodelling (Lust and Summers, 1981).

Certain drugs are "chondroprotective" in experimental secondary osteoarthritis; others can accelerate degradation (see 3.3.6 and 3.7). Alterations in mechanical stresses appear to lead to secondary osteoarthritis by effects on cell-cell communication and mediator release. Other mediators may be involved in the inflammatory response in the synovium and the clinical signs of pain and stiffness.

It is likely that changes in the synovium and especially in the cartilage matrix proteoglycan may reduce the diffusion barrier to mediators to the chondrocyte in osteoarthritic cartilage. There are undoubtedly complex inter-relationships between different mediators. The stimulation and inhibition feedback network remain poorly understood. Possible rôles for a number of mediators are discussed in this chapter.

2.2 Eicosanoids

Nonspecific cell injury due to mechanical or chemical trauma, ischæmia or cell death, or specific receptor-coupled phospholipase release stimulates the liberation of unsaturated fatty acids from the plasma membrane or from free triglycerides. These fatty acids include arachidonic acid which can be converted into eicosanoids.The eicosanoids are molecules which have various actions on the inflammatory process. The arachidonic acid biotransformation pathways are represented in diagrammatic form in FIG 3. There are two branches to the pathway; the cyclooxygenase pathway leads to the formation of the prostanoids including the prostaglandins (PGs), prostacyclin (PGI2) and thromboxanes (TBXs). The lipoxygenase pathway leads to the formation of the leukotrienes (LTs) and hydroxyeicosotetraenoic acids (HETEs) (Dawson and Willoughby, 1985).

Prostaglandin endoperoxide synthetase is present in the microsomes. LTB4 synthesis occurs in the cytoplasm, whilst LTC4, LTD4 and LTE4 synthesis occurs at the plasma membrane. Compartmental localisation may be important in the regulation of prostaglandin, leukotriene and HETE production (Kitchen and others, 1985). Different prostaglandins and leukotrienes often have antagonistic functions. Many of the effects of the prostanoids appear to be antiinflammatory (Dawson and Willoughby, 1985). Some of the actions of the eicosanoids are listed in TABLE 2 below. Many of the details of the interaction between the eicosanoids and between the eicosanoids and other mediators are unclear. Levels of arachidonic acid in articular cartilage increase markedly with age (Bonner and others, 1975). A four fold rise in arachidonic acid has been demonstrated two hours after experimental cartilage injury (Chrisman and others, 1981). Whether the eicosanoids are important in cartilage response to acute trauma is not known.

TABLE 2: SOME KNOWN ACTIONS OF SELECTED EICOSANOIDS

PROSTAGLANDIN E2:
- vasodilation
- increased capillary permeability
- enhancement of pain and changes in vasculature
- increase in cyclic adenosine monophosphate (cAMP)
- increase enzyme release
- ? chemotaxis enhancement

PROSTAGLANDIN F2∞:
- vasoconstriction
- decreased capillary permeability
- increased cyclic guanosine monophosphate (cGMP)

PROSTACYCLIN (PGI2):
- vasodilation
- decreased platelet adhesiveness
- increased vascular permeability
- ? inhibition of chemotaxis

THROMBOXANE A2:
- increased platelet adhesiveness

LEUKOTRIENE B4:
- chemotaxis
- increased vascular permeability

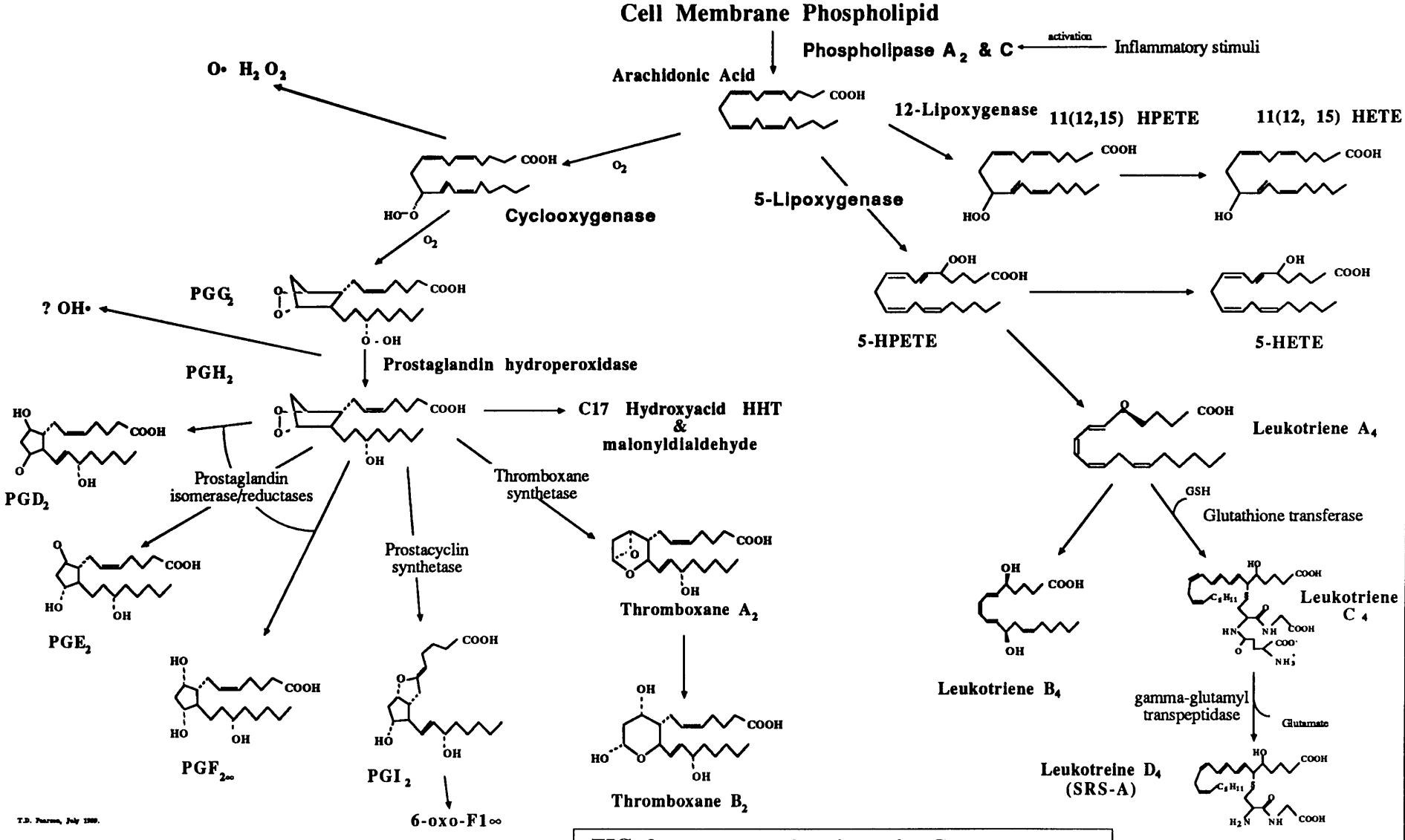


FIG 3: The Arachidonic Acid Cyclooxygenase and Lipoxygenase Pathways

2.2.1 Prostanoids

Cyclooxygenase converts arachidonic acid to PGG2 and further enzyme conversion liberates the various prostanoids. The prostaglandins have mediator and modulator activity. PGE2 mediates vasodilation. Many of the actions of the prostanoids are antagonistic to one another. For instance, thromboxane A2 (TBA2) and prostacyclin (PGI2) have antagonistic actions on platelet adherence and aggregation (Ortmann and Perkins, 1977; Dawson and Willoughby, 1985). Prostaglandins may have an important rôle in the fine tuning of inflammatory response (Lees and others, 1987).

Prostanoids are not stored in the tissues (Piper and Vane, 1971) but mild chemical and mechanical stimulation of tissues will induce their synthesis (Ferriera, 1967). More than twenty prostaglandins have been characterised (Higgins, 1985). Prostaglandins act synergistically as with other agents. Prostaglandin E2 and prostacyclin enhance pain and vascular permeability responses to kinins. They enhance peripheral pain perception (Moncada and Vane, 1977). Both PGE1 and PGI2 increase pain sensitivity (Higgs and Salmon, 1979). The pain threshold may be so drastically altered that normally painless stimuli become painful. Only at very high concentrations (greater than physiological concentrations) can prostaglandins cause pain directly. The effect of prostaglandins is cumulative and of relatively long duration (Dawson and Willoughby, 1985). Prostaglandins have also been implicated in pain perception in the central nervous system. They are produced within the CNS and may sensitise it to painful substances such as kinins (Weissman, 1977). Most prostaglandins are eliminated at their first passage through the lung, with very low concentrations reaching the systemic circulation. They can therefore be regarded primarily as local mediators or modulators (Weissman, 1977).

Prostaglandins have been identified in the synovial fluid of human patients with inflammatory arthritides such as rheumatoid arthritis (Robinson and Granda, 1974; Trang and others, 1977; Higgs and others, 1983). Small (pikogram) concentrations have been detected in chronic osteoarthritis in horses (Taminini and others, 1980) and in man (Brodie and others, 1980).

In vitro, $PGF2\infty$ has been demonstrated to be more potent than either PGE2 or PGD2 in enhancing cartilage degradation (Hubbard and others, 1986). Prostaglandins of the E series are known to destabilise lysosomal membranes and cause release of enzymes in cartilage. Teitz and Chrisman (1975) found that, in rabbits, chloroquine inhibited prostaglandin-induced articular cartilage damage but salicylate did not. The short-term incubation of intact canine articular cartilage slices with PGE1 and PGE2 caused significant depletion of hexosamine, a proteoglycan concentration marker, from the cartilage matrix compared to control cartilage. Chloroquine, a known inhibitor of DNA primer, prevented the prostaglandin-induced hexosamine depletion. The experiment suggested that PGE may directly induce cartilage degradation via a DNA-dependent RNA controlled synthesis of proteases (Fulkerson and others, 1979). PGE also appears to inhibit *in vitro* production of cartilage ground substance by chondrocytes in culture (Teitz and Chrisman, 1975).

2.2.2 Leukotrienes and Hydroxy Arachidonic Acid Products

The rôle of lipoxygenase products in inflammation remains poorly defined. Recent experiments have suggested that leukotrienes C4, D4, and E4 (previously known as slow-reacting substance of anaphylaxis or SRS-A) are primarily involved in immediate hypersensitivity reactions including bronchospasm and hypotension. LTB4 is a very potent chemotaxin, especially for polymorphonuclear leucocytes, can cause smooth muscle contraction and affects capillary permeability. LTB4 increases vascular permeability and augments prostaglandin effects (Higgins, 1985).

There is little evidence that lipoxygenase products are important mediators in chronic inflammation (Dawson and Willoughby, 1985). Lipoxygenase products have not been demonstrated in osteoarthritis, although raised concentrations have been identified in rheumatoid arthritis, spondylarthritis and psoriasis (Klickstein and others, 1980; Hammaström and others, 1975). LTB4 has been detected at increased concentrations in inflamed joints and soft tissues in horses (Higgins, 1985). The blockade of the cyclooxygenase pathway with low doses of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) may make available more arachidonate substrate for the uninhibited lipoxygenase pathway, and higher concentrations of leukotrienes may be generated (Higgs and Vane, 1983). Whether this of any practical significance is not known.

Though the eicosanoids are undoubtedly important in acute inflammation, other mediators are also important. Rats with a deficiency of essential fatty acids, such that eicosanoid generation was compromised, showed an acute inflammatory response similar to that in normal rats (Bonta and others, 1977). Most authors now consider that the eicosanoids are less important in chronic inflammatory conditions than in acute inflammation. From the evidence presented above, it can be concluded that the prostanoids, particularly PGE and PGF2∞, have effects on cartilage *in vitro* and may have actions in the inflammatory arthritides. However, only small concentrations have been detected in osteoarthritic synovial fluid and cyclooxygenase inhibitors do not inhibit the progression of disease. It is likely that prostaglandin release is responsible for augmenting painful stimuli and is a modulator of the synovitis present in some cases of osteoarthritis. This would explain why NSAIDs have proved so useful in controlling the symptoms of osteoarthritis.

The prostanoids are important because, currently, they are the most important inflammatory mediators which can be affected by drug therapy. The overall blockade of prostaglandin biosynthesis by NSAIDs results in the inhibition of anti-inflammatory prostanoids as well as pro-inflammatory prostanoids and may not be as useful as first thought. A selective inhibition of the formation of pro-inflammatory prostanoids, PGE2 and TXA2, would apparently be preferable. NSAIDs have not shown any beneficial effect on the progression of osteoarthritic changes in joints and many appear to accelerate cartilage degradation (see 3.3.6). It is now thought that monocyte and lymphocyte factors such as cytokines including interleukin-1 may be more important mediators (Weismann, 1977; Dawson and Willoughby, 1985; Howell, 1989).

2.3 Platelet Activating Factor

Platelet Activating Factor (PAF) which is derived from membrane phosphatidylethanolamine has received much interest and has been the subject of much recent study. Its precise rôle in acute or chronic inflammation is not yet clear but one of its effects is the stimulation of generation of reactive oxygen species (see 2.4). Other known effects of PAF are chemotactic effects, platelet aggregation and stimulation of lysosomal enzyme release (Dawson and Willoughby, 1985; Howell, 1989).

2.4 Reactive Oxygen Species

Reactive Oxygen Species (ROS) or oxygen-derived free radicals are formed predominantly by metabolic activity of neutrophils and macrophages. The interconversion of the endoperoxide prostaglandins by prostaglandin hydroperoxidase and the cyclooxygenase-dependent generation of PGG2 also liberate ROS (Halliwell, 1981; Halliwell and Gutteridge, 1984; Hitt, 1988). PAF stimulates ROS release (Dawson and Willoughby, 1985). Highly reactive molecules or ions can cause damage to proteins or other molecules close to the origin of their formation. It is believed that superoxide and secondary radicals probably have considerable significance in inflammatory conditions (Higgins, 1985; Hitt, 1988).

Interleukin-1 is known to stimulate ROS generation by chondrocytes which may contribute to proteoglycan damage or inhibition of synthesis (Tsukasa and others, 1988). Reactive oxygen species are known to depolymerise hyaluronic acid (Ahlengard, 1978; Greenwald, 1981) and also mediate an inhibitor of proteoglycan synthesis in articular cartilage culture (Bates and others, 1984). Hyaluronic acid and two subcomponents of the molecule have been demonstrated to have a ROS-scavenging action which increases in synovial fluid from human patients with rheumatoid arthritis (Sato and others, 1988).

In rheumatoid arthritis ROS may be an important mechanism of inflammation and damage (Hitt, 1988). One possible mechanism of blood-induced arthropathy is the iron enhanced generation of hydroxy free radicals which could then cause tissue damage, hyaluronic acid degradation and attack of the cartilage surface (Halliwell, 1981; Halliwell and Gutteridge, 1984; Madhok and others, 1988). ROS generated by the arachidonic acid cascade may be involved in synovial inflammation. Chondrocyte derived ROS may have effects on proteoglycan integrity in osteoarthritis.

2.5 Cytokines

The cytokines are a group of structurally different proteins and glycoproteins which are produced by cells in response to mitogenic or antigenic stimulation. They are classified by their effects on macrophage and lymphocyte target cells and on their origin. The biological effects of cytokines have been quite well elucidated and many have been sequenced and reproduced synthetically. The cytokines include the interleukins (IL), tumour necrosis factors (TNF), interferons (IFN) and osteoclast activating factor (OAF).

In osteoarthritis, wear particles or free proteoglycans may stimulate synovial cell production of cytokines and there is increasing evidence for an important rôle for cytokines in amplifying and controlling cartilage destruction and synovial proliferation with special reference to IL-1(∞ and ß) and the historically closely-related or synonymous factors *catabolin* (Dingle, 1981; Saklatvala and others, 1984) and *mononuclear cell factor*, and TNF∞ (Yocum and others, 1988). The exact rôle of cytokines in cell-cell communication, and the inter-relationships of IL-1, secondary messenger systems, final target enzyme responses and/or inhibitors of synthetic responses is not entirely understood.

Some of the experimental evidence that cytokines have a rôle in osteoarthritis and other arthritides is given in 2.5.1 to 2.5.7. A diagrammatic representation of some of the possible actions and interactions of IL-1 is given in FIG 4.

2.5.1 Joint Inflammation and Pain

When arthritis was induced in rats by the intraarticular administration of peptidoglycan-polysaccharide, subsequent intraarticular administration of IL-1 or TNF-∞ caused acute joint swelling, pain, and histological evidence of an acute inflammatory reaction. IL-1 was ten times as potent as TNF-∞. The effect was dose related and heat inactivated. The investigators proposed that IL-1 and/or TNF-∞ may have an important rôle in chronic synovitis (Stimpson and others, 1988).

2.5.2 Mediator effects

(a) Synovium:

IL-1 induces cyclooxygenase conversion of arachidonic acid acid to PGG2 in rheumatoid synovial cells (Mizel and others, 1981). Cyclooxygenase inhibitors decrease arachidonic acid conversion in cells stimulated by IL-1. Prostaglandins may be involved in IL-1 stimulation of Phospholipase A2 activation (O'Neill and others, 1987). Goddard and others (1988) found that PGE2 production by the synovium before IL-1 administration was similar for osteoarthritis and rheumatoid arthritis. IL-1 administration caused a significant increase in PGE2 production in both osteoarthritis and rheumatoid arthritis, although the reaction was more marked in the rheumatoid synovial cells.

IL-1, TNF-∞, and TNF-ß stimulate PGE2 production by synovial fibroblasts (Dayer and others, 1986; Amento and Hayes, 1988; Linsey, 1988). IL-1 and TNF-∞ are more potent than TNF-ß (Amento and Hayes, 1988). The cytokine activities have been demonstrated to be synergistic (Amento and Hayes, 1988).

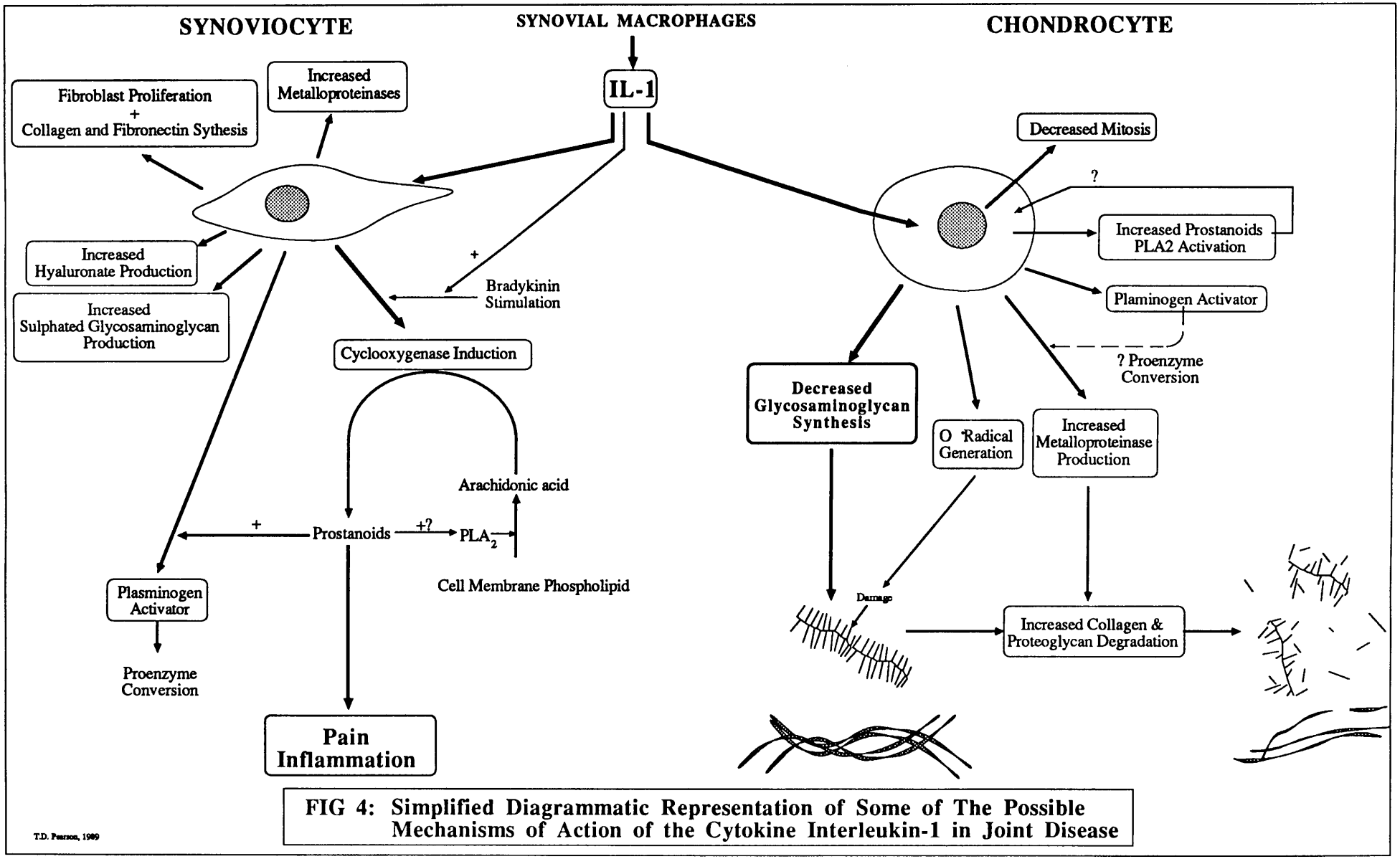


FIG 4: Simplified Diagrammatic Representation of Some of The Possible Mechanisms of Action of the Cytokine Interleukin-1 in Joint Disease

IL-1 and TNF have been found to enhance bradykinin-induced PGE2 release from rheumatoid synovial fibroblasts. IL-1∞ was more effective than IL-1ß or TNF-∞ and the latter were much more effective than IL-2. Both dexamethasone and indomethacin inhibited PGE2 release (93% and 97% respectfully). The study demonstrated that cytokines in inflammatory tissues enhance cellular responsiveness to bradykinin and so may promote the inflammatory component of arthritis (Batham and Wigley, 1988).

(b) Cartilage:

IL-1 activates Phospholipase A2 activity in rabbit chondrocytes (Chang and others, 1986) and induces chondrocyte release of prostaglandins and plasminogen activator (McGuire-Goldring and others, 1984; Evequoz and others, 1984a,b). Human recombinant IL-1ß stimulates chondrocyte production of PGE2, 6-keto-PGF1∞, and thromboxane B2 (Chin and Lin, 1988).

2.5.3 Enzyme release from synovium and chondrocytes

Interleukin-1 (IL-1) has been shown to stimulate the release of collagen and proteoglycan-degrading metalloproteinases from both synovial cells and chondrocytes (Barret and Saklatvala 1985; Pasternak and others, 1986). IL-1, TNF-∞, and TNF-ß stimulate collagenase production by synovial fibroblasts, IL-1 and TNF-∞ being more potent than TNF-ß. The cytokine activities are synergistic. IFN-gamma inhibits the cytokine stimulation of collagenase activity (Amento and Hayes, 1988).

Synovial cells stimulated by IL-1 produce Plasminogen Activator (PA)(Lindsey, 1988). Indomethacin and piroxicam inhibit IL-1 stimulated PGE2 production by 95% and sodium salicylate inhibited production by 80-90%. Indomethacin and piroxicam inhibit IL-1 stimulated PA production by over 80% but sodium salicylate inhibited production by only 25-50%. PA production is partially restored by the concomitant administration of PGE2. It is believed that PA production was inhibited partly via inhibition of prostaglandin formation (Lindsley, 1988).

IL-1 or other macrophage products are known to cause the release of collagenase and ß-glucoronidase from articular chondrocytes (Evequoz and others, 1984a&b). IL-1 stimulates cartilage degradation and the production of collagenase and proteoglycanase by human chondrocytes in vitro (Gowen and others, 1984). IL-1 is specific for the secretion of a specific metalloproteinase from chondrocytes (Schnyder and others, 1987).

2.5.4 Glycosaminoglycan Synthesis and Degradation

IL-1ß stimulates glycosaminoglycan production in human synovial fibroblast cultures (Yaron and others, 1987).Yaron and others (1988) have investigated the activities of cytokines in human synovial fibroblasts and articular cartilage cultures. In synovial fibroblasts they found that IL-1∞ and IL-1ß increased hyaluronate production up to five fold and TNF-∞ increased hyaluronate production 2.5 fold. Production of sulphated glycosaminoglycans increased by just under two fold when IL-1 or TNF were administered. IFN-gamma had a mild stimulatory effect. Indomethacin had no effect on the stimulation of hyaluronate production by cytokines but hydrocortisone caused a significant reduction in stimulation (Yaron and others, 1988).

In articular cartilage, cytokines caused a decrease in sulphated glycosaminoglycan production (Pettipher and others, 1986). The order of potency was IL-1ß > IL-1∞ >> TNF-∞. Neither indomethacin nor hydrocortisone influenced cytokine induced inhibition by either IL-1 preparation. The study indicated that cytokines released in inflammation may significantly effect glycosaminoglycan synthesis by synoviocytes and chondrocytes in joints (Yaron and others, 1988). Lymphokines induce cartilage proteoglycan degradation and synovitis *in vivo* (Taplits and others, 1979). IL-1 induces proteoglycan degradation in cultured articular cartilage with a loss of 60-80% of proteoglycan from the matrix after 4 days of treatment (Hardingham and others, 1987).

It is believed that IL-1 stimulates cartilage proteoglycan degradation and PGE2 release, and inhibits proteoglycan synthesis through independent post-receptor mechanisms. IL-1 is ten times more potent at inhibiting proteoglycan synthesis as it is at stimulating proteoglycan breakdown. The effects of IL-1 on proteoglycan metabolism occur before any PGE2 effect. In addition, NSAIDs have no effect on proteoglycan synthesis or breakdown at concentrations which totally block IL-1 induced PGE2 release. Anti-arthritic drugs which block IL-1 induced breakdown (eg Chloroquine) fail to block proteoglycan synthesis inhibition and in fact potentiate the inhibition seen with IL-1 alone (Arner and others, 1988).

2.5.5 Tissue anabolic and catabolic effects

IL-1 induces fibroblast proliferation in human synovium (Postlethwaite and Kang, 1983) and stimulates collagen and fibronectin synthesis by cultured rheumatoid synovial cells (Krane and others, 1985). IL-1 also has a profound but reversible cytostatic effect on chondrocytes which is not attributable to prostanoid or polyamine synthesis induction (Chin and Lin, 1988). IFN-gamma inhibits collagen synthesis by synovial fibroblasts (Amento and Hayes, 1988). Conversely, TNF-ß stimulates synovial fibroblast synthesis of collagen (Amento and Hayes, 1988).

2.5.6 Free Radical Generation/Immune Mechanism

An immune mechanism of cartilage degradation involving superoxide anions has been suggested by Tiku et al.(1988). Chondrocytes are potent cellular sources of reactive oxygen species and IL-1 and IFN-gamma cause a dose dependent increase in the release of superoxide anions from chondrocytes. These superoxide anions are known to alter the functional properties of proteoglycans. It was proposed that the effect of superoxide anions may augment the effects of increased collagenase and proteoglycanase release by chondrocytes in response to IL-1.

2.5.7 Bone metabolism

Some authors have demonstrated no effect of IL-1 on osteoblasts (Gowen and others, 1984). Others have demonstrated IL-1-induced bone resorption and suppression of bone collagen and osteocalcin synthesis. Therapeutic concentrations of diflunisal, indomethacin, mefenamic acid, naproxen, piroxicam, salicylate and sulindac had no effect on this activity. Pharmacologic concentrations of diclofenac, benoxaprofen, fenclofenac, indomethacin and sulindac sulphate did block IL-1 activity (McGuire-Goldring and others,1984). IL-1 may modulate bone metabolism via PGE2 release. It has been stated that lymphokine-mediated bone resorption requires endogenous prostaglandin synthesis (Bockman and Repo, 1981).

2.6 Growth Factors

Various factors which stimulate the growth of cartilage have been studied (Castor and others, 1985; Davidson and others, 1985; Sporn and others, 1986; Castor, 1989). Decreased filtering capacity of the damaged proteoglycan matrix in osteoarthritic cartilage may reduce the barrier to the diffusion of growth factors such as connective tissue activating peptide (CTAP), platelet-derived growth factor (PDGF), pituitary-fibroblast growth factor or insulin growth factor-1 (IGF-1 or somatotrophin C) which may amplify repair responses. Insulin appears to be essential for adequate synthetic responses in chondrocytes. Insulin growth factor-1 (IGF-1) appears to amplify responses and reacts with specific receptors as well as with insulin receptors on chondrocytes. IGF-1 has been found to stimulate proteoglycan synthesis in vivo and to inhibit catabolism *in vitro* (Schalkwijk and others, 1988). It may be that IGF-1 levels or changes in chondrocyte responsiveness are involved in inflammatory or degenerative diseases.

2.7 Chondrocyte-Derived Proteins

Chondrocytes from human patients with osteoarthritis produce "stress proteins" such as SP-70. These proteins are also produced by chondrocytes subjected to heat shock or oxygen deprivation. In osteoarthritis, friction may cause local increases in temperature or increased chondrocyte metabolism may induce oxygen deprivation in chondrocytes and the release of stress proteins. It is known that prolonged exposure of cells to stress proteins can cause interferences with nuclear function and this could be a mechanism by which chondrocyte metabolism decreases in severe, late-stage osteoarthritis. The elimination half life of stress proteins is known to be decreased in osteoarthritic cartilage (Kubo and others, 1985).

Fibronectin is a glycoprotein, the function of which is not fully understood. It may be involved in opsonisation, cell adhesion, migration, or differentiation. It is present in connective tissue matrices, in blood and on cell surfaces (Hynes, 1981; Ruoslahti and others, 1982). Fibronectin concentration increases in fibrillated cartilage and synovial fluid of osteoarthritic joints (Lust and others, 1986). Fibronectin synthesis is increased five-fold in osteoarthritic cartilage *in vitro* (Wurster and Lust, 1982; 1984). The function of fibronectin in damaged cartilage is not known (Brandt, 1986).

2.8 Proteoglycan as a mediator

Mechanical erosion of cartilage in early osteoarthritis leads to the liberation of "wear particles" of cartilaginous tissue into the synovial fluid. It appears that these wear particles cause cellular activation by either chemical or physical means (Dingle and others, 1979).

Osteoarthritic synovial fluid is known to contain greater than 100 μg/ml of cartilage proteoglycan (Gysen and others, 1982). Elevated levels of proteoglycans have been recovered from the synovial fluid of dogs after anterior cruciate ligament transection within three weeks of surgery (Heinegard and others, 1985). Exogenous proteoglycan subunits suppress the synthesis of collagen by chondrocytes *in vitro* (Hadley and others 1980). Boniface and others (1988) discovered that when autologous cartilage proteoglycan was injected intraarticularly twice a week, synovial hypertrophy, synovitis, erosion of the articular surfaces, and loss of articular cartilage metachromasia were rapidly induced in rabbits. Neutral collagenases and gelatinase enzymes were produced by synoviocytes and chondrocytes and the synoviocytes also produced factor(s) which were possibly related to IL-1 and which provoked the activation of chondrocytes. The authors proposed that proteoglycan fragments mediate some of the pathophysiological changes in arthritis.

The investigators were uncertain of the mechanism of synoviocyte activation. It was thought that an immunological reaction (ie. an antigen-induced arthropathy) was unlikely since, first, a reaction to proteoglycan administration was rapidly induced although the animal had not received a primary challenge. Second, immunisation is said to be poor by the intraarticular route. Third, the uniformity of the response was not suggestive of an immune response and, finally, no precipitating antibodies to proteoglycans were detected in the sera of rabbits administered intraarticular proteoglycan (Boniface and others, 1988). Some evidence of a humoral immune response is documented (Kresina and others, 1988).

Proteoglycans may have a more important rôle in the pathophysiology of osteoarthritis, where there are fewer apparent potential biochemical mediators than in rheumatoid arthritis where several potential mediator candidates have been identified.

2.9 Immune reaction in osteoarthritis

Partially degraded fragments from damaged cartilage are present in large amounts in synovial tissue. More fragments of cartilage are seen in osteoarthritis than in rheumatoid arthritis where cartilage lysis is more common. Though the rôle of antibody-antigen complex generation in osteoarthritis pathophysiology is uncertain, the exposure of normally hidden and therefore potentially immunogenic autoantigen in cartilage may contribute to the pathogenesis of osteoarthritis.

Some authors have found evidence of a humoral immune response to autologous cartilage proteoglycan which they proposed could participate in the induction of cartilage pathology (Kresina and others, 1988). A 550 kiloDalton glycoprotein fragmented in osteoarthritis has been shown to be immunologically cross-reactive (Fife, 1986).

Immunohistological investigations of phagocytes in osteoarthritic synovial fluid have demonstrated collagen Type II in 28% (3-54%) of synovial cells from osteoarthritis patients. The data indicated that type II collagen, which is not found in normal synovial fluid, is released from cartilage in osteoarthritis (Moreland and others, 1988). Auto-antibodies to canine collagen Types I and II have been detected in dogs with spontaneous anterior cruciate ligament rupture and osteoarthritis (Niebauer and Menzel, 1982; Niebauer and others, 1987; Bari and others, 1989). Autoantibodies to Type I, II, IX and XI collagen have been detected in humans with rheumatoid arthritis or osteoarthritis. Surprisingly, the autoantibodies were more common in less severe osteoarthritis or rheumatoid arthritis, or in early phases of the diseases (Charriere and others, 1988).

The reactivity of monoclonal anti-Type II collagen antibodies with cartilage and synovial tissues in osteoarthritis and rheumatoid arthritis has been investigated (Klareskog and others, 1986). Antibody reacted with collagen in cartilage of both the osteoarthritis and rheumatoid joint but did not react with normal joint cartilage. Antibody also reacted with cartilage fragments in the synovium of both rheumatoid and osteoarthritis joints as well as rheumatoid pannus. It was concluded that in the normal joint, cartilage antigenic determinants of collagen Type II are not exposed to antibody. However, in inflammatory or degenerative joint conditions, proteoglycans are released from cartilage and new antigenic determinants are exposed including Type II collagen (Gay and others, 1986; Klareskog and others, 1986).

In studies on autoantibody specificities of immune complexes sequestered in the articular cartilage of patients with osteoarthritis, Jasin (1985) reported that osteoarthritis cartilage contained three times the concentration of IgM and IgG of normal articular cartilage. Half the osteoarthritis specimens had significant positive Collagen Type II antibody titres. Fifty per cent of osteoarthritis menisci also had significant anti-Collagen Type II antibodies. It was suggested that autoimmunity could be a mechanism for the self perpetuating and chronic nature of cartilage degradation in osteoarthritis.

In horses with secondary osteoarthritis, circulating complement C1q-binding immune complexes were present in 82% of cases and in synovial fluid in 77%. Few horses had antibody to Type II collagen but anticollagen type I antibody was present in 25% of sera and 41% of synovial fluid (Niebauer and others, 1988). Immune complexes may initiate local tissue damage by activating the complement cascade and secondary release of lysosomal enzymes (Cooke and others, 1980; Cooke, 1981; Cooke, 1983). In experimentally induced secondary osteoarthritis, immunoglobulin-complement factor C3 deposition in cartilage has been reported (Moskowitz and Kresina, 1985). These complexes were likely to be associated with a secondary synovitis and the investigators believed that immune complexes may contribute to osteoarthritis pathology.

1.2.10 Crystal-induced inflammatory response

Hydroxyapatite crystals are sometimes seen in synovial fluid of osteoarthritic joints. It appears that they have the potential to stimulate a secondary inflammatory response. The mechanism may involve destabilisation of the synovial fibroblast plasma membrane and synthesis or release of PGE2, collagenase and neutral proteases (Mankin, 1981; Mankin, 1985; Howell, 1989; Hough and Sokoloff, 1989).

2.11 Enzymes

There have been many reports on the degradative enzymes and enzyme inhibitors present in normal and osteoarthritic articular cartilage (eg. Lack and Ali, 1967; Sapolsky and others, 1973; Harris, 1974; Ehrlich and others, 1975; Howell, 1975). A correlation between articular cartilage collagenase activity and osteoarthritis has been reported (Ehrlich and others, 1978).

Chondrolytic enzymes are both lysosomal and extralysosomal. Concentrations of cathepsin D, acid phosphatase and aryl sulfatase are raised in osteoarthritic cartilage. Acid proteases such as lysosomal enzymes, Cathepsins B, D, and F may be involved in terminal matrix protein degradation. They are most probably active on or near the chondrocyte plasma membrane since the pH has been found to be more acidic (Woessner and Howell, 1983). However, neutral proteoglycanases are now thought the primary enzymes responsible for proteoglycan degradation. Proteoglycan degrading neutral metalloproteinase (NMP) activity is increased 7-8 fold in fibrillated and eroded cartilage. Active NMP is found in highest concentration in the centre of erosions and decreases towards the margins. The major form of NMP is a latent form of M.W. 55,000 (Woessner, 1982). A second form has a M.W. of 24000-27000 (Sapolsky and Howell, 1982; Woessner and Selzer, 1984). Neutral metalloproteinase (NMP) and serine proteinase activities are also increased in experimentally induced osteoarthritis in dogs (Pelletier, 1987). An acid metalloproteinase which also has activity in the neutral pH range has been reported (Azzo and Woessner, 1986). The IL-1 stimulation of such chondrocyte enzyme production may be the mechanism of cartilage degradation (Evequoz and others, 1984a&b; Gowen and others, 1984; Barret and Saklatvala, 1985; Pasternak and others, 1986; Schnyder and others, 1987).

Chondrocytes secrete acid and neutral metalloproteinases as proenzymes (Woessner, 1982; Dean and others, 1988). These proenzymes then require extra-cellular activation. The most likely candidate for proenzyme activator is a serine protease such as plasminogen activator. The levels of proenzyme converting enzyme may be increased in osteoarthritis. There may be a cascade-type reaction such that the activated enzyme is able to catalyse the conversion of proenzymes secreted by the chondrocytes (Morales and others, 1983; Sapolsky and others, 1985; Dean and others, 1988).

Concurrently, specific tissue inhibitors of metalloproteinases (TIMPs) are also secreted and cover the metalloproteinases (Sapolsky and others, 1981; Killackey and others, 1983; Dean and others, 1988). A decrease in TIMPs has been proposed as another mechanism responsible for increased enzymatic destruction of the cartilage matrix (Dean and others, 1988).

When the acid and neutral metalloproteinase activities and levels of TIMP in osteoarthritic articular cartilage is compared to normal articular cartilage, a number of differences are apparent. In mild osteoarthritis lesions, there is a disturbance of the enzyme profile with an increase in acid metalloproteinase compared to normal cartilage. In moderate osteoarthritis, increased enzyme levels (both latent and active) of acid and neutral metalloproteinases were present. Although TIMP increases in mild and moderate osteoarthritis, the increase was less than that in metalloproteinase activity. In normal cartilage there is sufficient TIMP to "cover" the total metalloproteinase. In osteoarthritis, the overabundance of metalloproteinases which are not covered by TIMP has been postulated as a pathobiochemical phenomenon which makes the cartilage matrix liable to attack by activated metalloproteinases (Dean and others, 1988).

Synovial cells are able to synthesise neutral metalloproteinases, Cathepsin D and collagenase which may potentiate matrix degradation and may be associated with ROS tissue damage in some circumstances (Greenwald, 1981). Synovial fluid contains potent enzyme inhibitors including ∞-2-macroglobulin and ∞-1-antitrypsin. However, these inhibitors could be damaged by enzymes secreted by leukocytes in the synovium. In the later stages of cartilage erosion, synovial fluid enzyme damage may participate in the pathophysiology of osteoarthritis (Arnoczky and Marshall, 1981; Howell, 1989).

2.12 Summary

There is overwhelming evidence that mediators and enzymes are involved in the pathogenesis of both primary and secondary osteoarthritis. Recent studies have indicated that various mediators can promote or provoke osteoarthritic pathology. Certain drugs can inhibit experimentally induced and natural secondary osteoarthritis. It is now obvious that osteoarthritis is not purely a process of wear and tear.

There is substantial evidence that proteoglycan fragments present in synovial fluid can induce synovial inflammation and cartilage damage. The mechanism appears to be a mediator-receptor type of effect and not via an immune response. There is evidence to suggest that in osteoarthritic joints, collagen type II and others stimulate an immune reaction as cartilage fragments sequestered in the synovium and as previously "hidden" collagen is exposed as the cartilage is degraded. Hydroxyapatite crystals released from subchondral bone may be involved in synovial inflammation.

Research interest has concentrated in recent years on the cytokines. *In vitro* and *in vivo* experiments have demonstrated that interleukin-1 (IL-1) has actions on the synovium and chondrocyte which tend to mimic those of osteoarthritis. IL-1 is known to be released from the synovium in response to proteoglycan fragments or wear particles.

Effects of IL-1 on the synovium include increased synthesis and release of prostaglandin E and proteases and the promotion of pain and inflammation. Effects on the chondrocyte include a marked inhibition of proteoglycan synthesis and an increase in degradative enzyme production. Chondrocyte mitosis is inhibited and cartilage degradation increased. Various growth factors including insulin growth factor-1 (IGF-1) have stimulatory effects on cartilage. The rôle of recently discovered chondrocyte "stress proteins" and of chondrocyte associated glycoproteins such as fibronectin is still uncertain.

Although the prostaglandin inhibitors (NSAIDs) are of benefit in controlling some of the symptoms of osteoarthritis (pain and synovitis), they do not inhibit the disease process and there is little evidence that prostaglandins or leukotrienes are important mediators of the pathogenesis of the disease process in osteoarthritis. Prostaglandins are apparently important in the modulation of pain and synovial inflammation in clinical osteoarthritis. It is recognised that IL-1 stimulates prostaglandin synthesis in the synovium. Reactive species generated by PMNs and the prostaglandin interconversion may be involved in tissue damage. IL-1 generated ROS in articular cartilage may damage matrix proteoglycan.

Whatever the precise inter-relationships between mediators and between biochemical and physical factors, the net result is altered chondrocyte function. Alterations in proteoglycan synthesis and increased degradation by neutral metalloproteinases, possibly in association with a relative deficiency of tissue inhibitors of metalloproteinases (TIMPs) cause damage and loss of proteoglycan. The elasticity of the cartilage matrix is lost and the collagen network can be damaged by repeated impact loading. Proteoglycan loss may also expose the collagen to enzymatic attack and mechanical damage. The net result is cartilage fibrillation and erosion. Some of the possible events and interactions in osteoarthritis are represented in a simplified form in FIG 5. There is undoubtedly a complex network of interrelationships and mediator actions and there has been a temptation in the past to oversimplify the proposed mechanisms of the pathogenesis of osteoarthritis.

New ideas on mediator based mechanisms of cartilage damage and synovitis may lead to novel mediator-antagonist or agonist drugs which will affect the progression of osteoarthritic change and not just the symptoms. Agents may be developed which specifically antagonise the activity of cytokines in the joint, which mimic growth factors or which stimulate chondrocyte repair mechanisms. Even now, there are drugs available which have some of these actions and it is likely that disease-modifying drugs will eventually revolutionise the therapy of osteoarthritis.

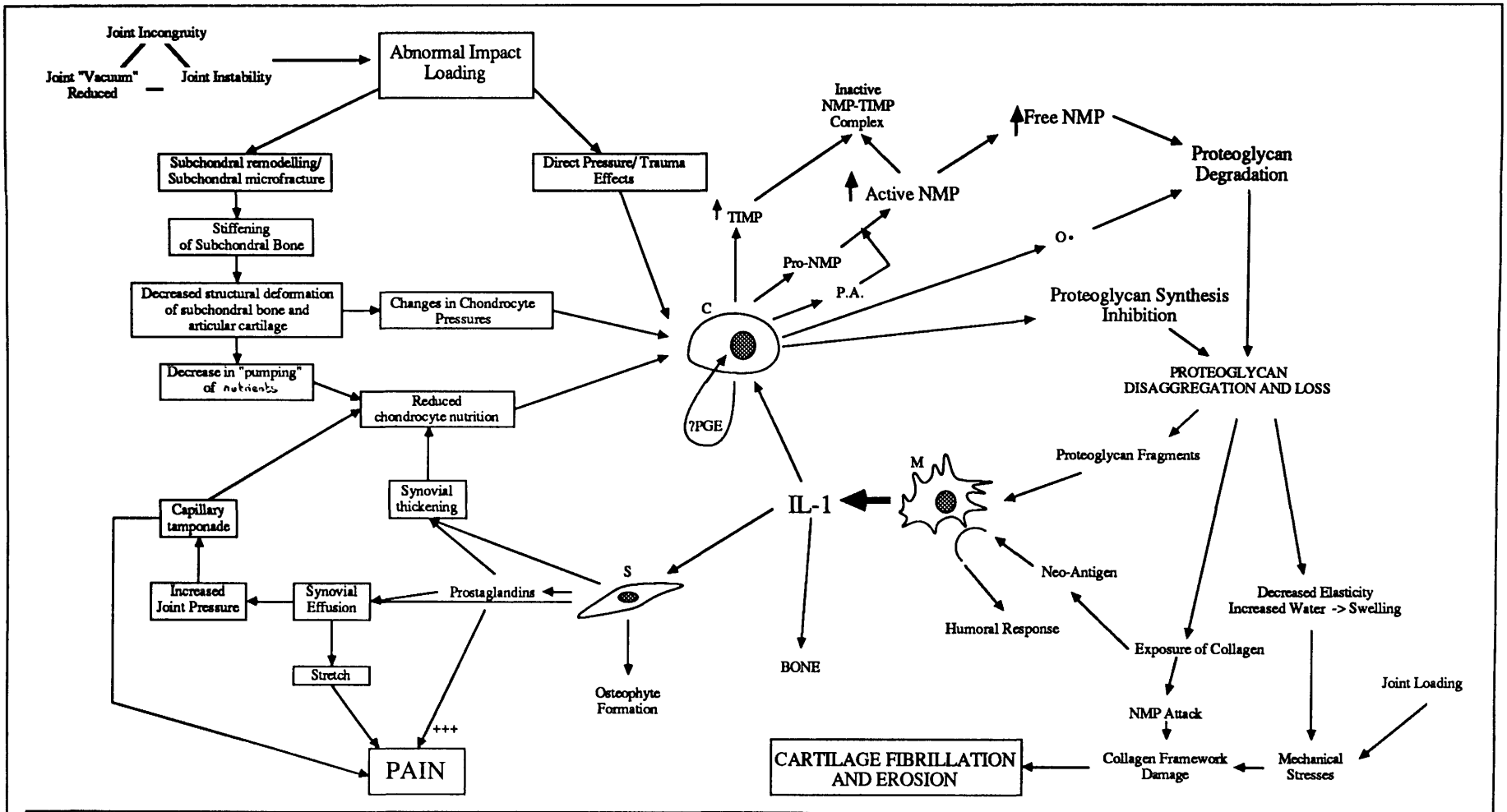


FIG 5: Simplified Diagrammatic Representation of Some of the Possible Mechanisms in the Aetiopathogenesis of Osteoarthritis
S = Synoviocyte; C = Chondrocyte; M = Synovial Macrophage;
TIMP = Tissue Inhibitors of Metalloproteinase; NMP = Neutral Metalloproteinase
Pro-NMP = Pro-Neutral Metalloproteinase; O • = Reactive Oxygen Species;
PGE = Prostaglandin E; IL-1 = Interleukin-1; P.A. = Plasminogen Activator

Chapter 3

Medical Therapy of Osteoarthritis in the Dog

Medical Therapy of Osteoarthritis in the Dog

3.1 General Concepts in the Treatment of Osteoarthritis in the Dog

It is important first and foremost to recognise the aims of owner and veterinarian in management of the osteoarthritic dog. These aims include pain relief, increased mobility and reduced disability, and the prevention of disease progression. It is important to recognise differences in the clinical problems and the disease severity experienced by the individual dog.

Pain is a major symptom of osteoarthritis in the dog as it is in man. The threshold of pain perception seems to be remarkably constant in different species (Vierck, 1976). Pain *tolerance* may vary widely between species and between individuals according to circumstances. A dog will often manifest the presence of pain by simply appearing less lively than usual. Where osteoarthritis affects a joint unilaterally, lameness is an almost ubiquitous sign of joint pain. Where an osteoarthritic joint is not apparently markedly painful on manipulation, it may still be causing chronic pain (Yoxall, 1978). A dog's "quality of life" may improve markedly when analgesics are given. The source of pain experienced by osteoarthritis patients has not been determined. Some possible causes are listed in TABLE 3. Human patients with osteoarthritis complain of "articular gelling" after a period of inactivity. The mechanism may be a subjective perception of increased resistance to motion, localised tissue oedema, accumulation of inflammatory metabolic products or motion causing muscle pressure on lymphatic or venous return.Weakness is largely the result of disuse muscle atrophy. The decrease in joint mobility or range of motion in joints affected by osteoarthritis may have many causes (see TABLE 4).

TABLE 3:

Possible Causes of Pain in the Osteoarthritic Joint

- Stimulation of nerve endings in
  - -synovium,
  - -joint capsule,
  - -periosteum,
  - -ligamentous or tendinous tissues by mechanical irritation or by inflammation;
- Nerve entrapment;
- Local circulatory disturbances associated with subchondral microfractures;
- Capsular tears;
- Impingement of deformed bone or osteophytes on adjacent soft tissues;
- Pressure during muscle spasm on nerves coursing through muscular tissue.

TABLE 4:

Possible intra-articular causes of reduced joint mobility:

- Luxation or subluxation of the joint;
- Capsular fibrosis, contraction and thickening;
- Intra-articular adhesions; Fibrous ankylosis;
- A tense effusion;
- Extreme thickening of the synovium;
- Intra-articular loose body
- Late bony ankylosis

Possible extra-articular causes of reduced joint mobility:

- Muscle spasm
- Tendon inflammation/shortening
- Subchondral bone fractures

Successful therapy of a case of osteoarthritis depends upon the education of the owner. The often progressive, irreversible nature of the disease and the unpredictability of the individual case must be explained. The veterinarian should differentiate between treating the causes or predisposing/aggravating factors and the use of NSAIDs for symptomatic relief. It must be explained that although analgesics can affect the symptoms in the short or medium term, the main aim is to change the progression or activity of the disease state by reducing further joint damage.

Therapy falls into four broad categories:

1. Corrective treatment for primary pathology
2. Managemental therapy
3. Medical therapy
4. Surgical therapy / salvage

3.1.1 Corrective Treatment

Many cases of canine osteoarthritis have an identifiable cause. The progression of secondary osteoarthritis can often be slowed or halted if corrective surgery for a primary cause, such as an ununited coronoid process or anterior cruciate ligament rupture, is performed early. In all ages of dogs, a full history and careful clinical examination often reveals a primary cause of joint instability or incongruity which can be ameliorated by surgery.

3.1.2 Managemental Therapy

(a) Exercise

Carefully thought out and tailored exercise regimes and mechanical stimulation of the involved tissues may help to arrest and even reverse the disease process (Bland, 1986). Human textbooks emphasise the importance of reducing joint loading in the therapy of osteoarthritis patients. Any activities such as running or descending stairs which involve excessive impact loading should be avoided. Several short periods of standing or walking are preferable to a single prolonged period. Swimming exercise is recommended in man, since the muscular tissues are exercised and joint mobility aided without impact loading of the joints.

A reasonable level of exercise is important in preventing stiffness as well as in maintaining quality of life. Cyclical loading of joints probably increases the flow of nutrients, eg glucose and amino acids to chondrocytes and the removal of metabolites via the synovial fluid and matrix. The supply of nutrients and removal of metabolites may be compromised if the joint is immobilised. Chondrocytes require mechanical stimulation to synthesise matrix components (Sokoloff, 1980). Immobilisation of joints causes the rapid development of a marked reduction in proteoglycan synthesis and aggregation (Palmoski and others, 1979).

Although hyaline cartilage is an excellent shock absorber, it is present in insufficient quantities at the joint surface to make a significant contribution to overall shock absorption. Bone is present in larger quantities and has a rôle in shock absorption. However, by far the greatest contribution to shock absorption is the neuromuscular reflex mechanism. Indeed, if a person has a short fall such that there is insufficient time for a neuromuscular response, he or she can sustain significant injuries. It is thus important to maintain musculoskeletal fitness to minimise impact loading damage of articular cartilage in cases of osteoarthritis.

Physiotherapy is very useful in man, and can be used in dogs where the dog is cooperative and the owner compliant. Heat application often reduces pain and stiffness in man, but the use of heat pads has not been assessed in dogs. Sometimes heat application intensifies joint pain and ice packs may be used in these cases. The use of acupuncture in osteoarthritis has been reported in man (Melzack, 1981) and in the dog (Janssens, 1986).

(b) Obesity

Although not confirmed as a *cause* of osteoarthritis, obesity contributes to excessive loading of the articular cartilage and may aggravate symptoms or accelerate cartilage breakdown. The difficulty in reducing weight when exercise has been reduced is a problem experienced in man as well as in dogs. An increase in weight associated with not adjusting dietary requirements when exercise has been reduced can cancel out the benefits of changes in exercise regime. Any dog presented with osteoarthritis which is obese should be strictly dieted. Many dogs will improve markedly if they are forced to adhere to a weight reducing diet. Conversely, treatment with exercise restriction and analgesics will often have a disappointing effect in a dog which remains or becomes obese. The aim is to keep the dog on the low side of the breed average weight.

3.1.3 Medical Management

Even with managemental changes, many osteoarthritic dogs will still require analgesic therapy. Analgesics provide symptomatic relief and reduce pain and disability associated with osteoarthritis. In man, long term use of NSAIDs for osteoarthritis is common. The use of these drugs in the dog in conjunction with other forms of treatment can greatly enhance the dog's "quality of life" by reducing pain and stiffness and increasing mobility. However, they must be used in conjunction with other forms of treatment such as owner education and exercise and dietary management. All too often veterinarians resort to the convenience of administering oral analgesic treatment in isolation without stressing the importance of exercise and dietary management in treatment. Owners should be warned that they are responsible for preventing their dog from acute trauma to an already damaged joint. Pain relief may cause a dog to over-use a damaged joint and cause accelerated disease progression unless the owner controls exercise. Beneficial effects of NSAID treatment include:

- pain relief
- decrease the duration and severity of morning stiffness
- decrease tenderness in the joint
- decrease joint swelling, temperature
- increase joint function

(Boardman and Hart, 1967).

3.1.4 Surgery

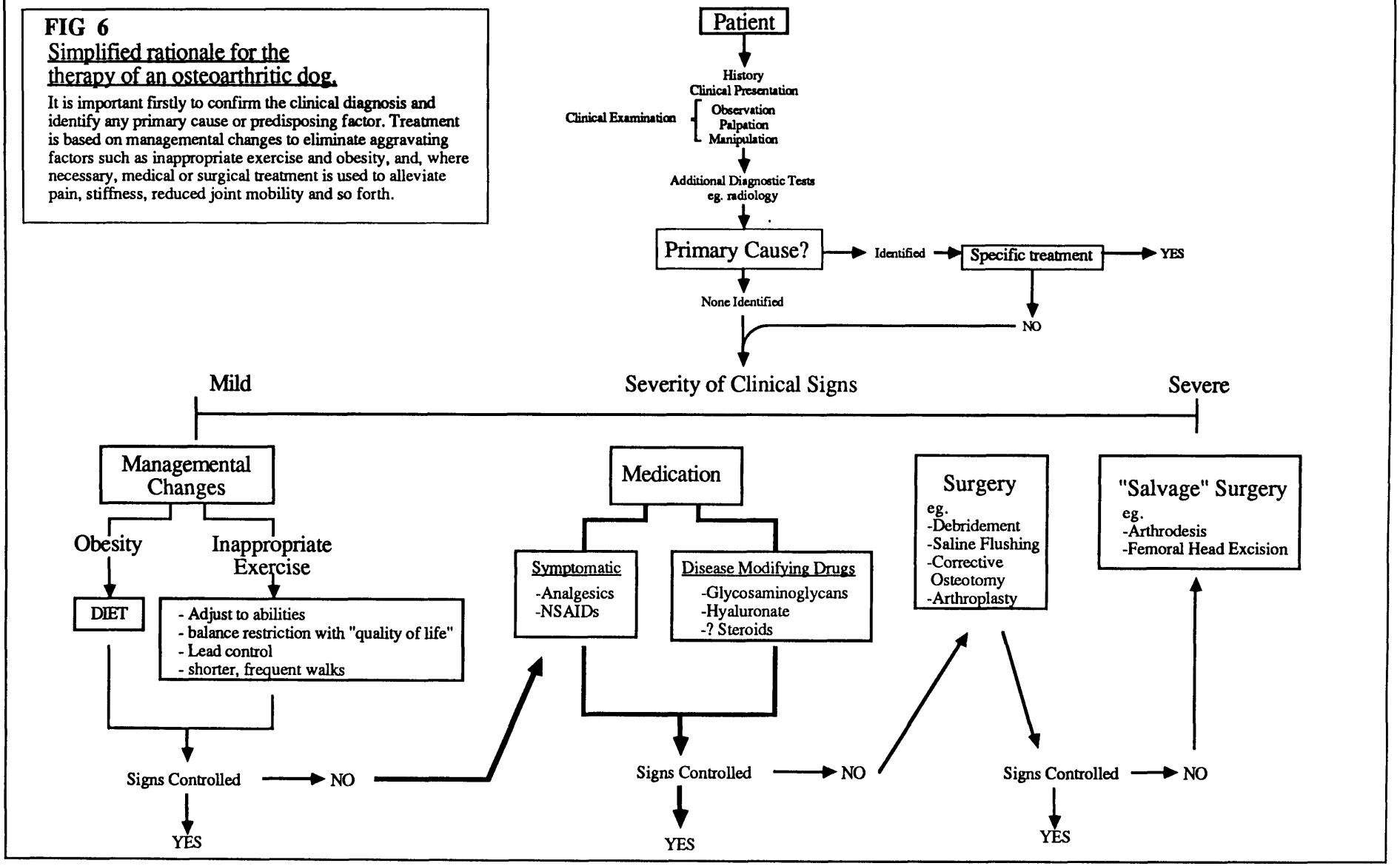
Arthrotomy and debridement, flushing or synovectomy of an osteoarthritic joint can markedly improve clinical signs in the short and medium term if managemental and medical therapy fails. Stress-reducing operations in man such as osteotomy have been demonstrated to increase the hip joint space, markedly relieve clinical signs, cause pseudocyst healing, improvement of bony outline by remodelling and osteophyte reduction, and a restoration of normal trabeculae (Bland, 1986). In the most severe cases "salvage" surgical procedures such as arthrodesis or femoral head excision may be required to ameliorate the clinical signs. Recently, some UK veterinary referral centres have begun canine hip joint replacement programmes.

An approach to the therapy of the osteoarthritic dog is given in FIG 6.

FIG 6

Simplified rationale for the therapy of an osteoarthritic dog.

It is important firstly to confirm the clinical diagnosis and identify any primary cause or predisposing factor. Treatment is based on managemental changes to eliminate aggravating factors such as inappropriate exercise and obesity, and, where necessary, medical or surgical treatment is used to alleviate pain, stiffness, reduced joint mobility and so forth.



3.2 Symptomatic Medical Treatment of Osteoarthritis in the Dog: Pure Analgesics

3.2.1 Paracetamol (Acetaminophen)

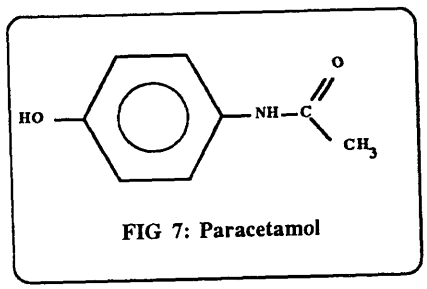


FIG 7: Paracetamol

Paracetamol is a weak reversible non-competitive cyclooxygenase inhibitor. It appears to be much more potent in the central nervous system than in the peripheral tissues (Higgs and Vane, 1983). Standard texts state that the analgesic efficacy of paracetamol is equivalent to that of aspirin but that paracetamol has no useful antiinflammatory effect (Booth, 1982). However, in a recent study of post-operative pain and inflammation after orthopaedic surgery in dogs, paracetamol demonstrated antiinflammatory and analgesic activity superior to that of aspirin (Mburn and others, 1988).

Paracetamol is quite safe within the recommended dosage limits. Clinical signs of toxicosis (cyanosis, depression, vomiting, facial oedema) are seen in dogs after oral administration of 200 mg/kg body weight (Hjelle and Gauer, 1986). Patients particularly at risk are those with hepatic microsomal enzyme induction, due to treatment with antiepileptiform drugs for example, since they can rapidly form large amounts of the toxic metabolic intermediate. Oral methionine or intravenous N-acetylcysteine are antidotes after acute paracetamol intoxication. They are converted *in vivo* to glutathione which can then react with the paracetamol metabolite to form non-toxic metabolites (Hjelle and Gauer, 1986). Gastric effects of paracetamol are minimal, probably because peripheral effects on cyclooxygenase are mild (Rubio and Papich, 1988). There are very few reports of hepatotoxicity associated with the therapeutic use of paracetamol (Prescott, 1986).

In man, patients are often treated with paracetamol if the patient is sensitive to aspirin since paracetamol is said to give comparative analgesia (Huskisson, 1974; Brandt, 1989) and paracetamol has been stated to be an effective alternative to aspirin for analgesic effect in dogs (Rubin and Papich, 1988) although its antiinflammatory activity is generally accepted as weak. It seems that paracetamol is potentially useful at a dose rate of 15 mg/kg every 8 hours (Jenkins, 1987). A maximum of 25 mg/kg tid has been recommended (Taylor, 1987).

3.2.2. Opiate derivatives

The less potent opioids such as codeine and propoxyphene have been used in situations where moderate analgesic action is required in cases of intransigent pain, especially pain of non-inflammatory origin. Codeine has about one quarter the potency of morphine but only one tenth of the potential for adverse reactions. Constipation or slight respiratory depression have been recognised side effects of codeine usage (Taylor, 1985).

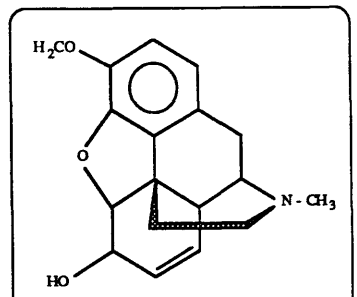


FIG 8: Codeine

Propoxyphene is often preferred to codeine because its duration of action is longer, it has less side effects and a higher therapeutic ratio than codeine. Medical evidence suggests that there is addictive potential in propoxyphene, and discretion should be used in dispensing it to owners (Yoxall, 1978). Opioids may cause drowsiness at higher doses. Pentazocine may cause hallucinations in small animals and is a Schedule 3 Controlled Drug.

The mixed agonist-antagonist pentazocine is available in tablet form. In clinical trials in man, pentazocine tablets were no more effective than paracetamol (Huskisson, 1974). In rheumatoid arthritis, pentazocine tablets were not superior to placebo (Nuki and others, 1973).

Distalgesic® is a human preparation containing dextropropoxyphene 32.5 mg and paracetamol 325 mg. The combination of paracetamol and dextropropoxyphene is said to be more effective than the individual component drugs (Messick, 1979).Some authors recommend the use of Distalgesic® at 16.5 mg dextropropoxyphene bid for small dogs, and up to 32.5 mg tid in large breeds (Yoxall, 1978).

In man, codeine and other narcotic analgesics are rarely required for pain control in osteoarthritis and it is advised that, if they are used, the period of use is short (Brandt, 1989). Yoxall (1978) advises that veterinarians avoid the use of codeine preparations where it is combined with other analgesics. However, some authors have recommended that codeine can be used at 2 mg/kg bid alone or in combination with aspirin or paracetamol with good effect (Taylor, 1985).

3.3 Symptomatic Medical Treatment of Osteoarthritis in the Dog: General Properties of Non-Steroidal Anti-Inflammatory Drugs

3.3.1 Introduction

The Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) [Anti-Inflammatory Analgesics; Non-Narcotic Analgesics; Aspirin-like Drugs] have three major types of effect: analgesic; antiinflammatory; and antipyretic. The analgesic efficacy of NSAIDs is usually lower than the opioids (Broom and others, 1986), though efficacy varies with dose rates and types of peripheral and central pain (McKellar, 1989). However, they do not cause dependency. Their antiinflammatory properties can be useful in osteoarthritis and other musculoskeletal disorders. Most NSAIDs have analgesic activity, but the antiinflammatory activity appears more variable. Some such as aspirin and indomethacin have potent antiinflammatory activity whilst others such as naproxen and meclofenamate have moderate antiinflammatory activity.

NSAIDs have been widely used in the therapy of osteoarthritis in man and animals for many years. They relieve pain and may reduce swelling due to secondary inflammation but there is little evidence that they have any beneficial effects on the underlying process. It is not clear at this time whether the activity of NSAIDs in the therapy of osteoarthritis is purely analgesic or whether it is a combination of analgesic and anti-inflammatory activity. However, antiinflammatory analgesics have been demonstrated to be more efficacious in the therapy of osteoarthritis than pure analgesics (Doyle and others, 1981). In man, three quarters of osteoarthritic joints show evidence of an inflammatory response (Howell, 1981; Dieppe, 1984). It would therefore be expected that NSAID treatment would lead to a improvement in many clinical cases. The anti-inflammatory effects of aspirin are only apparent at about six times the analgesic dose. The dose of many NSAIDs which is required to give an analgesic effect is often less than the dose required for anti-inflammatory effect (Dawson and Willoughby, 1985). The main differences between the NSAIDs are the incidence of side effects and the therapeutic index.

3.3.2 Mechanisms of Action

(a) - Prostaglandin synthesis inhibition

The eicosanoid formation pathway is represented diagrammatically in FIG 10. Most NSAID activity appears to be due to the inhibition of prostaglandin synthesis by reversible or irreversible inhibition of the enzyme cyclooxygenase (Vane, 1971).

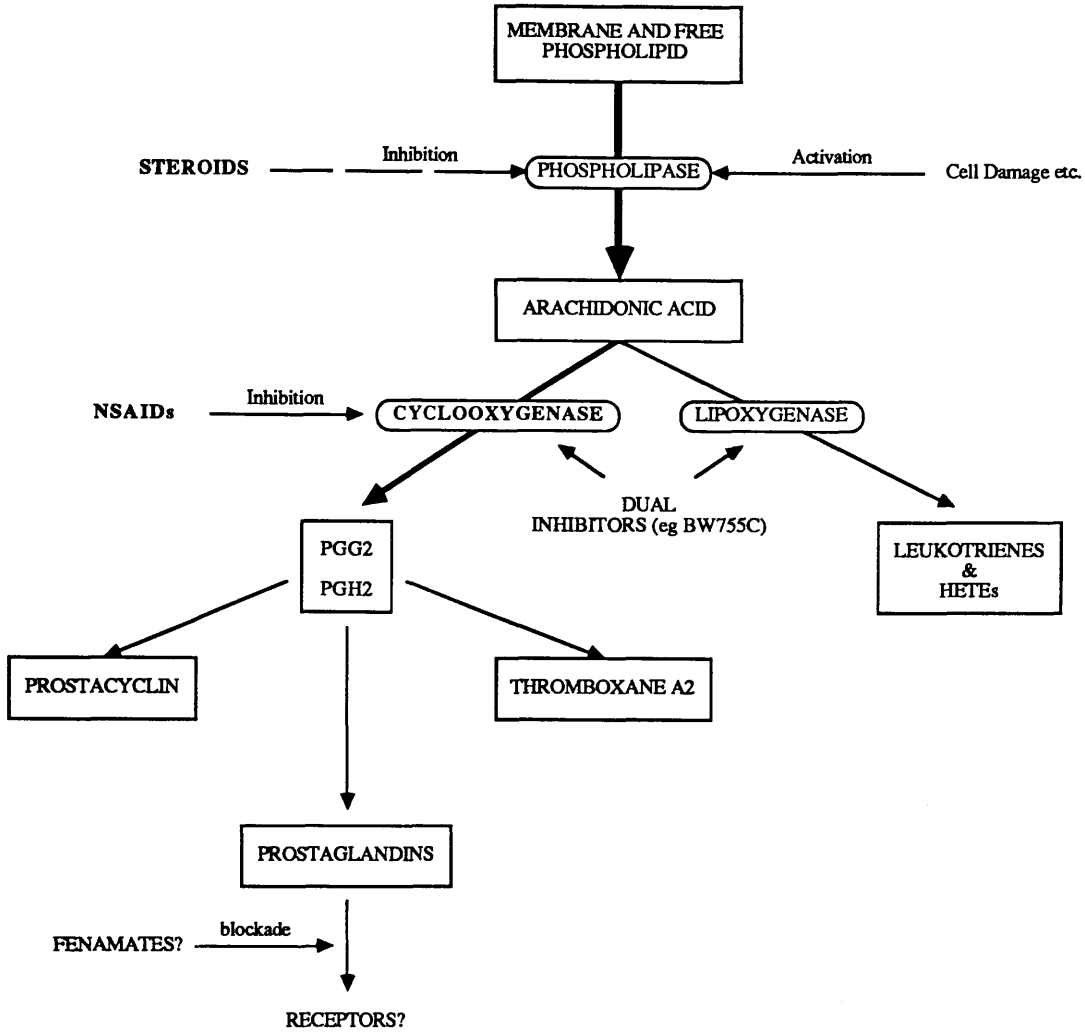


FIG 10: Simplified diagram of the arachidonic acid cascade and the possible sites of action of NSAIDs, steroids and dual inhibitors

It is known that aspirin acetylates the cyclooxygenase enzyme at or near the active site and so irreversibly inhibits prostaglandin biosynthesis. It appears that most of the acidic NSAIDs compete with arachidonic acid for the active site of the cyclooxygenase enzyme and, unlike aspirin, reversibly inhibit cyclooxygenase (Ferriera and Vane, 1973). Some of the NSAIDs may act on a separate site of the cyclooxygenase enzyme [ie reversible non-competative inhibition] (Rainsford, 1984b). The inhibition of cyclooxygenase by NSAIDs varies in different tissues as well as between species (Mills, 1974; Lewis and Sanford, 1975; Patrono and others, 1976). The reasons are not known. This may account for the differences in clinical efficacy between NSAIDs in the treatment of different conditions and variations in efficacy between individuals and in different species (Higgs and Salmon, 1985).

Some NSAIDs such as alclofenac, azaproprazone, and benoxaprofen are weak prostaglandin synthesis inhibitors but still have antiinflammatory activity. Some NSAIDs are not cyclooxygenase specific and have effects on lipoxygenase and other enzymes (Kitchen and others, 1985). Other actions have been described which, at least in some NSAIDs, may have important therapeutic effects.

(b) - Prostaglandin antagonism

Some NSAIDs may have antagonistic actions on theoretical eicosanoid receptors (Sanner, 1976). Fenamates, diclofenac, indomethacin and phenylbutazone are potent and selective inhibitors of prostaglandin E1-induced adenyl cyclase activity stimulation (Ortmann and Perkins, 1977). This effect occurred well within therapeutic prostaglandin synthesis inhibiting concentrations of the drugs. The fenamates are believed to inhibit the action of the prostaglandins at membrane receptors (Dawson and Willoughby, 1985).

Many NSAIDs inhibit 15-hydroxy prostaglandin dehydrogenase (PGDH), the enzyme responsible for PGE2 and PGF2∞ breakdown. However, this effect only occurs at very high drug concentrations in most cases (Brooks and others, 1986).

(c) - superoxide dismutase activity

Phenolic compounds can act as scavengers of reactive oxygen species (ROS) released in peroxidase conversion of prostaglandin endoperoxide PGG2 (Rainsford, 1984b). Levels of different individual prostaglandins E2, F1∞, I2, and D2 can increase or decrease depending on direct inhibition or radical scavenging activities (Dewhurst, 1980). Copper, zinc and antioxidants such as ascorbic acid and ∞-tocopherol inhibit PGE2 formation (Lands and Rome, 1976).

(d) - stabilisation of lysosomal membranes

The stabilisation of lysosomal membranes and the inhibition of the release of lytic enzymes including phospholipases is a property of some NSAIDs as well as SAIDs. The effect is concentration and pH dependent. Changes in prostaglandin concentrations and direct drug effects may alter cyclic nucleotide concentrations and so influence lysosomal enzyme release. This may be particularly true where LTB4 is inhibited since this leukotriene is a potent labilizer of lysosomal membranes. In addition, NSAIDs may inhibit free radical generation and so decrease radical induced lysosomal membrane damage (Rainsford, 1984b; Dawson and Willoughby, 1985; Kitchen and others, 1985).

(e) - antagonism of histamine/bradykinin

Most NSAIDs have only mild effects on the early phase of acute inflammation where kinins and histamine predominate. There is evidence, however, that these drugs may influence the release or action of these mediators (Lewis and Whittle, 1977; Rainsford, 1984). They may also inhibit histamine and kinin induced prostaglandin release (Kitchen, 1985; Dawson and Willoughby, 1985).

(f) - inhibition of cell chemotaxis and regulation of leukocyte function

Effects on leukocyte migration have been described and have been ascribed to effects on the chemotaxin LTB4 or membrane stabilisation effects (Smith, 1978). NSAIDs uncouple oxidative phosphorylation. The result is decreased glycogen availability and changes in membrane permeability. Increases in intracellular c-AMP inhibit leukocyte chemotaxis. NSAIDs may affect the responsiveness of leukocytes to chemotaxins (Kitchen and others, 1985). Whether these effects are important *in vivo* is unknown (Rainsford, 1984; Dawson and Willoughby, 1985).

(h) -inhibition of mucopolysaccharide synthesis and collagenase production, and uncoupling of oxidative phosphorylation

NSAIDs affect connective tissue metabolism. Most NSAIDs inhibit adenosine triphosphate (ATP) synthesis pathways (Kitchen, 1986). This effect and NSAID activity on glycosaminoglycan-biosynthetic enzymes and effects of prostaglandins and NSAIDs on glycosaminoglycan-degrading enzymes tend towards an overall anti-catabolic and anti-anabolic action (Peters and others, 1975; Rainsford, 1984).

3.3.3 General Pharmacokinetics

Most of the NSAIDs are rapidly absorbed from the proximal small intestine or stomach after oral administration. Peak plasma concentrations occur at 1-2 hours after administration. Peak concentrations are delayed and reduced when NSAIDs are administered with food but feeding generally has no effect on total oral bioavailability (Lombardino, 1985). The structure and chemistry of the NSAIDs leads to their preferential distribution in inflamed sites. Most of the NSAIDs have a high affinity for plasma proteins. In inflamed tissue, the extravas ation of plasma proteins through damaged capillaries may concentrate the amount of NSAIDs. Local therapeutic concentrations of NSAIDs may be retained after plasma concentrations have declined to subtherapeutic levels (Dawson and Willoughby, 1985; Higgins, 1985; Rainsford, 1985; Lees and others, 1987). Prolonged effects of NSAIDs have been reported where plasma concentrationshave become undetectable (Lees and others, 1987).

When drugs have a pKa of between 3 and 7.5, as the acidic NSAIDs, their reabsorption from the renal tubule will be sensitive to alterations in urinary pH. Excretion of salicylate increases markedly as the urine is alkalinised (Lombardino, 1985). Similar findings for other NSAIDs or acidic metabolites may be important in the treatment of overdosage or in the adjustment of dosages in performance animals.

Enterohepatic recirculation of the NSAIDs is common in the dog (Duggan, 1975; Risdall and others, 1978; Willis and Kendall, 1978; Tsuchia and others, 1980; Freh and Rieh, 1981; Cosenza, 1984; McKellar, 1989). Conjugates in the bile may be cleaved in the gut to regenerate the free acid which can then be reabsorbed in the lower intestine. This regeneration of active drug may cause local mucosal irritation and damage and prolong the half-life of the drug (FIG 11). The process appears to be particularly important in the dog since, in this species, secretion of conjugated metabolites in the bile is the main excretory pathway for many NSAIDs. This in part explains the gastrointestinal toxicity of a number of NSAIDs which are considerably less damaging in people since, for most NSAIDs, renal excretion of conjugates predominates in man (Lombardino, 1985).

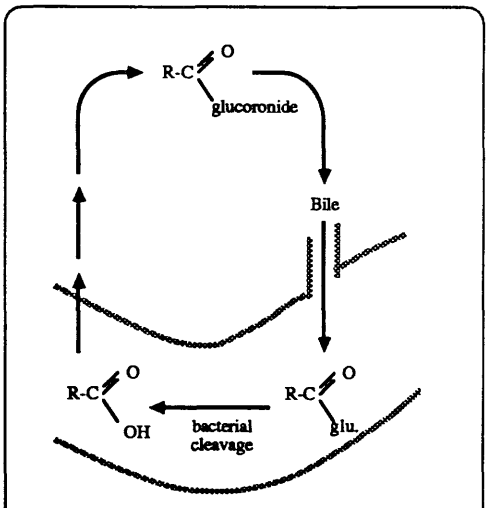


FIG 11:
Enterohepatic Recirculation

† pKa = pH at which a salt is half ionised

In addition to species variation in metabolic and excretory pathways, different breeds of dogs show different rates of drug clearance. For instance, beagles clear certain drugs more quickly than mongrels (Freh and others, 1979). Conversely, they are more susceptible to the toxic effects of other drugs (Walker, 1985). Individual variation in absorption, distribution and clearance of drugs is also very great in man and in the dog (McKellar, 1989; Goetzl and Goldstein, 1989).

3.3.4 Adverse Reactions

The NSAIDs have many adverse effects in common since most side effects are attributable to the inhibition of prostanoid biosynthesis (Dearden and Nicholson, 1984).

(a) Gastrointestinal

In human patients admitted to hospital with acute upper intestinal haemorrhage, aspirin is implicated in 50% and other NSAIDs in 20%. NSAIDs are associated with increased incidence of perforating peptic ulcers, especially in elderly patients (Ivey, 1986). Gastrointestinal intolerance appears to be mediated by a combination of local and systemic effects (Phillips, 1973; Cosenza, 1984; Rainsford, 1984a; Brooks and others, 1986; Ivey, 1986; Rubin and Papich, 1988)(FIG 12 & FIG 13).

The NSAIDs are generally weak organic acids with pKa values of 3-6. At lower pH values (ie in the stomach) the drugs are largely unionised and are therefore lipid soluble and able to diffuse through biological membranes. In this form the drugs can diffuse through the lipid bilayer of the gastric lining cells. Once within these cells, the drugs tend to re-ionise at the relatively greater pH in the cytoplasm and can become trapped within the cell. The resulting prolonged and relatively high concentrations of NSAID within these cells probably contributes to gastrointestinal effects (La Du and others, 1972; Rainsford, 1984a; Ivey, 1986). Aspirin which has an irreversible effect on cyclooxygenase will have persistent effects in the gastric mucosa after absorption whereas reversible inhibitors effects are terminated when the drug has been absorbed. Thus drugs which are reversible cyclooxygenase inhibitors and which are rapidly absorbed should be better tolerated by the gastric mucosa (Wiseman, 1983).

Mucosal prostaglandins inhibit acid secretion and appear to have a "cytoprotective effect" by promoting mucus secretion and strengthening the mucosa against back-diffusion of acid from the gastric lumen to the submucosal tissues where it can cause damage (Ivey, 1986). PGI2 is produced by cells in the gastric mucosa. It inhibits gastric acid production (Whittle and others, 1978).

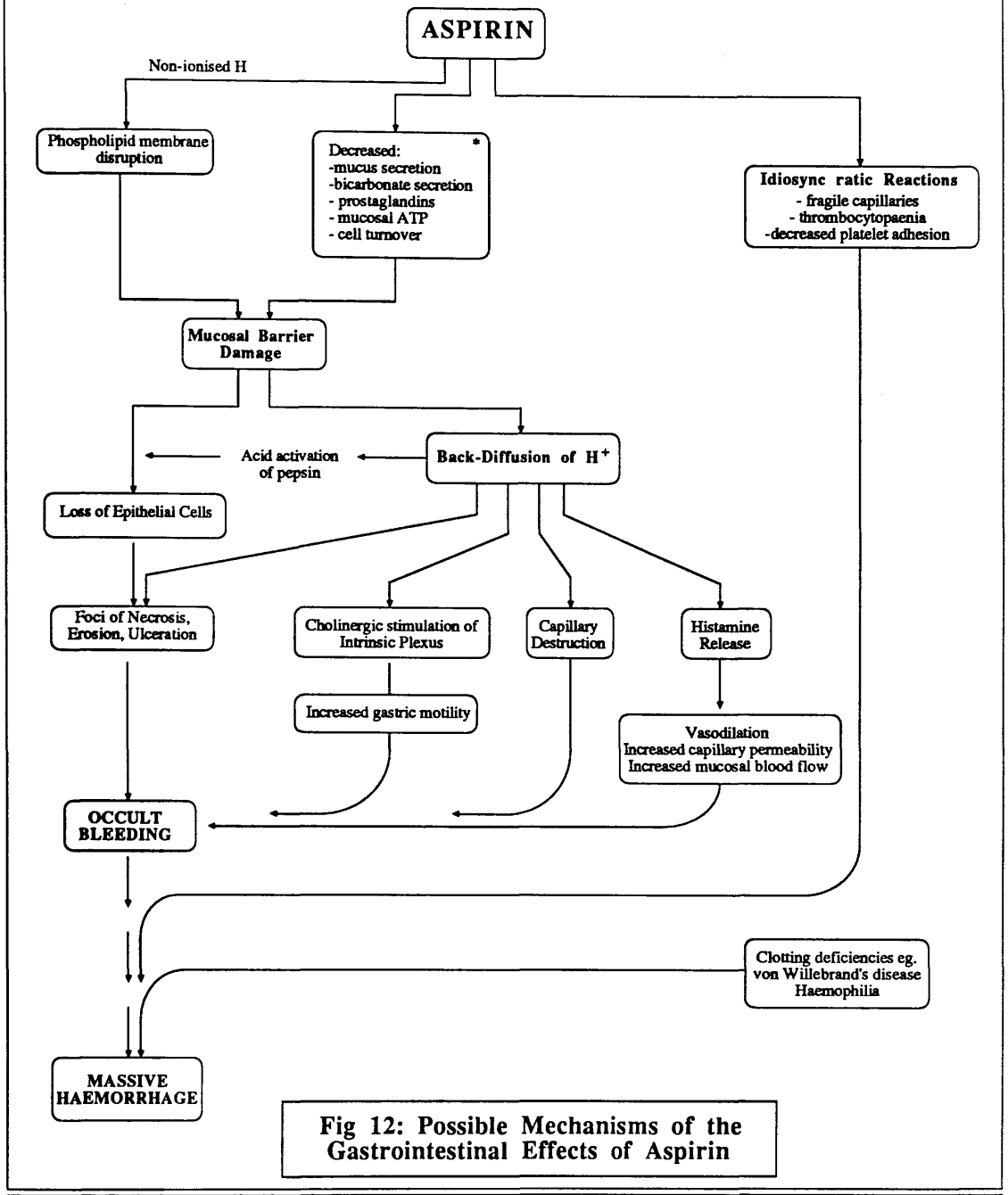


Fig 12: Possible Mechanisms of the Gastrointestinal Effects of Aspirin

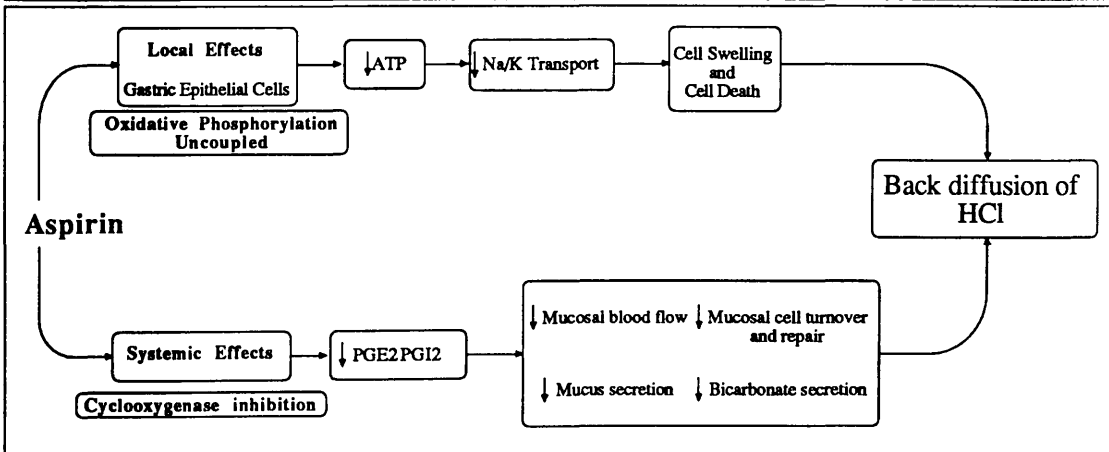


Fig 13: Possible Local and Systemic Effects of Aspirin on the Gastric Mucosa

Both PGI2 and PGE2 are important in the maintenance of gastric blood flow by local vasodilation. NSAIDs which inhibit prostaglandin biosynthesis thus enhance vasoconstriction and acid secretion such that ischaemia, necrosis and ulceration can occur (Goodman and others, 1980; Ivey, 1986; Jenkins, 1987).

Gastrointestinal intolerance can occur whether the NSAID is given orally or systemically. However, gastric effects are worse when drug is administered orally and absorption from the stomach is possible since this will result in higher local concentrations than if the drug were administered parenterally or in a form which was not absorbed from the stomach (Ivey, 1986). To minimise adverse effects, NSAIDs are generally given with food in man or are administered in enteric coated preparations which reduce the local effects on the gastric mucosa (Booth, 1982; Ivey, 1986). Recent interest has been shown in new prodrugs such as fenbufen (see 3.4.6) and sulindac (see 3.4.7) which are converted to active metabolites after absorption and should therefore avoid high gastric mucosal concentrations and local induction of pathology. Enterohepatic recirculation occurs for many NSAIDs in the dog and can cause prolonged local concentrations of drug in the intestinal mucosa and so may be an important mechanism of gastrointestinal intolerance (see 3.3.3). Chronic blood loss with aspirin treatment is apparently common at therapeutic doses in the dog (Phillips, 1981).

(b) Renal toxicity

Prostaglandins are involved in renal blood flow autoregulation, glomerular filtration, tubular ion transport, modulation of renin release and water homeostasis. Renal prostaglandins do not appear to be important in the control of resting renal blood flow or glomerular filtration rate in the normal animal. In contrast, in adverse conditions prostaglandins exert a protective effect to preserve renal perfusion where systemic vasoconstriction has been induced by mediators such as noradrenaline, alpha adrenergic stimulation and angiotensin II (FIG 14). In the normal animal NSAIDs are unlikely to have any damaging effects. However, in hypovolaemia and states of decreased renal perfusion, inhibition of cyclooxygenase, and hence the inhibition of renal prostaglandin synthesis, causes a severe reduction in renal perfusion and reversible or irreversible renal insufficiency (TABLE 5) (Kincaid-Smith, 1986; Rubin, 1986).

Prostaglandins in the kidney have an important rôle in salt and water homeostasis. NSAIDs can cause sodium and water retention and oedema. If the retention of water is disproportionate, hyponatraemia can develop. Inhibition of the renin-angiotensin-aldosterone system can cause hyperkalaemia. NSAIDs reduce the diuretic, natriuretic and anti-hypertensive effects of diuretic drugs. NSAIDs also counteract the anti-hypertensive effects of the ß-adrenoceptor antagonists, probably via their action on renal prostaglandins (Day and others, 1983; Rubin, 1986).

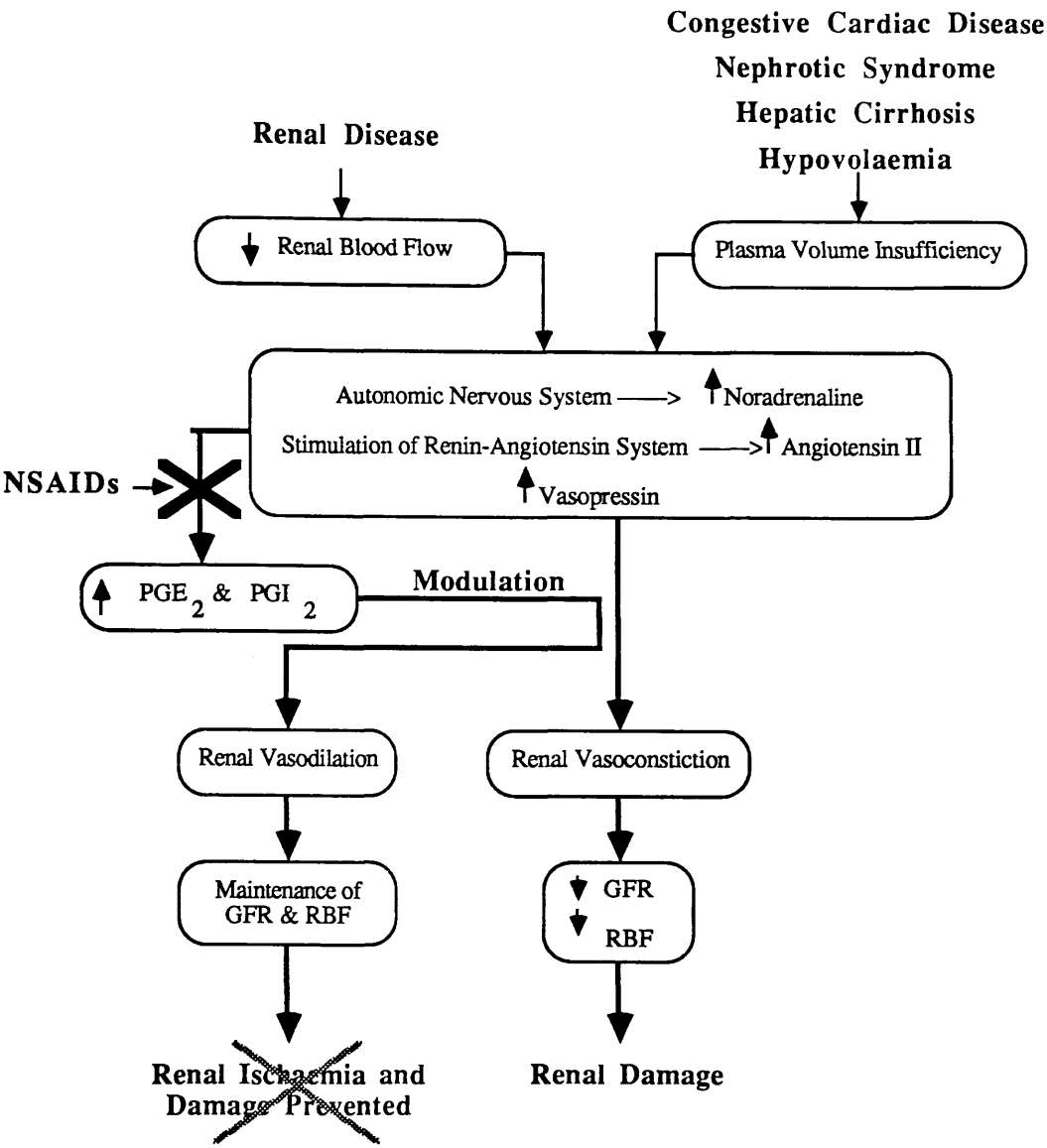


FIG 14 Possible mechanism of the protective effect of prostaglandins in the kidney and the nephrotoxic effects of the NSAIDs

TABLE 5: Pathological Conditions Which Predispose to Nephrotoxicity of NSAIDs

1. Reduced circulating blood volume eg.
   -water deprivation
   -diuretic therapy
   -haemmorhage
   -nephrotic syndrome

2. Animals in a vasoconstrictive state eg.
   -general anaesthesia

3. Sodium retention eg.
   -congestive cardiac disease
   -hepatic cirrhosis

4. Preexisting renal insufficiency

TABLE 6: Pathological Conditions Associated with NSAID Nephrotoxicity

1. - Acute renal insufficiency
   (especially in preexeisting congestive cardiac failure, cirrhosis, nephrotic syndrome, hypovolaemia secondary to diuresis).
   In dogs, high doses of ibuprofen cause acute renal failure.

2. - Papillary necrosis
   (described in horses treated with phenylbutazone; associated with hypovolaemia due to fluid loss or water deprivation)

3. - Nephrotic syndrome and interstitial nephritis
   (possibly T-lymphocyte mediated immune mechanism.
   Reversible if treatment is withdrawn)

4. - Sodium and fluid retention
   (augment oedema-inducing disease such as congestive cardiac failure; decrease efficacy of diuretics eg. frusemide)

5. - Potassium balance
   (hyperkalaemia associated with NSAID treatment is reported in man; risk increased in sodium depleted patient)

Acute and chronic clinical syndromes which have been associated with the use of NSAIDs are listed in TABLE 6. In man, there is evidence to suggest that uroepithelial tumours also occur as a complication of prolonged NSAID use (Kincaid-Smith, 1986).

(c) Central nervous system (CNS)

In man, NSAIDs often cause adverse CNS signs including tremors, weakness, headache, blurred vision, confusion, agitation and ataxia (Dodge, 1979). Such effects are rarely identified in animals. Dullness is a common reported side effect of NSAIDs but it is unclear whether this is due to CNS effects or to abdominal discomfort or dyspepsia. Salicylate induced seizures have been reported in a dog (Schubert, 1984).

(d) Hepatotoxicity

Drugs such as ibufenac, fenclofenac and benoxaprofen have been withdrawn from the human market because of hepatotoxicity, and liver damage has been reported on occasion for virtually all NSAIDs. Little is known of the mechanisms of hepatotoxicity of NSAIDs. Liver enzyme values may be slightly elevated with many NSAIDs in man. There may be more potential for hepatotoxicity with certain NSAIDs. In man, these include diclofenac, sulindac, pirprofen and phenylbutazone (Prescott, 1986).

(e) Dermatological

Rashes, pruritis, and urticaria are common in people treated with NSAIDs (Rainsford, 1984; Lombardino, 1985; Brooks, 1986). Skin side effects are poorly documented in dogs.

(f) Haemopoetic

The inhibition of platelet aggregation by NSAIDs is due to platelet prostacyclin inhibition which reduces platelet aggregation and thromboxane inhibition and reduced platelet-capillary wall adhesion. Increased bleeding time may be of consequence if there is a preexisting bleeding disorder such as von Willebrands disease, other coagulation disorders or gastrointestinal ulceration.

Bone marrow depression has been reported in dogs treated with phenylbutazone but is apparently very much rarer than the syndrome in man (Miller and Kind, 1962; Ndiritu and Enos, 1977; Schalm, 1979; Watson and others, 1980).

(g) Pseudoallergic and Hypersensitivity Reactions

Pseudo-allergic adverse reactions to NSAIDs are common in man and are probably associated with the protein binding properties of the drugs. Cellular immunity usually results in dermatological signs. Asthma and anaphylactic responses are documented in man. Extrapolating from work in man, care should be exercised in dogs with a known history of hypersensitivity reactions, food allergy or atopy (Szczeklik, 1986).

(h) Pregnancy

Salicylates and other NSAIDs prolong gestation and have demonstrated teratogenicity in certain animal studies. Unless treatment is imperative, NSAID treatment should be avoided in pregnant animals (Heymann, 1986).

3.3.5 Drug Interactions

(a) Antacids and Food

Antacids decrease the gastrointestinal side effects of NSAIDs. However, the rate and extent of absorption of some NSAIDs can be reduced. Administration of NSAIDs and antacids with food may antagonise any antacid-induced reduction in drug absorption (Tolbert and others, 1981). Excretion of active drug is only affected by urinary pH in selected cases where the NSAID is excreted unchanged eg. salicylate. Large doses of oral antacids will raise urinary pH and promote excretion of salicylate (La Du and others, 1972; Day and others, 1983).

Administration of NSAIDs with food decreases the incidence and severity of gastrointestinal side effects. In general, the administration of NSAIDs with food delays and reduces peak plasma concentrations but does not affect total oral bioavailability (Day and others, 1983; Rainsford, 1985; Lombardino, 1985; Brooks, 1986).

(b) Anticoagulants

Displacement of warfarin from plasma proteins is not now thought to be the primary mechanism by which the activity of coumarin anticoagulants is enhanced by phenylbutazone and oxyphenbutazone (Day and others, 1983). Phenylbutazone and oxyphenbutazone inhibit the metabolism of the S-isomer of warfarin. The S-isomer is five times as potent as the R-isomer. Thus, phenylbutazone and oxyphenbutazone both markedly enhance the anticoagulant activity of warfarin (O'Reilly and others, 1980).

At higher doses salicylates appear to inhibit vitamin K dependent synthesis of factors VII, IX, and X but this is not thought clinically significant. Interaction with warfarin has not been closely investigated. Earlier reports that other NSAIDs including aspirin, diflunisal and meclofenamate potentiated the effect of warfarin on prothrombin complex activity are now believed to be incorrect. In more recent work, none of the NSAIDs has shown any effect. NSAIDs *will* augment any bleeding tendency induced by anticoagulant therapy because of their effects on platelets and gastrointestinal bleeding (Day and others, 1983). NSAIDs will displace other highly plasma protein bound drugs which may have significance where the displaced drug has a narrow therapeutic index (McKellar, 1989).

(c) Diuretic and Hypertensive Drugs

The hypotensive effects of propranolol are inhibited by indomethacin, the effect possibly due to the inhibition of vasodilatory prostaglandin induction or direct sodium retentive effects (Watkins and others, 1980). The hypotensive actions of hydralazine, prazosin, captopril or a reduced sodium diet are inhibited by indomethacin in man. The diuretic and natriuretic effects of frusemide are inhibited by aspirin or indomethacin. The effect may involve the inhibition of prostaglandin-mediated vascular effects of frusemide. Where NSAIDs are administered concurrently with ß-blockers, antihypertensives or diuretics the doses of the latter drugs may need to be increased to have the same desired effect (Day and others, 1983).

(d) Corticosteroids

Patients treated concurrently with corticosteroids and aspirin have higher rates of clearance of salicylate. As the dose of steroid is reduced, plasma salicylate concentrations may rise (Muirden and Barraclough, 1976). Corticosteroids may potentiate the ulcerogenic activity of the NSAIDs (Hamori and others, 1968; Day and others, 1983; Cosenza, 1984; Ivey, 1986).

(e) NSAID Combinations

NSAID combinations often increase the incidence of adverse reactions without an increase in efficacy. Co-administration of salicylates with other NSAIDs reduces the plasma concentrations of the other NSAID. In rare cases the combination product may have enhanced activity. Generally, however, it is advised that single NSAIDs are used rather than NSAID combinations (Day and others, 1983).

3.3.6 NSAIDs and Cartilage

In man, indomethacin has been associated with increased joint destruction in cases of hip osteoarthritis (Rönningen and Langeland, 1979). Early theories proposed that pain relief encouraged increased usage of the joint and so increased further damage. It has also been suggested that the mechanism of disease promotion was interference with the repair of microfractures in the subchondral bone by prostaglandin synthesis inhibitors. Aspirin treatment of dogs with experimental anterior cruciate ligament transection increases the degeneration of cartilage (Palmoski and Brandt, 1983b).

At concentrations approximating to normal pharmacological plasma levels, salicylate had no effect on degradation of proteoglycan in normal cartilage *in vitro* (Palmoski and Brandt, 1979). However, it is believed that inhibitors of prostaglandin synthesis may also inhibit proteoglycan biosynthesis. Salicylate and other NSAIDs have been found to inhibit proteoglycan synthesis in normal canine articular cartilage (Kalbhen and others, 1967). Diclofenac, indomethacin, piroxicam and sulindac sulphide have no significant inhibitory effect on proteoglycan synthesis in normal canine articular cartilage (Palmoski and Brandt, 1980).

The suppressive effect of salicylates on proteoglycan synthesis have been found to be more profound in osteoarthritic cartilage, where basal proteoglycan synthesis is 3 to 5 times that in normal cartilage (Palmoski and others, 1980). This was not a general chondrocyte toxic effect, since net protein synthesis was not affected. It has been suggested that NSAIDs may inhibit enzymes involved in the early stages of chondroitin sulphate synthesis such as UDP glucose dehydrogenase. Oral aspirin administration to dogs with developing osteoarthritis aggravated the degeneration of articular cartilage. There was no apparent effect on *normal* cartilage *in vivo* (Palmoski and Brandt, 1983a,b).

In chickens, intraarticular injection of NSAIDs including ibuprofen, phenylbutazone, sodium salicylate, fenamic acid and indomethacin causes severe osteoarthritic changes (Kalbhen and others, 1978). Oral treatment with aspirin, phenylbutazone, indomethacin, ibuprofen and naproxen of mice with a genetic predisposition to an osteoarthrosis (C57 black mice) promoted the development of osteoarthrosis. Diclofenac showed chondroprotective effects and pirprofen had no effect (Maier and Wilhelmi, 1979; 1982).

The effect of salicylate on degenerative cartilage *in vivo* with sparing of normal cartilage may be related to the proteoglycan concentration of the matrix and the resultant decrease in fixed negative charge density of the glycosaminoglycan polymers which allows increased diffusion of weakly anionic NSAIDs into the cartilage. Proteoglycan depletion rather than cartilage fibrillation determines the effect of salicylate and indomethacin on osteoarthritis cartilage (Palmoski and Brandt, 1985). There is no evidence that the chondrocyte of osteoarthritic articular cartilage is any more susceptible to the effects of salicylate or other NSAIDs on proteoglycan metabolism (Slowman and Brandt, 1987). The proteoglycan metabolism effect appears to be unrelated to their inhibitory effects on prostaglandin synthesis (Palmoski and Brandt, 1984). *In vitro* experiments have indicated that the variation in the effects of different NSAIDs on joint cartilage is related to the drug concentration in synovial fluid which is dependent upon the dose administered, which in turn depends upon the potency and toxicity of the drug (Palmoski and Brandt, 1985).

Antiinflammatory agents can combine antagonistic effects and in any given situation it is hazardous to predict the predominance of anti-anabolic or anti-catabolic activity (Wilhelmi, 1983). It has been proposed that aspirin may inhibit the release of lysosomal hydrolases and that the beneficial effects of aspirin on synovium may be more important than any detrimental effects on articular cartilage (Miller and Smith, 1966). Cartilage degeneration has been demonstrated to be inhibited by salicylate by some investigators (Simmons and Chrisman, 1965). In Guinea Pigs with osteoarthritis induced by transection of the anterior cruciate ligament, neither piroxicam nor indomethacin had any positive or negative effect on clinical progression. The protein concentration of the cartilage matrix was altered in treated animals (Baragi and Schwartz, 1986).

Normal chondrocyte proteoglycan synthesis is not inhibited by diclofenac, a potent inhibitor of cyclooxygenase. This property is not due to partitioning such that diclofenac failed to reach the chondrocytes (Brandt and others, 1988). Kalbhen and others (1987) have found that diclofenac has a stimulatory effect on chondrocytes *in vitro* and has chondroprotective properties.

The effect of piroxicam on normal articular cartilage has been studied. In isolated articular cartilage, piroxicam has no effect on cell proliferation nor on incorporation of radiolabelled sulphate into matrix macromolecules. *In vivo*, dogs treated with piroxicam for 8 weeks had no ultrastructural differences to normal controls. At concentrations *in vitro* which are comparable to therapeutic serum levels, piroxicam was found to suppress catabolism-inducing factor(s) in osteoarthritis in 11 of 12 specimens. There was no inhibition of total protein synthesis: drug-induced suppression was selective (Mohr and others, 1984).

Herman and others (1986) found piroxicam to have no significant effect on proteoglycan release from normal cartilage and the investigators proposed that the drug-mediated effects were at the level of the synovial tissues. Indomethacin and salicylate had no effect on the synthesis of catabolism-inducing factor by osteoarthritic synovium. There was no *consistent* blocking effect on osteoarthritis catabolic factor activity using any of the NSAIDs studied. However, the investigators concluded that piroxicam may be an effective blocker of catabolism-inducing factor generated in rheumatoid arthritis synovium, if not in osteoarthritis synovium (Herman and others, 1987). Piroxicam does not inhibit sulphate incorporation into proteoglycans or cell proliferation (Mohr and others, 1983). Recent studies have demonstrated chondrocyte stimulation by piroxicam *in vitro* (Poriau and others, 1987).

It has been stated by some authors that the inhibitory effects of antirheumatic drugs on proteoglycan synthesis are negligible compared with their ability to inhibit degradative enzyme damage of cartilage (Chrisman and others, 1981b). Some authors have suggested that NSAID effects on serum sulphate concentrations may contribute to chondrocyte proteoglycan synthesis inhibition (deVries and others, 1988). Ghosh (1988) concludes that the *in vivo* significance of all the experimental evidence for cartilage effects of NSAIDs is still uncertain. However, it may be desirable to use a NSAID which has proven chondroprotective or no chondrocyte inhibitory effects (eg diclofenac, piroxicam, pirprofen, ketoprofen).

3.4 The Available Data on Individual NSAIDs and their Use in the Dog

3.4.1 Aspirin and Other Salicylates

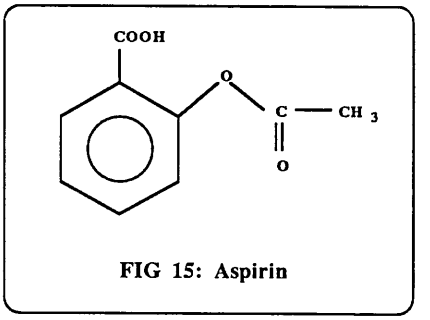


FIG 15: Aspirin

Aspirin is rapidly hydrolysed in plasma to salicylate. Peak concentration of salicylate are attained 1 to 2 hours after plain aspirin is administered per os. Salicylate is about 60-70% plasma protein bound. The half life of the salicylate is dose-dependent, increasing as the administered dose of salicylate is increased.At usual dosages the mean plasma half life in the dog is 8 to 9 hours (Davis and Westfall, 1973). A decrease in blood pH will lead to a decrease in drug ionisation and increased distribution. Synovial fluid concentrations of salicylate are approximately one half of the plasma concentrations (Rowland and others, 1967).

Therapeutic plasma concentrations of salicylate are considered to be 100 to 300 ug/ml by some authors (Yeary and Brandt, 1975) but as little as 50 ug/ml by others (Davis, 1980). Twenty-five mg/kg every 8 hours maintains therapeutic concentrations of 170-190 ug/ml (Yeary and Brandt, 1975). Peak concentrations are attained 4 hours after buffered aspirin is given and up to 8 hours after enteric coated aspirin (EC.ASA) is given. EC.ASA produces the greatest fluctuations in serum salicylate concentration (Lipowitz and others, 1986).

Most dogs tolerate aspirin well. However, any dosage can cause gastroduodenal ulceration (Cosenza, 1984). Emesis, gastric haemorrhage and abdominal pain have been well documented (Hurley and Crandal, 1964; Taylor and Crawford, 1968; Fisher and others, 1972). Fifty to 100 mg aspirin/kg/day consistently induces gastric pathology. Doses over 50 mg/kg often induce emesis (Yeary and Brandt, 1975). Overt gastrointestinal haemorrhage can occur after a single dose of aspirin in man. This is thought to be an idiosyncratic reaction (Ivey, 1986).

Plain aspirin is most irritating to the gastric mucosa (Lipowitz and others, 1986). Buffered aspirin preparations are associated with reduced epigastric discomfort but they do not reduce gastrointestinal damage (Day and others, 1983). Enteric coated aspirin (EC.ASA) preparations are associated with less enteric blood loss since the small intestine is less affected by local effects than the stomach (Lipowitz and others, 1986).

Since absorption of aspirin from enteric coated preparations is delayed for six hours or more, use is restricted to long-term medication. Food postpones the exit of EC.ASA tablets from the stomach and delays peak plasma concentrations of salicylate after EC.ASA administration. Multiple meals can cause completely unpredictable patterns of plasma salicylate concentration (Nap and others, 1989). Smaller EC.ASA granules may not be retained in the stomach and so may allow more predictable and rapid plasma concentrations of salicylate to be achieved (Anslow and others, 1984).

Allergy or pseudoallergic intolerance to aspirin occurs in man. No allergies are documented in animals. Aspirin has been associated with congestive cardiac failure and pulmonary oedema in man. Acute poisoning can occur with aspirin. Clinical signs include vomiting, abdominal pain, CNS signs and hypokalaemia in the early stages. In the later stages the signs are pyrexia, pulmonary oedema, convulsions, coma, severe dehydration and ketosis, and death may occur.

In the dog, it has been reported that therapeutic plasma concentrations of salicylate are not maintained by use of plain aspirin at 10 mg/kg every 8 hours. Twenty-five mg/kg every eight hours of plain, buffered or enteric coated aspirin are effective (Yeary and Brandt, 1975; Lipowitz and others, 1986). Other authors suggest 10-20 mg/kg every 12 hours may be clinically effective (Davis, 1980; Haskins, 1987; Jenkins, 1987). Clinical experience suggests that the lower dose rate provides analgesic effect (Carmichael, 1989). Aspirin is still the most popular drug for the treatment of osteoarthritis in man and the standard by which other drugs are judged. It has been stated that in the face of more effective and potentially less toxic NSAIDs, the salicylates probably have no place in veterinary medicine (Yoxall, 1978).

Diflunisal is a fluorophenyl derivative of salicylic acid. Unlike aspirin, it does not possess an O-acetyl group and so it does not acetylate proteins. The activity of diflunisal is intrinsic and not related to *in vivo* conversion to salicylate. Diflunisal has approximately three to ten times the anti-inflammatory activity of aspirin.

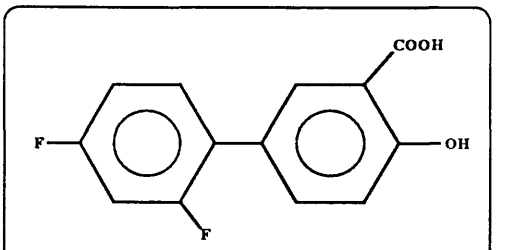


FIG 16: Diflunisal

In man, diflunisal has reduced gastric effects and ototoxicity compared with aspirin. Cross-allergy with aspirin may occur (Lombardino, 1985). A single dose of 10 mg/kg in dogs had no adverse effects on gastric secretion volume or acidity. In the dog, diflunisal apparently has similar side effects to aspirin on the gastrointestinal tract and kidney but with a higher therapeutic index. In one canine study, oral dosing at 25 mg/kg/day for 3 months had no toxic effects. It has not been properly evaluated for efficacy and toxicity in dogs to date.

3.4.2 Phenylbutazone and Other Pyrazolones

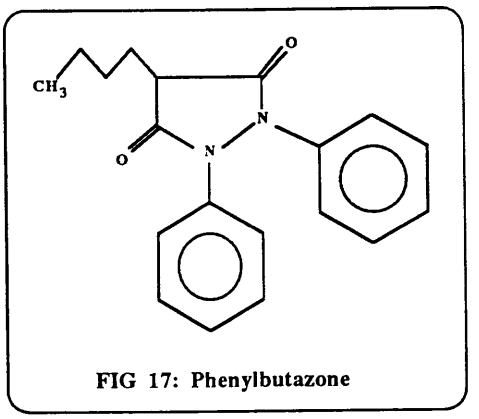


FIG 17: Phenylbutazone

Phenylbutazone has been withdrawn from general availability on prescription for human use in the UK because of toxicity; notably fluid retention (sufficient to cause cardiac failure), aplastic anaemia, and agranulocytosis. In the last twenty years at least 1000 people have died from aplastic anaemia or neutrop enia associated with the use of phenylbutazone or oxyphenbutazone (Brooks and others, 1986). It is still licensed to treat ankylosing spondylitis under specialist supervision.

Phenylbutazone is rapidly and completely absorbed from the small intestine and is extensively protein bound (Brooks and others, 1986). After intramuscular injection of phenylbutazone absorption is delayed compared with oral administration, probably because of local tissue binding and precipitation. Intramuscular injection is also very painful and very irritant, especially to nervous tissue. In man, accidental injection close to nerves has been associated with nerve damage (Fowler, 1983).Plasma half life of phenylbutazone in the dog has been reported to range from 1.3 to 5.2 hours (McKellar, 1989).

The pyrazolone derivatives induce drug metabolising microsomal enzymes in the liver. As a consequence, tachyphylaxis to phenylbutazone can develop over a period and the dose rate required for a beneficial effect may need to be increased. Phenylbutazone metabolism is accelerated by hepatic microsomal inducers such as phenobarbitone, griseofulvin and phenytoin and is inhibited by the phenylbutazone metabolite oxyphenbutazone.

Recognised contraindications to phenylbutazone treatment are existing peptic ulceration, liver disease, bleeding disorders and cardiac insufficiency (Fowler, 1983). Adverse reactions are widely reported in the dog, including an "idiosyncratic reaction" in a Dachshund (Tandy and Thorpe, 1967). Myelotoxicity and blood dyscrasias have been reported in the dog, but seem to be less common than in man (Miller and Kind, 1962; Ndiritu and Enos, 1977; Schalm, 1979; Watson and others, 1980). Phenylbutazone appears less toxic in the dog than in man. This may be associated with the much shorter half life in the dog (<6 hours cf. 72 hours in man).

A dose rate of 22 mg/kg every eight hours has been recommended by some authors (Haskins, 1987; Rubin and Papich, 1988). To maintain therapeutic plasma concentrations a dose regime of 15 mg/kg qid has been recommended (Nielson and others, 1969). Other authors suggest up to 20 mg/kg/day divided is sufficient (Taylor, 1987).

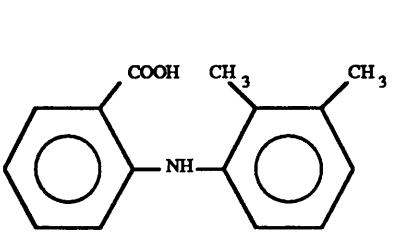
Azaproprazone is reported to have low toxicity, but blood levels are not readily achieved in dogs. In man, the dosage of azaproprazone is 10-20 mg/kg/day. In the dog, to achieve similar plasma concentrations a daily dosage of 60-120 mg/kg would apparently be required (Jones, 1976). This dose rate will cause adverse reactions, at least in certain breeds. Beagle dogs treated at 25-100 mg/kg/day rapidly showed toxicity with signs including anorexia, rapid weight loss, anaemia, reticulocytosis and leukocytosis, blood in faeces, pyloric ulcers, gastrointestinal inflammation and deaths. Azaproprazone also had effects on bone marrow. Beagles seem to be particularly sensitive to the gastrointestinal effects of azaproprazone since mongrel dogs treated at 50 mg/kg/day for 12 weeks showed no clinical signs or post mortem pathology (Walker, 1985).

Dipyrone administered at 50 mg/kg orally is rapidly and almost completely absorbed to give maximum blood concentrations of about 40 ug/ml 1.5-2 hours after dosing. The elimination half life is about 5 hours (Christ and others, 1973). Booth (1982) recommends 30 mg/kg sid or bid for chronic treatment. In man, skin rashes are common but gastrointestinal signs are rare (Brogden, 1986).

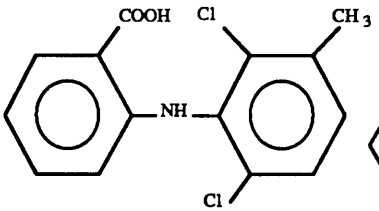
3.4.3 Fenamates

The fenamates are N-arylanthranilic acids. Their structure is related to that of flunixin and diclofenac (FIG 17). The fenamates inhibit prostaglandin synthesis (Scherrer, 1985; Brooks and others, 1986). Meclofenamic acid is one of the most potent inhibitors known (Scherrer, 1985). The prostaglandin synthesis inhibitory effects of the fenamates are enhanced up to 100 fold in the presence of certain enzyme "cofactors" such as phenols and indoles (Egan and others, 1978).

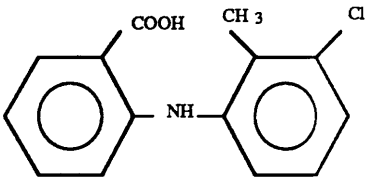
The antiinflammatory activity of the fenamates does not correlate well with prostaglandin biosynthesis inhibition and other mechanism of action may be important. The fenamates also inhibit some of the actions of some prostaglandins at physiological concentrations. It has been suggested that the fenamates inhibit the tissue response to prostaglandins by occupying receptor sites. Not all prostaglandins or all actions are inhibited and there is variation in potency between species (Scherrer, 1985).



Mefenamic Acid



Meclofenamic Acid



Tolfenamic Acid

FIG 18

Mefenamic acid is rapidly absorbed after oral administration with peak plasma concentrations in a maximum of 2 to 4 hours. In dogs, most of the drug is excreted in the faeces with only small amounts appearing in the urine. Enterohepatic recirculation occurs to a varying extent in different species. Oral administration of mefenamic acid to dogs at 50 mg/kg 5 days per week for 103 consecutive weeks was not associated with any adverse clinical signs or tissue reaction. At 100 mg/kg/day, slight hepatic damage was reported at histological examination. 300 mg/kg/day divided for four consecutive weeks was not associated with clinical signs or tissue reaction (Parke-Davis Veterinary).

Tolfenamic acid is available for use in dogs and cats in France (Tolfedine®). A human preparation is also available (Clotan®). It can be administered by subcutaneous, intramuscular or oral routes. When administered subcutaneously at 4 mg/kg tolfenamic acid had a plasma half life of 6.9 hours (± 1.9 hours) with maximum plasma concentrations of 4.4 (±0.6) ug/ml at about 1.5 hours after administration. Serum thromboxane levels were inhibited by up to 80% at this dose rate (McKellar and Galbraith, 1989). Enterohepatic recirculation has been reported (Vetoquinol Advertising Literature; McKellar and Galbraith, 1989).

Haskins (1987) suggests that meclofenamic acid (Arquel®) can be used in dogs at a dose rate of 2.2 mg/kg/day. However, the drug manufacturers (Parke-Davis Veterinary) and Taylor (1987) suggest that 0.5-1 mg meclofenamic acid/kg/day divided for up to 21 days may be more appropriate. Taylor (1987) advises that, for a maintenance regime, the dose rate is decreased to every second or third day after 1 to 3 weeks. Arquel® is available in sachets for use in horses. Each 10g sachet contains 500 mg which is sufficient for a dog weighing between 500 and 1000 kg! Very small quantities will require to be weighed out for use in dogs. A 25 kg dog will require between 0.25 and 0.5 g/day (Parke-Davis Veterinary).

Mefenamic acid (Ponstan®) may be useful at 10-40 mg/kg/day in divided doses (Taylor, 1987). The manufacturer suggests a dose rate of 40-60 mg/kg divided b.i.d. After 1 to 3 weeks, the dosage should be reduced to 10-60 mg/kgin divided daily doses on every second or third day (Parke-Davis Veterinary). Ponstan® is available as 25 mg capsules, a 50 mg/ml suspension or as 250 mg and 500 mg tablets.

A dosage of 4 mg tolfenamic acid/kg/day divided in two doses is said to maintain satisfactory plasma concentrations without accumulation of the product. The recommended period of treatment is only 3 to 5 days (Vetoquinol Advertising Literature).

The fenamates are the preferred analgesics of some authors and at some veterinary colleges. The main problem associated with their use is diarrhoea. Diarrhoea does not seem to be dose related and usually resolves in 3-4 days whilst treatment continues. In dogs in which diarrhoea continues, the dose should be reduced or treatment withdrawn and reinstituted at a lower dose rate once the diarrhoea resolves. In most cases the diarrhoea resolves. Treatment should be withdrawn if diarrhoea is severe or if there is blood in the faeces. Vomiting and renal toxicity have been reported (Parke-Davis Information).

3.4.4 Flunixin

Flunixin meglumine is a potent NSAID which is approved for use in the horse in many countries including UK and USA. Oral and injectable preparations have recently been approved for use in dogs in the UK. Flunixin is a more potent analgesic than aspirin or phenylbutazone.

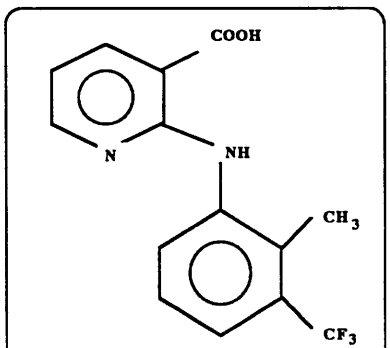


FIG 19: Flunixin

The duration of clinical efficacy of the drug in dogs does not correlate with the relatively short half life (Rubin and Papich, 1988) of 3.7± 1.2 hours after intravenous injection (Hardie and others, 1985). After oral administration at 1.1 mg/kg , flunixin is rapidly absorbed. Peak plasma concentrationsof 4 to 6 ug/ml occur about one and a quarter hours after drug administration and flunixin has a plasma half life of 2 to 3 hours. (McKellar and Lees, 1989; McKellar and others, 1989). More recent studies have indicated that the elimination half life may be much longer (14-15 hours) than indicated in earlier studies (McKellar and Galbraith, 1989). In a clinical trial on an oral formulation in dogs, flunixin was as effective as phenylbutazone in the treatment of chronic musculoskeletal pain and inflammation (Kelly and Benitz, 1988).

The suggested dose rate of flunixin is 1.1 mg/kg daily for up to 3 days, with the course repeated no more often than every 2-3 weeks. Daily treatment intervals can be used since flunixin has been shown to persist in inflammatory tissue (Lees and others, 1987). Flunixin has a narrow therapeutic index in the dog but the once a day treatment regime will allow almost complete elimination of the drug from plasma and so reduce the potential for toxicity and accumulation (Rubin and Papich, 1988). However, flunixin can only be used for up to 3 days since longer term use has been shown to cause gastrointestinal inflammation and ulceration (Cosenza, 1984). No problem with reduced analgesia at the end of the inter-dosing period has been identified in clinical trials (Benitz and Lichtenwalner, 1986).

3.4.5 Piroxicam

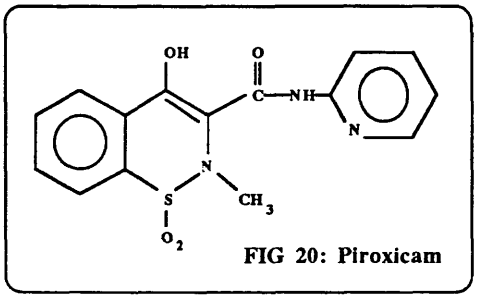


FIG 20: Piroxicam

The oxicams are a novel group of NSAIDs which are N-heterocyclic carboxides of 1,2-benzothiazine-1,1-dioxide (Brooks and others, 1986). Piroxicam is the most popular of the oxicam class. In the dog, peak plasma concentrations of piroxicam are reached around two hours after oral administration. Piroxicam has an extended plasma half-life of 37 to 40 hours in the dog (Lombardino and others, 1973; Wiseman, 1983). It is completely absorbed from the gastrointestinal tract and is 99% plasma protein bound. Enterohepatic recirculation in man maintains plasma concentrations and extends the half life (Wiseman, 1983). The similar kinetics in the dog suggest that enterohepatic recirculation occurs. Piroxicam accumulates in synovial fluid (Brooks and others, 1986). No clinically important interactions with other drugs have been reported in man (Wiseman, 1983; Wiseman, 1985).

In man, therapeutic doses of piroxicam are better tolerated than those of indomethacin, phenylbutazone or aspirin. In dogs, piroxicam has been used at a dose rate of 0.3 mg/kg every 48 hours in clinical cases of osteoarthritis and for analgesic and antiinflamnmatory effect post-operatively at Glagow Veterinary School since 1984 with an incidence of side effects approximately equivalent to or better than that of other NSAIDs. Gastrointestinal intolerance is most common and diarrhoea is more common than emesis.

Gastrointestinal ulceration and haemorrhage have been reported in a dog treated for ten days with piroxicam at 0.8 mg/kg every 48 hours (Thomas, 1987). In dogs treated for 12 to 18 months at 1mg/kg/day renal papillary necrosis has been reported (Wiseman, 1983). Transient rises in liver enzymes are reported in man. The therapeutic index of piroxicam is superior to that of aspirin in the dog (Teelman, 1983).

In man, piroxicam has a rapid onset of action. Analgesia is effected in less than 2 hours in most cases and the effect of piroxicam fades about 48 hours after treatment is withdrawn (Wagenhauser, 1980). The long duration of action of piroxicam also means that night time pain relief is often improved in comparison with shorter duration NSAIDs, sleep may be more sound and morning stiffness decreased (Wiseman, 1983). In man, piroxicam has been shown to be a more effective analgesic than aspirin in the therapy of osteoarthritis (Gordon and others, 1980). Improved effects are apparent when treatment for osteoarthritis is continued for longer periods (Pitts and others, 1982). Piroxicam has equivalent efficacy to aspirin, naproxen and indomethacin whilst it is generally better tolerated. It is more effective than indomethacin and equivalent to phenylbutazone in acute musculoskeletal disorders (Wiseman, 1985).

In the dog, the long half life of piroxicam means that dosing once a day or every other day maintains therapeutic concentrations. It has high potency and so a low dose of 0.3 mg/kg every 48 hours seems effective and well tolerated. Some authors have stated that piroxicam should not be recommended for use in dogs until further safety and efficacy studies have been performed (Rubin and Papich, 1988).

3.4.6 Propionic Acid Derivatives

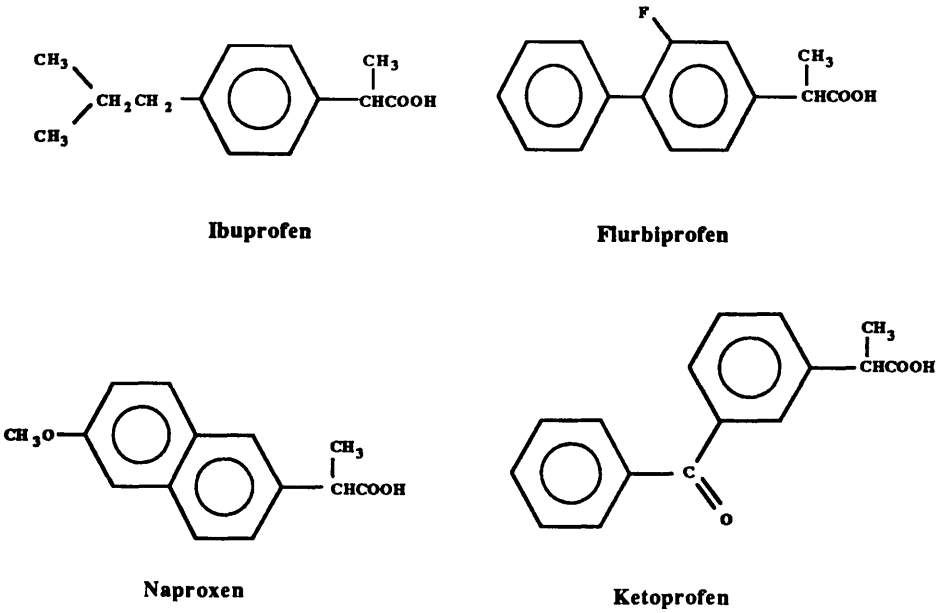


FIG 21: Some of the Propionic Acid Derivatives

With the exception of Naproxen, the Propionic acid derivatives are administered as racemates (mixtures of enantiomers). In most cases only the S (Sinister) form is active. *In vivo* conversion of the R to the S form has been demonstrated for some of the propionic acid derivatives and may increase their efficacy *in vivo* (Brooks and others, 1986).

Naproxen

Naproxen is rapidly absorbed after oral administration and peak plasma levels occur at 0.5 to 3 hours. Naproxen is 68-100% bioavailable orally (Frey and Rieh, 1981). It is 99% plasma protein bound. The half life of naproxen in the dog varies from 35 (Runkel and others, 1972) to 92 hours (Frey and Rieh, 1981) compared to 6 hours in the horse and 12 hours in man. Enterohepatic recirculation is proposed as the mechanism which causes the prolonged half life of naproxen in the dog. The dog is the only species investigated in which faecal excretion predominates. Slow elimination is not due to extensive protein binding since the horse and man have similar degrees of protein affinity but much shorter half-lives (Frey and Rieh, 1981).

Naproxen has been used in man (Naprosyn®) and the horse (Equiproxen®) without a high incidence of adverse effects (Allison and others, 1985). Although the single toxic dose of naproxen in the dog is high (LD50 > 1g/kg), dogs are relatively intolerant of the gastrointestinal effects of naproxen. Gastrointestinal changes are observed in dogs treated at 5 mg/kg/day whilst 15 mg/kg/day is toxic. A dose of 1.5 mg/kg/day is tolerated for 3 months without signs of toxicity (Hallesy and others, 1973). There are many reports of naproxen-induced gastroenteropathy in dogs in the literature (eg. Roudebush and Morse, 1981; Steel, 1981; Gilmour and Walshaw, 1987). This is apparently related to predominantly biliary excretion and less urinary excretion in the dog compared to other species (Segre, 1983).

In various clinical trials in man, naproxen has equivalent or greater efficacy to aspirin (Segre, 1983) and has the advantage of requiring only one daily dose. Therapeutic concentrations of naproxen (>30 ug/ml) can be maintained when naproxen is administered at 1.2-2.8 mg/kg once daily (Frey and Rieh, 1981). It appears that naproxen can be used with caution in the dog at a once daily maintenance dose of 2 mg/kg/day with or without a single loading dose of 5 mg/kg (Jenkins, 1987; Rubin and Papich, 1988). However, the dog appears to be particularly sensitive to gastrointestinal side effects of naproxen.

Ibuprofen

Ibuprofen is rapidly absorbed after oral administration and is 96% plasma protein bound. Maximum plasma concentrations are attained between 0.5 and 3 hours after oral administration. Its elimination half life in the dog is about 3.5 to 6 hours (Scherkl and Frey, 1987). Some authors have reported that ibuprofen is metabolised slowly in the dog (Mills and others, 1973).

Ibuprofen is a popular drug in man because it is associated with a lower incidence of gastrointestinal adverse reactions than the salicylates (Smith and others, 1985). It is available without prescription in the UK. However, the drug appears to cause gastric irritation and ulceration more frequently in dogs. Gastrointestinal toxicity may relate to enterohepatic recirculation in this species. It has also been suggested that dogs are at increased risk of gastrointestinal ulceration due to ibuprofen treatment because of a higher rate of gastrointestinal absorption, longer drug half life, and prolonged blood concentrations (Adams and others, 1969).

There are a number of reports of ibuprofen toxicity in dogs. Acute ingestion of large doses can cause vomiting, diarrhoea and renal dysfunction (Spyridakis and others, 1986). Earlier papers advocated use of ibuprofen at a maintenance dose of 16 mg/kg/day (Yoxall, 1978). However, treatment with ibuprofen at 12-15 mg/kg/day causes repeated and consistent vomiting (Scherkl, 1987). Recent papers suggest a dose rate of 8 mg/kg/day *may* be better tolerated (Taylor, 1987; Rubin and Papich, 1988) or that 10 mg/kg every 24 to 48 hours may be useful (Jenkins, 1987). However, Lessel (1970) found that dogs treated at 8 mg/kg/day for 30 days developed gastric ulceration. In an earlier study, dogs treated with ibuprofen at 8 mg/kg/day for 30 days showed no clinical signs but intestinal inflammation and gastric ulceration were apparent at necropsy (Adams and others, 1969). Haskins (1987) suggests a dose rate of 5 mg/kg/day.

Ibuprofen is generally not recommended for routine use because of its gastrointestinal toxicity and because it offers no advantage over less toxic analgesics such as aspirin and phenylbutazone (Rubin and Papich, 1988).

Flurbiprofen has a half-life in the dog of 35-40 hours. It is largely excreted in the urine unchanged and no metabolites have been detected in canine plasma. Enterohepatic recycling is very probable in the dog (Risdall and others, 1978). Severe dose related gastrointestinal damage at 1-16 mg/kg has been described. Flurbiprofen is much more toxic in dogs than in other species. There have been several reports of severe gastrointestinal adverse reactions and nephrotoxicity (Correspondence, 1987). Flurbiprofen should not be used in the dog.

Ketoprofen

Ketoprofen is a mixed inhibitor of the cyclooxygenase and lipoxygenase pathways and has potent antibradykinin activity (Julou and others, 1976a,b; Dawson and others, 1982; Walker, 1980; Julou and others, 1971). It has structural similarities to arachidonic acid and to Leukotriene A4 (Harris and Vavra, 1985). Ketoprofen has potent analgesic and antiinflammatory activity. It has not demonstrated any damaging effects on articular cartilage.

Studies in the dog at 1 mg/kg have indicated less than 90% absorption with peak plasma levels of 1.5 ug/ml at 1 hour. Ketoprofen is eliminated in a complex manner and the terminal phase of elimination (half life = 34 hours) accounts for negligible amounts of absorbed ketoprofen. Primary and secondary phases of elimination have much shorter half lives of 0.85 hours and 4.3 hours respectively. Excretion is primarily as conjugates in the urine (Populaire and others, 1973; Heusse and Populaire, 1978; Upton and others, 1981). The dose recommended in man is 3-4 mg/kg/day. More rapid clearance and lower peak plasma concentrations in the dog suggest that higher and more frequent dosages would be required to maintain therapeutic concentrations. In man, controlled-release oral preparations allow single daily dosing convenience whilst ketoprofen may have increased safety compared to NSAIDs with longer half lives because it is rapidly eliminated (Harris and Vavra, 1985). Slow release preparations may be of use in the dog. Further study is required on the efficacy and safety of ketoprofen in dogs.

Fenbufen

Fenbufen is a prodrug and has no intrinsic inhibitory activity on prostaglandin synthesis. After absorption it is converted to the active metabolite biphenylacetic acid (BPAA) which is a potent cyclooxygenase inhibitor and has marked antiinflammatory activity. The duration of action is much longer than for indomethacin, aspirin or phenylbutazone (Greenberg and Bernstein, 1985).

In the dog, fenbufen is rapidly and completely absorbed after oral administration and peak plasma concentrations are attained in 1-2 hours. Relatively high plasma concentrations of BPAA are maintained for seven hours. Elimination is mainly in the urine as diol derivatives. Fenbufen and its metabolites are over 98% protein bound at therapeutic concentrations (Chiccarelli and others, 1980). Fenbufen should have less gastrointestinal toxicity than other NSAIDs in the dog since there should be no local effects on prostaglandin inhibition. Doses of 16 and 40 mg/kg/day for 18 months were non-ulcerogenic in dogs. 100 mg/kg/day did induce ulcers (Sloboda and Osterberg, 1976). Fenbufen may prove a useful drug in the dog.

3.4.7 Acetic Acid Derivatives

Indomethacin

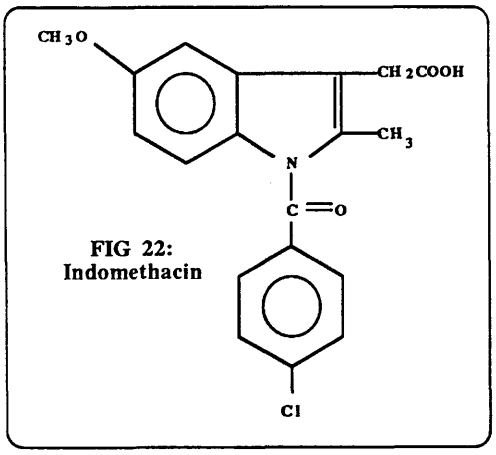


FIG 22:
Indomethacin

Indomethacin is a very effective antiinflammatory, analgesic and antipyretic. However, indomethacin has a high potential for gastrointestinal toxicity in carnivores and gastrointestinal haemorrhage after its use has been widely reported. Extensive enterohepatic recirculation may contribute to indomethacin's toxicity by repeatedly reexposing the gastrointestinal mucosa to high concentrations of the drug. A dose of 0.5 mg/kg can be toxic in dogs compared to the toxic dose in man of about 20 mg/kg (Duggan, 1975). Authors agree that indomethacin is not suitable for use in the dog because of its common and wide ranging side effects (Nicoloff, 1968; Ewing, 1972; Duggan, 1975).

Sulindac

Sulindac has a similar structure to indomethacin. It is a pro-drug and is only converted to an active metabolite in the body or by gut flora (FIG 22). The active sulphide inhibits both cyclooxygenase and lipoxygenase pathways and can act as a free radical scavenger. Only small amounts of the active sulphide are excreted in the bile. Sulindac and its sulphone metabolite are excreted in the bile and can be converted to active sulphide by the gut flora and reabsorbed (enterohepatic recirculation). Thus, the gastrointestinal tract is exposed predominantly to prodrug and repeat exposure to active sulphide is limited. It would be expected that gastrointestinal effects would be lessened. Sulindac demonstrates low activity on renal cyclooxygenase which may be due to an inherent lower sensitivity of this isoenzyme to the drug or to differential distribution and formation of the sulphide (Rhymer, 1983). Sulindac may therefore be less nephrotoxic than other NSAIDs.

Sulindac has been demonstrated to be more effective than aspirin in osteoarthritis in man and better tolerated and equivalent to ibuprofen. Gastrointestinal side effects are the most common but abnormalities of liver function, dermatological and central nervous system signs, oedema, congestive cardiac failure, thrombocytop enia and leucop enia have all been reported (Rhymer, 1983; Brooks and others, 1986). Sulindac has not been assessed for use in dogs.

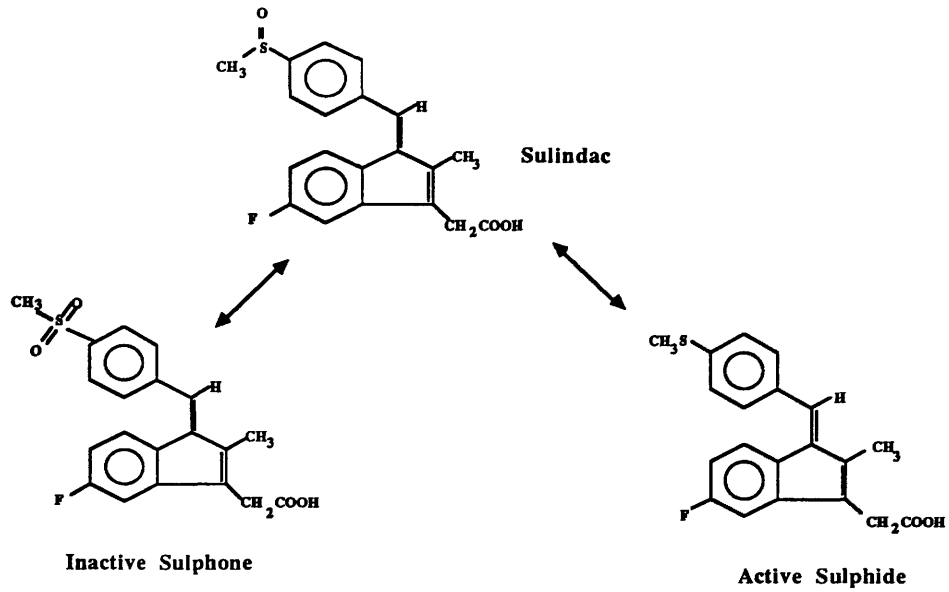


FIG 23: Sulindac and its Metabolites

Diclofenac has a protective effect on cartilage in certain animal models (see 3.3.6). It is a popular drug in man since gastrointestinal tolerance to diclofenac is greater than that for aspirin (Brooks and others, 1986). However, during chronic administration to dogs, adverse reactions included gastrointestinal haemorrhage, ulceration and perforation and secondary anaemia. Side effects were more common than in studies in primates. The increased toxicity in the dog is probably dependent upon the different metabolism in this species. In man, hydroxylation and taurine conjugation followed by urinary excretion is the main elimination pathway. In the dog up to 80-90% of excretory products are direct conjugates in the bile. The direct conjugate is rapidly hydrolysed in the gut to yield the active drug which is reabsorbed (ie. enterohepatic recirculation). Enterohepatic recirculation prolongs plasma half life and increases the local exposure of the intestinal mucosa to active drug and so is most probably responsible for the relative intolerance of dogs to gastrointestinal effects (Reiss and others, 1978; Willis and Kendall, 1978; Tsuchia and others, 1980).

Alclofenac has central analgesic activity equivalent to codeine and antiinflammatory activity equivalent to phenylbutazone. Investigators have reported that vomiting may be a problem in clinical cases. It is relatively slowly excreted in the dog and in this species a dose rate of 50 mg/kg bid has been suggested (Yoxall, 1978).

3.5 Dual Cyclooxygenase and Lipoxygenase Inhibitors

Some of the NSAIDs already used in man such as benoxaprofen have dual inhibitor properties. However, their principal activity is on cyclooxygenase and their clinical effects are believed to be mainly due to inhibition of prostanoid synthesis. The phenylpyrazoline compound BW755C (3-amino-1-(trifluoromethyl)- phenylpyrazoline) has activity against both lipoxygenase and cyclooxygenase. BW755C was as effective as phenylbutazone in reducing adjuvant induced arthritis in rats and its beneficial effects continued after treatment stopped (Higgs, 1978). In addition, BW755C has no apparent effect on PGI2 synthesis in the gastric mucosa following oral administration (Whittle and others, 1980) and has not been associated with ulcerogenicity. Antileukotrienes and dual inhibitors have not yet been shown to be useful clinically. In some cases (eg. benoxaprofen) toxicity has been a problem; others require large doses. Poor penetration into inflammed tissue has been reported (Lees, 1987).

Dual inhibitors of both arachidonic conversion pathways may have superior efficacy in arthritides where leukotrienes are important mediators. It has been suggested that dual inhibitors of 5-lipooxygenase and cyclooxygenase may be more effective than selective cyclooxygenase inhibitors in rheumatoid arthritis (Griswold and others, 1988).

3.6 Application of Symptomatic Treatment of Osteoarthritis in the Dog

Even with managemental changes, many osteoarthritic dogs still require analgesic therapy. However, it must be explained to owners that although analgesics can affect the symptoms in the short or medium term, the object is to change the progression or activity of the disease state by exercise pattern and weight adjustment. Owners should be warned that they are responsible for preventing their dog from further traumatising an already damaged joint. Pain relief may cause a dog to over-use a damaged joint and cause accelerated disease progression unless the owner controls exercise and obesity.

In contrast to the wide range of analgesic drugs available in man, there are relatively few drugs which have been evaluated for efficacy and tolerance in dogs except as part of the data for registration for human use. Very few NSAIDs have been registered for use in dogs. Registration and marketing may not be considered economically justifiable. NSAID manufacturers may not wish to risk the use of their products in dogs since adverse reactions in animals may reflect badly on their use in man. However, there are a number of NSAIDs which are being tested for use in dogs and other companion animals with a view to future registration for veterinary use.

The non-narcotic analgesics and combinations which are presently available for use in the dog are listed in TABLE 7. Phenylbutazone and flunixin are the only NSAIDs which are formulated without other drugs. Phenylbutazone is the most popular analgesic used to control osteoarthritic symptoms in the dog. It has been widely used for many years and has a good safety record. Flunixin has only recently been registered for use in the dog. It is a potent analgesic but can only be used for a maximum of three days since prolonged therapy often results in gastrointestinal intolerance. In osteoarthritis, this limits its use to the control of pain and inflammation in acute exacerbations.

Three combination products are available. Predno-Leucotropin® Tablets may soon be replaced by PLT ® Tablets. Both contain the NSAID cinchophen in combination with prednisolone. In the former product the urinary acidifier hexamine was also present. The NSAIDs and steroids act at different levels of the arachidonic acid conversion pathways and have complementary actions. Cinchophen and prednisolone may have synergistic activity, but prednisolone may also potentiate the ulcerogenic effects of cinchophen. Available data on cinchophen and prednisolone in combination is detailed in section 5.1.

Paracetamol is available in two combinations. Paracetamol is an analgesic but has little demonstrable antiinflammatory activity according to most authors. In Budale-V® Tablets it is formulated with butobarbitone and codeine. The combination is sedative and so is not appropriate to long term treatment of the osteoarthritic dog. In Pardale-V® Tablets, paracetamol is in combination with codeine and caffeine. Since paracetamol has peripheral analgesic effects and codeine has central activity the two drugs may be synergistic (Messick, 1979; Taylor, 1985). Caffeine is included to potentiate the analgesic component. Caffeine increases renal blood flow and may reduce nephrotoxic effects of NSAIDs. The mild diuretic effect of the drug may increase the rate of urinary excretion. Any action may be due to the general euphoria experienced due to the central stimulatory effects of caffeine but there is little evidence that caffeine is an important ingredient in these combinations (Burgen and Mitchell, 1978).

Many other NSAIDs which are marketed for human use in the UK have been used in the dog. Pharmacokinetic and toxicity studies on NSAIDs have revealed great differences between the species. Many of the NSAIDs have much longer half lives in the dog and most are excreted in the bile rather than in the urine as in man. Enterohepatic recirculation occurs to varying degrees for many of the NSAIDs and prolongs plasma half life and increases the exposure of the gastrointestinal tract to local high concentrations. It is thus potentially very dangerous to extrapolate dosages or toxicity data from one species to another.

Drug	mg/tablet	Trade Name & Manufacturer	Dose Recommendations
Analgesics			
Paracetamol Butobarbitone Codeine phosphate	250 mg 60 mg 10 mg	Budale-V ® Tablets [Arnolds Veterinary Products]	"Medium sized dog": 1-2 tablets every 8 hours [≈ 8 - 25 mg paracetamol/kg every 8 hours]
Paracetamol Codeine phosphate Caffeine hydrate	400 mg 9 mg 10 mg	Pardale-V ® Tablets [Arnolds Veterinary Products]	"Medium sized dog": 1-2 tablets every 8 hours [≈ 15 - 35 mg paracetamol/kg every 8 hours]
NSAIDs			
Phenylbutazone	100 mg 200 mg	Flexazone ® Tablets [BK Veterinary Products]	100-600 mg/day divided; reduce to 50-100 mg/day as maintenance dose. Dose close to feeding.
Phenylbutazone	100 mg 200 mg	Phenogel ® Tablets [Duphar Veterinary Limited]	200 - 600 mg/day. Reduce according to response.
Phenylbutazone	100 mg 200 mg	Phenylbutazone Tablets [Animalcare Ltd.]	2 to 20 mg/kg/day by mouth
Cinchophen Hexamine Quinine HCl	280 mg 100 mg 70 mg	Leucotropin ® Tablets [BK Veterinary Products Ltd.]	≈ 35 - 62 mg cinchophen/kg/day divided bid*
NSAID-Steroid Combination			
Cinchophen Prednisolone Hexamine	200 mg 1 mg 100 mg	Predno-Leucotropin ® Tablets [BK Veterinary Products Ltd.]	≈ 25 - 44 mg cinchophen/kg/day divided bid*

® : Trademark

* : Dosage recommendation expressed in tablets for ranges of weights eg 10 to 20 kg : 1 tablet bid.

Table 7: Oral Preparations Containing Analgesic and Non-Steroidal Antiinflammatory Drugs Registered for Veterinary Use in the United Kingdom (June 1989).

Certain NSAIDs have increased toxicity in the dog. Indomethacin and flurbiprofen have shown serious toxicological reactions and should be avoided. Therapeutic doses of ibuprofen are potentially toxic and diclofenac has increased toxicity in the dog compared to man because it is excreted in the bile. NSAIDs which have been used in dogs with some success and without a high incidence of adverse reactions are listed with dosage recommendations in TABLE 8. An owner should always be warned when the drug used is not registered for use in dogs.

In all NSAID pharmacokinetic studies, one of the most striking findings is the massive variation in plasma concentrations in individual animals (McKellar, 1989). In addition to individual variation in dose-response characteristics, some patients will respond better to one NSAID than to another. The reasons are not known (Kantor, 1983). Since there is such a substantial degree of individual variation in the kinetics, clinical response and adverse reactions of a particular drug in any one animal, it is important to adjust the dose to the response rather than assuming that an average recommended dose or dosage interval are appropriate. The dog should initially be treated at a mean recommended dose rate. If the desired effect is not achieved, the dose rate should be increased in increments towards the maximum recommended dosage until a clinical response is apparent or until side effects occur. If one drug causes side effects or is ineffective at the maximum recommended dosage then a second drug should be tried in a similar manner. It is rare to find a dog which cannot tolerate treatment with any NSAID.

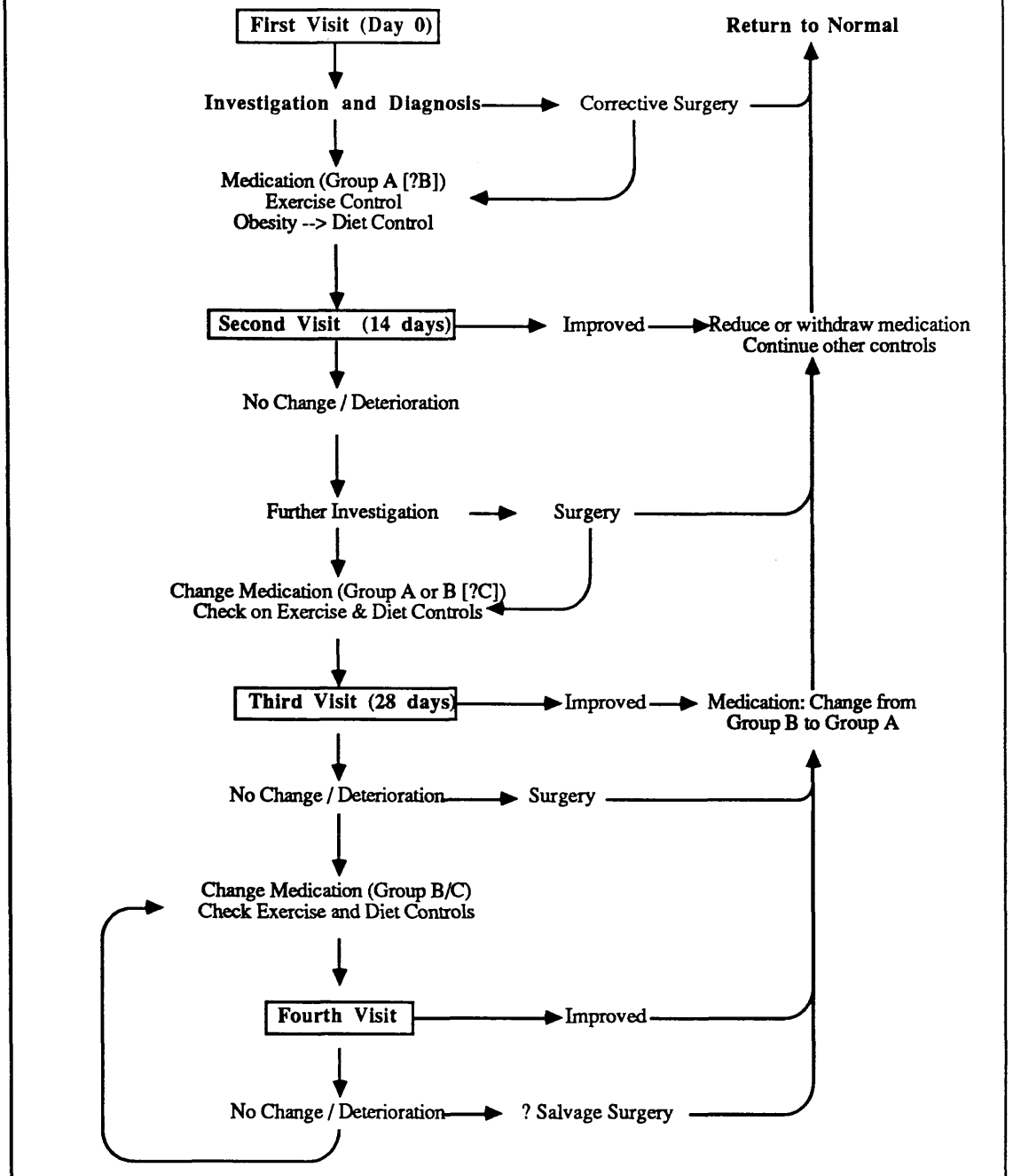
Treatment should be started with a drug which has a low incidence of adverse reactions and preferably with a NSAID which is registered for use in the dog, since this will, in the near future†, be a guarantee that toxicity and efficacy studies have confirmed its safety and effectiveness (Group A: FIG 24). Dogs will respond to NSAID therapy within 10 to 14 days, at least in terms of analgesic effect. If there is no response in this period or if adverse effects occur, then the NSAID should be discontinued and a different NSAID from the same group should be tried. If this also proves unsatisfactory, then more potent (mg/kg) but potentially more toxic NSAIDs should be tried (Group B; Group C: FIG 24). There is a case for allowing the owner to use a number of the Group A or A&B NSAIDs in succession and to then decide which drug is most efficacious. Once the clinical condition has been controlled, it is important to review the disease state at intervals. In many situations the frequency and/or dose of drug can be reduced or the drug withdrawn. The dog should not be under nor overdosed. A dog should not be made to suffer unnecessarily because of inappropriate dosage or overlong dosage intervals, but neither should the dog run the risk of adverse effects as a result of a dosage that is excessive or needlessly frequent. Small breed dogs are often overdosed by owners or by veterinarians. Care in calculating dosages is important to avoid either under or overdosing.

† Revised veterinary drug registration procedures

Table 8:
NSAIDs and Combinations available which may be useful in the therapy of osteoarthritis in dogs
* short term only

1. Haskins, 1987;
2. Rubin and Papich, 1988;
3. Nielson, 1969;
4. Taylor, 1987;
5. Manufacturer's Recommendation (BK Vet. Products Ltd.);
6. Jenkins, 1987;
7. Manufacturer's Recommendation (Arnolds Vet. Products);
8. Manufacturer's Recommendation (Kirby-Warrick Animal Health);
9. Yeary and Brandt, 1975;
10. Lipowitz and others, 1986;
11. Davis, 1978;
12. McKellar, 1989;
13. Manufacturer's Recommendation (Parke-Davis Veterinary);
14. Manufacturer's Recommendation (Vetoquinol [France])

Drug	Preparation / Tradename	Suggested Dose Rates and Regimes	
		Maximum in Literature	Minimum in Literature
Phenylbutazone	Flexazone®; Phenogel® Phenylbutazone Tablets	22 mg/kg every 8 hours [1,2] 15 mg/kg every 6 hours [3]	up to 20 mg/kg/day [4]
Cinchophen/Prednisolone	PLT® Tablets	25-44 mg/kg/day divided b.i.d. [5]	
Paracetamol - Codeine - Caffeine	Pardale-V® Tablets	approx. 15-30 mg paracetamol every 8 hours [7]	
Flunixin *	Finadyne®	1.1 mg/kg s.i.d. MAXIMUM OF THREE DAYS [8]	
Aspirin	Many	25 mg/kg every 8 hours [2, 9, 10]	10 mg/kg every 12 hours [11]
Paracetamol	Many	<25 mg/kg every 8 hours [4]	15 mg/kg every 8 hours [6]
Piroxicam	Feldene®	0.3 mg/kg every 48 HOURS [12]	
Mefenamic acid	Ponstan®	40-60 mg/kg/day divided b.i.d. [13] Decrease dose after 7-10 days.	10-40 mg/kg/day divided [4]
Meclofenamic acid	Meclomen®; Arquel®	2.2 mg/kg/day [1] Decrease dose after 7-10 days	0.5-1 mg/kg/day divided [13]
Tolfenamic acid *	Clotam®/Tofedine®[France]	4 mg/kg/day divided b.i.d. [14] MAXIMUM OF 5 DAYS	
Naproxen	Naprosyn®	2 mg/kg s.i.d maximum (? every second day)[2, 6]	



GROUP A Veterinary Registered	GROUP B Tried and Tested	GROUP C Less experience; seem useful	GROUP D AVOID USE
- Phenylbutazone	- Aspirin	- Piroxicam	- Indomethacin
- Cinchophen + Prednisolone	- Paracetamol	- Mefenamic Acid	- Flurbiprofen
- Paracetamol + Codeine + Caffeine		- Meclofenamic Acid	- Ibuprofen
- Carprofen [when available]		- ? Naproxen	- ? Diclofenac

FIG 24: Management of the Chronically Lame Dog

Many NSAIDs have a duration of analgesic activity far in excess of that predicted by their relatively short plasma half life. There is increasing evidence that drugs with short half lives can be given less frequently than would predicted by their plasma concentrations without compromising their effectiveness. Pharmacokinetic studies have demonstrated that some NSAIDs collect in synovial fluid and may be sustained at therapeutic concentrations locally after plasma concentrations have reduced. There is also evidence that cyclooxygenase inhibition persists after NSAIDs have become undetectable in the synovial fluid. This suggests that NSAIDs can be given less frequently without reducing their analgesic or antiinflammatory effectiveness (Brooks and others, 1986).

A number of other factors should be considered when deciding on the NSAID and the dosage initially used. Age has effects on absorption, distribution, metabolism and excretion of certain NSAIDs which possibly include ketoprofen, piroxicam, and naproxen. Salicylate affinity for plasma proteins is reduced in older people and the increased free drug concentrations may increase the risk of toxicity. Adverse reactions increase in incidence with increasing age (Greenblat and others, 1986).

Genetic factors are known to affect the rate of aspirin metabolism and the kinetics of the drug in man (Greenblat and others, 1986). Variations in the rate of metabolism, excretion and toxicity of NSAIDs and other drugs have been demonstrated between breeds of dog. Beagles generally metabolise and excrete drugs more rapidly than mongrel dogs (Freh and others, 1978). Since many of the pharmacokinetic and toxicity trials on NSAIDs are performed in beagles, doses may have to be reduced in other breeds. Conversely, beagles are more sensitive to the toxic effects of certain NSAIDs than mongrel dogs (eg. Azapropazone (Walker, 1985)).

Owners should always be warned of the possible side effects of any treatment including the NSAIDs. It should be explained that side effects can occur after a prolonged period. If a NSAID has side effects, these effects are more likely to be prolonged if the drug has a long half life. The veterinarian should seek the owners cooperation in reducing the dose and frequency of NSAID treatment to a minimum by explaining the risks of chronic therapy. Many NSAIDs cause fluid retention, interfere with antihypertensive effect of ß-blockers and diuretics. Acute renal failure associated with their use has been widely reported in man. Care should be exercised in dogs with renal disease, hepatic disease, congestive cardiac disease, sodium depletion or on long-term diuretic therapy (Hart, 1987). Patients with impaired renal or hepatic function may have a decreased rate of clearance of drug and metabolites and the dosage and frequency of dosing of NSAID should be decreased accordingly. Prolonged use of NSAIDs may have a direct effect on cartilage breakdown and repair and some drugs may reduce proteoglycan synthesis and cartilage regeneration.

In the future the disease modifying drugs (DMDs) described in section 3.7 are likely to become more important since they affect the progression of osteoarthritis and not just its symptoms. However, the NSAIDs will probably remain important drugs since the DMDs are generally more expensive, some may require intraarticular injection, and all are unlikely to completely ameliorate the symptoms or halt the progression of osteoarthritis. When used with managemental adjustment and, where appropriate, surgical correction, NSAIDs can greatly benefit the osteoarthritic dog by reducing pain and stiffness, and enhancing mobility and "quality of life". It is the responsibility of the veterinarian to consider all factors which may affect the efficacy of treatment and the probability of side effects (TABLE 9). The use of non-registered drugs should be restricted to dogs which have not responded to registered drugs. The non-registered NSAIDs should be used with care and at carefully calculated, recommended canine dose rates. These dose rates should be taken from the most recent veterinary literature since some earlier papers (eg Taylor, 1985) suggest drugs and dose rates now known to be potentially harmful. NSAIDs must be used with care and the owner must be made fully aware of the potential drawbacks of treatment and how they can be minimised.

TABLE 9: Factors to Consider in Selection of a NSAID for the Therapy of an Osteoarthritic Dog

DOG	DRUG	OWNER
DISEASE SEVERITY	SAFETY	INFORM
	EFFICACY	
Age		About Osteoarthritis
	Veterinary Registration:	
Other Disease:	If not:	Symptomatic Treatment
Cardiac Insufficiency	Legal Responsibility;	vs.
Renal; Hepatic Disease	Warn Owner	Treatment ffecting
	Increased Care	Disease Progression
Other Treatment:	Adhere to Vet. Literature	
Diuretics	Recommendations	Importance of Management
ß-Blockers		-exercise
Anti-Epileptics	DOSE CALCULATION	-obesity
	Kinetics / Interdosing Interval	
	[?cartilage effects]	Risks of Chronic Therapy with NSAIDs
	Remember	
	INDIVIDUAL VARIATION	Side Effects

MINIMUM EFFECTIVE DOSE

REGULAR REASSESSMENT

3.8 Disease Modifying Drugs [DMDs]

3.8.1 Introduction

In recent years it has become clear that the NSAIDs do not inhibit the progression of osteoarthritis and that some of the NSAIDs may promote osteoarthritic change by inhibiting chondrocyte proteoglycan production (see 3.3.6). Concurrently, research in human and veterinary fields has demonstrated that other drugs can inhibit the ultra-structural, biochemical and anatomical changes associated with natural and experimentally induced osteoarthritis. These disease modifying drugs (DMDs) may become widely used in the therapy of osteoarthritis in the future (DiPasquale and others, 1986; Doherty, 1989). Some of the drugs investigated are discussed in this section.

3.8.2 Steroidal Anti-Inflammatory Drugs [SAIDs]

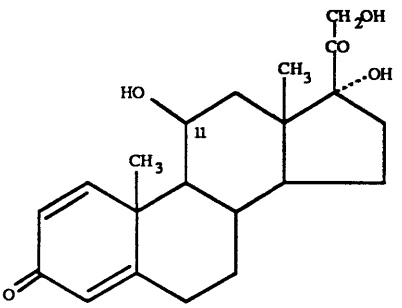


FIG 25: Prednisolone [Prednisone: 11ß= O]

Glucocorticoids are known to inhibit the release of arachidonate and other polyunsaturated fatty acids from cell membranes or free triglycerides. More than one mechanism has been described. Glucocorticoids are known to induce the production of a protein at the nuclear level. This protein "*lipomodulin* " is inhibitory to phospholipases A2 (PLA2) and C which are responsible for arachidonic acid liberation (FIG 26) (Flower and Blackwell, 1979; Blackwell, 1980; Hirata, 1980). Glucocorticoids may have a direct effect on PLA2 (Manz and others, 1980) and may also inhibit cyclooxygenase (Hawkey, 1982). In osteoarthritis and rheumatoid arthritis an increased specificity of PLA2 for arachidonic acid has been reported (Loeser and others, 1988). Suppression of endogenous eicosanoid release by corticosteroids only appears to occur in a subset of possible steroid-receptor bearing target cell types (Sebalt and others, 1988). Other mechanisms have been described and may be important (Green and Lutsky, 1986).

Corticosteroids are well absorbed after oral administration. Ninety percent of endogenous corticosteroid is bound to transcortin, a specific corticosteroid-binding globulin whilst 5 to 8% is bound to plasma albumin which acts as a low affinity/high capacity steroid reservoir. Most of the synthetic steroids, with the exception of prednisone/prednisolone, have a low affinity for transcortin and are bound predominantly to albumin (Lan and others, 1982).

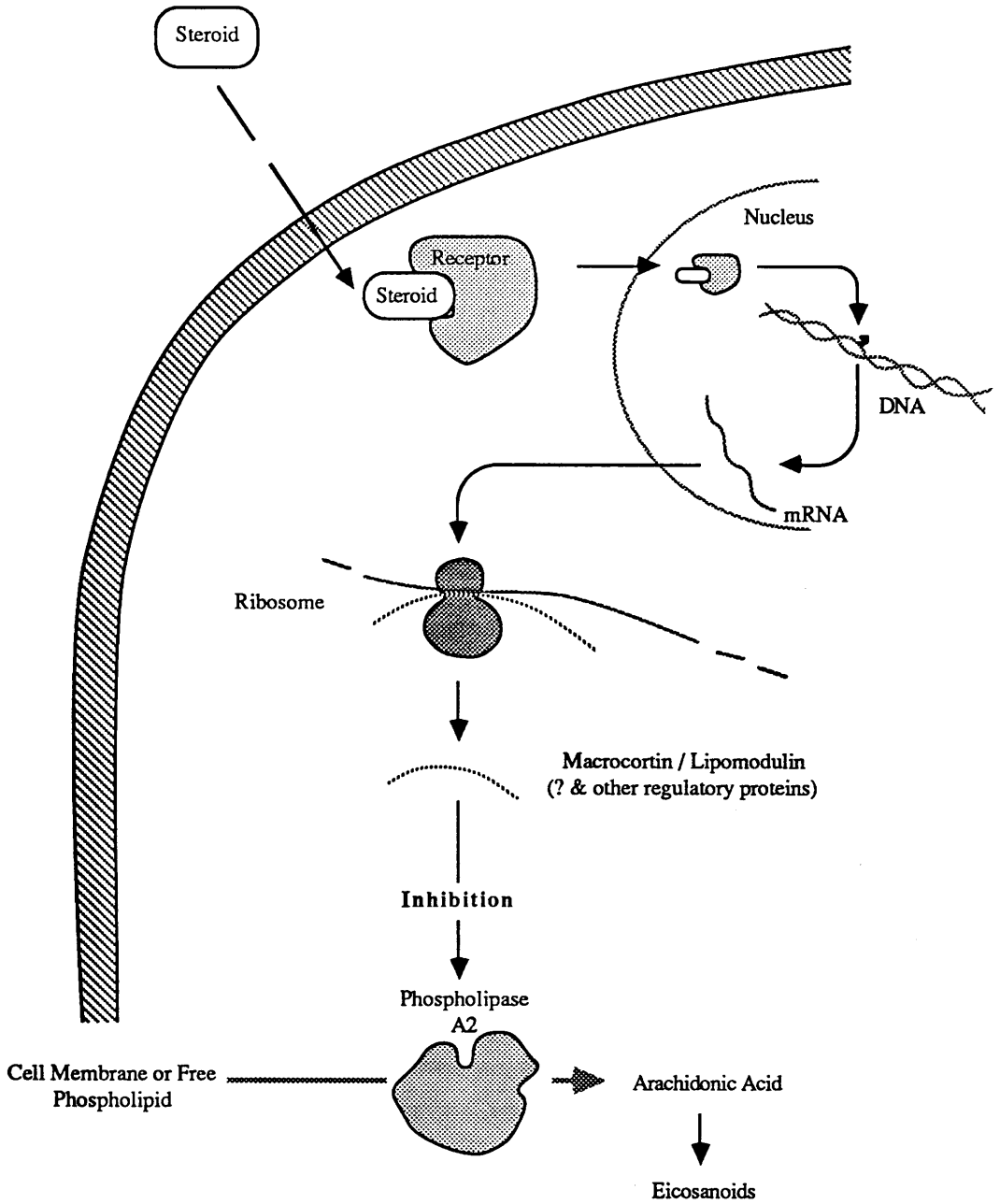


FIG 26: Possible mechanism of action of the corticosteroids
Steroid binds with cytoplasmic receptor and the resulting complex migrates to the nucleus where it interacts with the nuclear DNA to induce the formation of regulatory proteins responsible for the antiinflammatory and other actions of steroids. The regulatory proteins include macrocortin / lipomodulin which inhibits the conversion of phospholipid to arachidonic acid by phospholipase A2.

Binding properties cause differences in the pharmacokinetics and metabolism of the synthetic corticosteroids. There is a large variation in the rate of clearance of exogenous steroids between individuals. Corticosteroids are metabolised predominantly in the liver but also in other tissues (Dorfman and Ungar, 1965). Within two hours of the intraarticular injection of corticosteroids they are present in the cells of synovial fluid or the synovial membrane (Zacco and others, 1954). Corticosteroid free in the joint is hydrolysed or may proceed to the systemic circulation.

3.8.3 Steroids and the Joint

Intraarticular corticosteroids have been used extensively in human and equine osteoarthritis (McKay and Milne, 1976; Friedman and Moore, 1980; Gray and Gottlieb, 1983). In the horse, texts recommend intraarticular steroids as a way of rapidly reducing joint pain associated with traumatic arthritis or osteoarthritis. Steroid treatment is also said to reduce synovial effusions in conditions such as bog spavin (tarsal hydrarthrosis) and promote the formation of more normal synovial fluid (Hackett, 1982).

Low concentrations of corticosteroids stimulate cell division (Macieira-Coelho, 1966). Corticosteroids are very effective *in vitro* at inhibiting cartilage breakdown in synovium stimulated and control cultures (Steinberg and others, 1986). An *in vivo* protective effect has been described for rabbit articular cartilage. Hydrocortisone prevented spontaneous and synovium-induced proteoglycan release independently. The extent of cartilage degradation and the corticosteroid responsiveness were both dependent upon the disease activity and not the type of disease. There was a 24-48 hour lag period before proteoglycan breakdown in coculture, suggesting that synovial factors are required for initiation or induction of degradation. Contact between the synovium and articular cartilage was not required. A brief exposure to synovium caused a major degradative response in subsequent cartilage culture (Ackerman and others, 1983). When triamcinolone hexacetonide was administered to rabbits at 0.1 mg/kg/day it was found to prevent the loss of chondrocytes and matrix proteoglycans from articular cartilage, decrease articular surface disruption and decrease the frequency and size of osteophytes in chemically induced articular cartilage damage (Williams and Brandt, 1985).

In dogs, oral administration of prednisone at 0.20-0.25 mg/kg/day blocks a rise in synovium-induced cartilage neutral metalloproteoglycanase activity in Pond-Nuki experimental osteoarthritis (Pelletier and others, 1985a,b). Although prednisone blocks the increase in total and active neutral metalloproteinase activity in osteoarthritic cartilage and the level of active enzymes is reduced close to levels in control animals, the increase in proteoglycan concentration which might be expected does not occur since prednisone inhibits the synthesis of proteoglycan by chondrocytes (Silberberg and others, 1966).

It appears that low dose steroids inhibit the early induction phase of cartilage breakdown. Later applications when the breakdown has been activated may be relatively ineffectual. Prednisone may inhibit the synthesis or release of soluble factors from the synovium or may act by cell receptor or intra-cellular mechanisms on enzyme synthesis in chondrocytes (Pelletier and others, 1985a,b). Steroids are known to inhibit some activators such as plasminogen activator (Hamilton and others, 1981). Alternatively, steroids may promote the synthesis of free endogenous inhibitors (TIMP). Collagen degradation is suppressed at physiological levels of corticosteroids. Proteoglycan degradation is inhibited only at pharmacologic levels (Steinberg and others, 1986). In addition, corticosteroids suppress hyaluronic acid synthesis by synovial villi. This may be a mechanism by which steroids reduce the joint hyaluronic acid content and promote the resolution of synovial effusion (Colombo and others, 1983).

The use of larger doses of corticosteroids systemically or intraarticularly is associated with well documented adverse reactions in man and animals. Long term systemic steroids in man have been associated with osteoporosis, pathological fracture, aseptic necrosis, growth plate disturbances and stunting, as well as the effects on other body systems. To avoid these effects, intraarticular steroids have been used since 1951. The first reports of adverse joint effects were reported in 1958, and since that time many doctors have reported accelerated joint destruction. Corticosteroids are known to promote degeneration of articular cartilage (Bentley and Goodfellow, 1969; Chandler and Wright, 1958; Miller and Restiffo, 1966; Moskowitz and others, 1970; Goldberg and others, 1976). In experiments *in vivo* , changes have been induced by local steroid treatment (Greenwald and others, 1986). Multiple steroid injections into joints causes a "corticosteroid arthropathy" with fibrillation, chondrocyte degeneration, loss of matrix proteoglycans and cyst formation (Goldberg and others, 1976). Corticosteroid arthropathy is reported in horses treated with intraarticular corticosteroids for osteoarthritis and in chip fractures. Early theories proposed that the acceleration of osteoarthritic changes seen were a result of analgesia and consequent overuse. Other theories have included mechanical trauma from crystalline preparations, vasculitis, subchondral osteoporosis and microfractures, and chondrocyte metabolism effects.

Experiments have demonstrated that corticosteroids inhibit chondrocyte production of proteoglycans by up to 60% and of collagen by up to 80%, and decrease osteoblast activity in subchondral bone. It seems that corticosteroids adversely effect the synthesis of matrix macromolecules and reduce cartilage turn-over. Subchondral bone effects may result in microfractures and promote joint damage.

Septic arthritis is a potentially disastrous complication of intraarticular steroid injection. It usually arises from arthrocentesis but can result from the haematogenous seeding into the immunosuppressed joint. In experimental animals it has been demonstrated that both intraarticular and systemic steroid treatment reduces the number of bacteria required to establish infection in a joint. Corticosteroids also promote bacterial joint destruction and may mask the early signs of septic arthritis. Clinical signs may be apparent within 24 hours or may take weeks or months to develop, depending on the initial bacterial load and type and the subsequent inflammatory reaction.

In the horse, the intraarticular use of steroids has been recommended to be confined to temporary palliative treatment of joint disease. They are used to prolong the performance career in cases such as the racehorse with a progressive osteoarthritis. Their use in acute traumatic synovitis may also be indicated. Intraarticular steroids may be beneficial when lesions are confined to soft tissues of the joint, except in injuries involving joint laxity. The minimum dose and frequency for effect is recommended (Hackett, 1982). In man, intervals of 4-6 months between intraarticular steroid injections are recommended. It is advised in man and the horse that joint loading is minimised for at least two weeks after injection (Owen, 1978; Hackett, 1982; Brandt, 1989).

Though the incidence of steroid arthropathy and septic arthritis in people treated with intraarticular steroids is low, many physicians are doubtful of their usefulness. Modern texts of rheumatic disease in man state that there is no place for systemic corticosteroid or adrenocorticotrophic hormones in the management of osteoarthritis since the side effects associated with the prolonged use of these drugs outweigh any potential beneficial effects (McKay and Milne, 1976; Hart, 1983; Brandt, 1989).

3.8.4 Glycosaminoglycan Polysulphate Esters [GAGPS]

When the evidence that proteoglycan fragments can induce synovitis (see 2.8) is considered, it is perhaps surprising that polysulphated glycosaminoglycans such as Adequan®, Arteparon and pentosampolysulfate have anti-arthritic effects in experimental models of osteoarthritis in animals. The proposed explanation is that the lower molecular weights of these compounds, (2000-12000 daltons), are below that which is required to mediate the inflammatory reactions demonstrated by larger sulphated polysaccharides. It has been shown that low molecular weight polyanions will inhibit the activation of macrophages by high molecular weight anions (Schlorlemmer and others, 1980; Steinberg and others, 1980).

A number of possible mechanisms of action for GAGPS have been proposed. GAGPS has been reported to stimulate glycosaminoglycan synthesis in certain cell systems (Verbruggen and Veys, 1977; Verbruggen and Veys, 1979; Von der Mark, 1979) Although GAGPS stimulates glycosaminoglycan synthesis in chondrocytes (Nevo and Dorfman, 1972; Huang, 1974) it only does so at high concentrations. GAGPS inhibits collagen and proteoglycan catabolism in human articular cartilage (Adam, 1980). Leukocyte accumulation is reduced in experimental models of cartilage degradation. This may be important *in vivo* since cartilage exposure to PMN-derived metalloproteinases or chondrocyte-active mediators may be reduced (Francis and others, 1989).

Glycosaminoglycan polysulphate ester has been found to be a potent inhibitor of a variety of enzymes including cathepsin B1, serine proteases such as cathepsin G and elastase (Kruze and others, 1976; Stephens and others, 1980) and ß-glucuronidase, N-acetylglucosaminidase, hyaluronidase and stromolysin (Kalbhen, 1970; Greiling and Kaneko, 1973; Lees, 1989). Most known protease inhibitors are toxic *in vivo* or suppress cellular synthetic function and most agents administered systemically or intraarticuarly fail to concentrate in cartilage for a sufficient period. However, following intramuscular injection, GAGPS concentrates in articular cartilage to give concentrations of 10^{-6} M: sufficient to inhibit serine proteases and metalloproteinases *in vitro*. It is retained in effective concentrations for up to 8 days. It is distributed diffusely throughout the cartilage when ^{3}H-GAGPS studies have been performed (Ghosh, 1985).

GAGPS may bind to proteoglycans and glycoprotein in the matrix and protect the substrate from enzymatic degradation. GAGPS is known to stimulate hyaluronate synthesis. GAGPS inhibition of hyaluronidase may rectify hyaluronate metabolism and allow the regeneration of proteoglycan aggregates of normal size (Howell, 1986).

Twice weekly intraarticular injections of GAGPS at 1 mg/kg had a significant beneficial effect on morphological parameters of disease severity in experimentally induced osteoarthritis in rabbits. In osteoarthritic controls, there were 5-10 fold increases in active neutral metalloproteinase at 12 and 20 weeks, and 10 fold increases in neutral serine proteases at 20 weeks. No thiol protease activity was detected. GAGPS injections suppressed the enzyme activity levels to normal or below normal range values. GAGPS either directly at chondrocyte level or via synovial cell mediator actions suppressed net neutral protease activity. In addition GAGPS treated animals had chondrocyte cell counts double those of controls. Unlike the osteoarthritis controls they were not located in brood capsules. GAGPS used prophylactically and therapeutically prevented the 35-40% reduction in hexuronate incorporation seen in untreated osteoarthritis controls (Howell and others, 1986).

In dogs with experimentally induced osteoarthritis, glycosaminoglycan polysulfuric acid ester (GAGPS) administered **intramuscularly** at 4 mg/kg twice weekly was found to substantially protect the cartilage. Cartilage swelling was increased in the untreated control group but remained near normal in the group treated with GAGPS, suggesting that GAGPS treatment preserved the collagen network. Total and active metalloproteinases were elevated in the untreated controls but only the total metalloproteinase content was increased in the GAGPS treated group (Altman, 1988). These findings have also been demonstrated after intraarticular use in dogs (Altman and others, 1989). GAGPS treatment was associated with a reduction in cartilage pathology, decreased collagen disruption and decreased collagenase activity.

GAGPS has been widely used and is licensed for use in horses (Adequan®) by intramuscular and intraarticular routes and various studies have demonstrated its clinical efficacy (Tew, 1982; Snow, 1983; Hamm and other, 1984; Collins, 1989).

3.8.5 Hyaluronic Acid / Hyaluronate

Hyaluronic acid is a constituent of normal synovial fluid which is secreted by synoviocytes and which has lubricant and shock absorption properties (FIG 27). It is also a component of a thin, filamentous layer which is present on the surface of normal cartilage (Balazs and others, 1966; Balazs and Darzynkiewicz, 1973). Synovectomy appears to lead to the loss of this layer and degenerative changes in articular cartilage. Hyaluronate injection of synovectomised rabbits restores the filamentous layer and prevents further damage (Toyoshima, 1978).

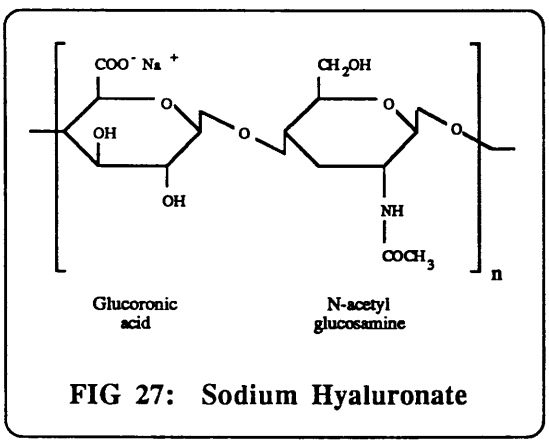


FIG 27: Sodium Hyaluronate

In vitro studies have suggested that hyaluronate may have a chondrocyte-regulatory function such that it influences the synthesis or release of proteoglycans (PGs). Hyaluronate is a potent inhibitor of proteoglycan synthesis. Depolymerised hyaluronate retains activity on chondrocyte PG synthesis but not on fibroblasts (Sommarin and Heinegard, 1983; Abatangelo and others, 1989).

It appears that hyaluronate binds to specific sites on the chondrocyte surface. Hyaluronate thereby inhibits PG synthesis by blocking glycosaminoglycan chain initiation by specific inhibition of either normal core protein synthesis or the xylosyl-transferase which initiates chondroitin sulphate chain synthesis. This mechanism seems important in the control of cartilage matrix proteoglycan (Sommarin and Heinegard, 1983; Abatangelo and others, 1989). Hyaluronate may also affect the release of enzymes or mediators from the synovium (Schiavinato, 1989). Sodium hyaluronate does not apparently modify joint inflammation (Hilbert, 1985). It appears that hyaluronic acid improves the intraarticular environment rather than having any anti-inflammatory or analgesic action (Higgins, 1985).

Hyaluronic acid was first reported to be useful in an intraarticular combination with corticosteroids (Rydell, 1970). The intraarticular use of hyaluronic acid has proved to be useful in the therapy of osteoarthritis in man and in the horse (Rydell, 1971; Asheim, 1976; Wigren, 1978; Rose RJ, 1979). Severe cases are often unresponsive to therapy. Sodium hyaluronate has been found to significantly delay osteoarthritic changes if administered soon after joint instability occurs or reduce disease progression if given up to seven weeks after initiation of experimental stifle osteoarthritis in the dog (Schiavinato and others, 1989).

3.8.6 Glucosamine

Glucosamine is a proteoglycan/glycosaminoglycan precursor. Glucosamine promotes chondrocyte proteoglycan synthesis (Karzel and Domenjoz, 1968 ; Vidal y Plana and others, 1978; Vidal y Plana and others, 1980). It is under study in man but appears to be chondroprotective when used orally and has proven therapeutic benefit in osteoarthritis equivalent to or even greater than that of NSAIDs (Vidal y Plana and others, 1978; Drovanti and others, 1980; Vaz, 1982).

3.8.7 Orgotein

Orgotein is the generic name adopted in 1971 for Cu-Zn superoxide dismutases (SOD). Orgotein is derived from bovine liver and has a molecular weight of about 31,500.

Orgotein catalyses the reaction:

$$O_2^- + O_2^- + 2H \longrightarrow H_2O_2 + O_2 \longrightarrow H_2O + {}^1/_2\, O_2$$

and suppresses the reaction:

$$O_2^- + H_2O_2 \longrightarrow OH\cdot + OH^- + O_2$$

It is proposed that Orgotein is a scavenger of free radicals, and so prevents lysosomal membrane destabilisation. Orgotein is a potent anti-inflammatory at an effective dose of ≥ 0.5 mg/kg. In the dog, orgotein displays first order kinetics. It is rapidly cleared from plasma. Two hours after administration 55% is present in the urine and 29% in the kidney (Huber and others, 1980). Orgotein is digested if given by mouth. If given parenterally, it is cleared rapidly be the kidneys. However, when given subcutaneously or intramuscularly in the dog it has a long duration of effects (Huber and others, 1980).

Orgotein has very low toxicity. A single dose twenty thousand times the clinical dose is safe as is administration at 160 times the therapeutic dose for 30 days (Huber and others, 1983). Orgotein has very low immunogenicity despite its bovine derivation. The copper and zinc in orgotein are tightly bound to the polypeptide and have no clinical effect. The safety of the drug is believed to be due to its extracellular distribution and rapid accumulation and clearance by the kidney (Huber and others, 1980; Huber and others, 1983). Orgotein does not interfere with other drug actions.

Some authors have reported the effect of orgotein in osteoarthritis as disappointing (Huber and others, 1980). However, many authors have reported its usefulness in traumatic and soft tissue injuries in the horse (Decker and others, 1974; Faull and others, 1976; Linton, 1976). Ahlengard et al (1981) found it to have good efficacy in horses that had been lame for shorter periods, if no intraarticular fractures were present. In man, injection of orgotein into arthritic knee joints caused statistically significant improvement clinically, in pain and joint use parameters. Orgotein is apparently as effective as gold or steroids in the treatment of rheumatoid arthritis in man (Menander-Huber, 1981; Goebel and Storck, 1983). Orgotein has been used in dogs with locomotor dysfunction and was found to significantly improve many cases (Breshears and others, 1974).

The estimated dosage, extrapolated from studies in man, is 2-4 mg intraarticularly every 7-14 days for up to 5 treatments or 0.1 to 0.3 mg/kg in 1 ml saline intramuscularly every other day for up to several weeks.

3.8.8 Dimethylsulphoxide (DMSO)

DMSO is a highly polar organic solvent. It is well absorbed through the skin. DMSO scavenges free radicals and particularly hydroxy radicals (Wong and Reinertson, 1985). There is some evidence of beneficial action in post-traumatic inflammation. The mechanism and benefits are controversial however and medical texts advise against its use (Brandt, 1989).

3.8.9 Ascorbic Acid

Ascorbic acid (Vitamin C) has anabolic effects on cartilage. In man and rabbits, ascorbic acid is required for chondrocyte protein synthesis (Krystal and others, 1982). Also, it stimulates chondrocyte proliferation and proteoglycan synthesis *in vitro*. Vitamin C may protect against cartilage erosion by increasing chondrocyte synthesis (Schwartz, 1981). However, it is believed that dogs do not require exogenous vitamin C in addition to that synthesised endogenously and dietary supplementation would probably not be appropriate or necessary.

3.8.10 Cytokine Effectors

The compound CP-66,248 which has biological activity against Leukotriene B4 and Interleukin-1 biosynthesis *in vitro* and *in vivo*, has been found to be more efficacious in the treatment of human osteoarthritis than a placebo treatment but had a similar incidence of side effects (Davis, 1988).

3.9 Summary

The recent evidence that steroids have a chondroprotective rôle when used in early osteoarthritis at low doses contrasts with the wealth of data that at higher doses administered intraarticularly they can induce osteoarthritic changes in normal joints or promote damage in osteoarthritic joint. If steroids have protective effects at doses which do not suppress adrenal function significantly, their oral use at low doses may be useful in early osteoarthritis. The use of higher doses of steroids intraarticularly is of doubtful value. The potential for adverse effects on the joint is great. Greater benefits are attainable with some of the newer DMAs without the same risk of septic arthritis or articular cartilage damage.

Both hyaluronic acid and glycosaminoglycan polysulphate (GAGPS) esters have proven chondroprotective effects in experimental models of osteoarthritis. Hyaluronic acid appears to effect chondocyte synthesis of proteoglycan and may be involved in proteoglycan aggregation and the maintainence of a diffusion barrier between the synovium and the chondrocyte. GAGPS has effects on chondrocyte proteoglycan synthesis, and on degradative enzyme production and activation. Both GAGPS and hyaluronate are licenced for use in equidae and have been used with some success. Experimental studies in dogs have shown that they markedly delay the progression of secondary osteoathritis.

GAGPS has the advantage that when administered intramuscularly it concentrates in articular cartilage. Hyaluronate must be administered intraarticularly. The GAG precursor glucosamine appears to have chondroprotective properties. It may be very useful since it can be administered by mouth. There is an urgent need for clinical efficacy studies in naturally occurring osteoarthritis in dogs, particularly with GAGPS but also with hyaluronic acid and glucoasamine.

There is conflicting evidence on the efficacy of the reactive oxygen species scavenger orgotein in osteoarthritis. It may be more useful in rheumatoid arthritis where there is more evidence that ROS are important in the inflammatory reaction. The use of dimethylsulphoxide (DMSO) is generally not recommended.

In the near future, it is likely that DMDs will be used increasingly in man and in animals. Other drugs which have effects on the mediators of osteoarthritis pathogenesis such as IL-1 or which mimic growth factors or chondroprotective mediators will probably augment the symptomatic treatment of osteoarthritis with NSAIDs which do not have antagonistic activity on chondrocyte metabolism. At present, when used appropriately the NSAIDs are extremely useful in the amelioration of the symtoms of osteoarthritis whilst factors which predispose to further damage are corrected and similar drugs will probably remain important in the future.

Chapter 4

The NSAID Carprofen and its Use in the Therapy of Canine Osteoarthritis

The NSAID Carprofen and its Use in the Therapy of Canine Osteoarthritis

4.1 Carprofen

4.1.1 Structure and Chemistry

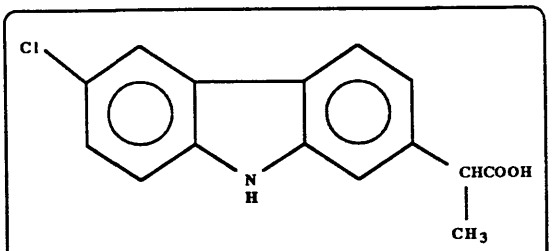


FIG 28: Carprofen

Carprofen ad us. vet contains the substance known chemically as alpha-methyl-6-chlorocarbazole-2-acetic acid. It is a tricyclic compound (a carbazole) and a propionic acid derivative. Carprofen (Ro-20-5720) was originated at Hoffman-La Rôche Research Laboratories. Carprofen, like most other propionic acid derivatives, is a racemic compound. Carprofen has a pKa of 4.7.

4.1.2 Activity and Mechanism of Action

Carprofen inhibits prostaglandin synthesis by reversible inhibition of cyclooxygenase. However, carprofen is a much less potent cyclooxygenase inhibitor than indomethacin *in vitro* and *in vivo* (indomethacin IC50†=0.50 μM; carprofen IC50=48 μM). The approximate order of potency of cyclooxygenase inhibition is:

Indomethacin, tolmetin Na, naproxen > **carprofen** = piroxicam > ibuprofen >>benoxaprofen.

(Baruth and others, 1985).

Carprofen is a potent inhibitor of prostanoid biosynthesis in rheumatoid synovial cell culture (chronic inflammation) and in rat peritoneal polymorphonuclear leucocytes (PMN). Carprofen is less potent than indomethacin in synovial culture but equipotent in the rat peritoneal PMN model and is twice as potent as benoxaprofen in both models (Dayer and others, 1977; Dayer and others, 1980). Carprofen is apparently inactive against lipoxygenase *in vitro*. However, carprofen is a moderately potent phospholipase inhibitor *in vitro* (IC50=120 μM; cf. indomethacin 370 μM, benoxaprofen 440 μM). These concentrations are quite high and the *in vivo* significance of these findings is uncertain.

† IC50 = Concentration of drug which inhibits cyclooxygenase activity by 50%.

Carprofen is a more potent inhibitor of the release of arachidonic acid from cellular lipid than many other NSAIDs (about 100 μM). High *in vitro* concentrations of carprofen inhibit complement activation in man (DiPerri and others, 1982). Carprofen may have effects on neutrophil chemotaxis (Tursi and others, 1982). In animal models, carprofen has demonstrated potent antiinflammatory and analgesic activity and is well tolerated. The antiinflammatory activity of carprofen is greater than that expected from its effects on cyclooxygenase. Carprofen has activity superior to aspirin and equivalent to indomethacin in both acute (carrageenan-induced oedema, acute adjuvant arthritis) and chronic (established adjuvant arthritis) inflammatory models. In acute inflammatory models in the rat, 2 mg/kg carprofen is equivalent to 68 mg/kg aspirin. The antiinflammatory activity of carprofen is equipotent to indomethacin in acute adjuvant arthritis in rats. In general, the order of antiinflammatory potency of the common NSAIDs is:

carprofen ≈ indomethacin, piroxicam, diclofenac > phenylbutazone > ibuprofen > aspirin

(Maeda and others, 1977; Strub and others, 1982; Jeunet, 1982).

The analgesic activity of carprofen is similar to that of indomethacin and greater than that of aspirin (Randall and Baruth, 1976; Strub and others, 1982).

4.1.3 Pharmacokinetics in the Dog

After oral administration, carprofen is very rapidly absorbed. Peak concentrations are proportional to the administered dose. In beagle studies with doses of 1, 5, and 25 mg/kg, peak plasma levels were attained after 2 hours (Rôche Internal Data). Carprofen's elimination half-life ($t_{1/2\beta}$) in the dog has been reported as 12-24 hours. Plasma concentrations show a biphasic or multiphasic decline. There is no evidence of either drug accumulation or of microsomal enzyme induction or tachyphylaxis (Rubio and others, 1980). In a pharmacokinetic study by the author carprofen at 4 mg/kg administered orally was rapidly absorbed to give peak plasma concentrations between 26.1 and 44.3 μg/ml and a mean elimination half life ($t_{1/2\beta}$) of about 9 hours (6.5 to 13.7 hours) (see 4.2).

In man, absorption of carprofen is delayed by administration with food but total bioavailability is not affected. An oral dose of 100 mg produces plasma concentrations of 6 to 16 ug/ml (Ray and Wade, 1982) and multiple daily doses of 150 mg (ie. approximately 2 mg/kg) orally produce plasma concentrations between 3 and 20 ug/ml (Crevoisier, 1982). The elimination half life in man is 13 to 27 hours (Ray and Wade, 1982).

Carprofen readily diffuses into the synovial fluid although peak concentrations are lower and are reached about 6 hours after peak plasma concentrations (Ray and others, 1979). Concentrations in synovial fluid in man are 30 to 103% of serum concentrations (Enthoven and others, 1987). The plasma half life in older people is reduced although clearance is not affected (Blumenthal and others, 1980). In man, hepatic cirrhosis does not effect pharmacokinetics (Holazo and others, 1985).

In the dog, the elimination of carprofen is primarily by biotransformation. Biliary secretion and faecal excretion account for 60-70% of the administered dose. The main metabolic pathways are direct conjugation of carprofen to an ester glucoronide and oxidation of carprofen to C7 and C8 phenols and subsequent glucoronyl conjugation. The metabolites are rapidly eliminated and do not accumulate (Rubio and others, 1980). In man, urinary excretion of the glucoronide ester predominates (Maeda and others, 1977). In man, enterohepatic recirculation of carprofen occurs (Ray and Wade, 1982). There is no evidence of enterohepatic recirculation in the dog (Rubio and others, 1980).

4.1.4 Use in Man

Carprofen (Imadyl®; Rimadyl®) is available for use in man in a number of countries but not in the UK. Indications for the use of carprofen in man have included osteoarthritis; rheumatoid arthritis; ankylosing spondylitis; capsulitis; extra-articular rheumatic conditions such as tendonitis, bursitis, synovitis and soft tissue injuries; and the relief of pain following acute trauma. In man, carprofen has proven beneficial in symptomatic relief in rheumatoid arthritis (Dickey and Huleatt, 1980; Standell, 1982) and osteoarthritis (Dickey and others, 1979; Klein, 1982; Stein and others, 1983). Carprofen has a rapid onset of action and a longer duration of action than aspirin. It has equivalent efficacy to indomethacin in the therapy of osteoarthritis in man (Dickey and others, 1979). In man, carprofen is used at approximately 5 mg/kg/day in two divided doses (Jeunet, 1982; Baruth and others, 1985; Lombardino, 1985). Once a satisfactory response is seen, the dosage is reduced to the minimum effective dose.

4.1.5 Dosage and Administration

The preliminary recommendations from Hoffman-La Rôche were that carprofen be used in all species at 0.5-0.7 mg/kg/day for a maximum of 3 months.

4.1.6 Tolerance and Toxicity

The following side effects have been reported in man:

-Gastrointestinal: epigastric discomfort, nausea, heartburn, diarrhoea.
-CNS: Dizziness, headaches, drowsiness.
-Skin: Rash, pruritis, erythema, urticaria.
-Others: dysuria, increased frequency of urination, visual disturbances, mild peripheral oedema.

Side effects in man are usually mild and transient. Where a skin rash occurs, it is advised that treatment is withdrawn, as for other NSAIDs.Transient abnormalities in liver function tests have been reported.Treatment of overdosage is symptomatic. There is no specific antidote to carprofen overdosage.

Carprofen, like other NSAIDs will produce gastric irritation when administered at sufficiently high doses. However, the safety ratio (therapeutic dose: ulcerogenic dose) is much greater for carprofen than for many other NSAIDs. In the rat, the safety ratios are:

Carprofen ≈ 32
Indomethacin ≈ 2
Aspirin ≈ 0.9

Carprofen is very much less ulcerogenic than indomethacin in rats [carprofen MED§ = 64 mg/kg p.o.; indomethacin MED = 4 mg/kg p.o.] (Rôche Internal Data; Baruth and others, 1985).

Experimental studies have indicated that the dog is particularly resistant to the ulcerogenic activity of carprofen (Maeda, and others, 1977). Carprofen is not ulcerogenic in the dog at doses which would be expected to have an effect. In tests for occult blood in the faeces of dogs receiving various NSAIDs, carprofen has been shown to be tolerated orally at 3 to 30 mg/kg/day whereas indomethacin, aspirin, piroxicam and phenylbutazone administration was associated with occult faecal blood. The latter drugs were often active even after a single dose. Studies on the rôle of hepatic function and ß-glucoronidase function on the ulcerogenicity of carprofen in rats have suggested that intestinal glucoronidase activity is an important factor but variations in biliary excretion and hepatic metabolism are not (Dairman and others, 1976; McClain, 1976).

§ MED = Minimum effect dosage which induces ulcers in experimental animals

No adverse clinical or pathological effects on the gastrointestinal tract were seen in dogs treated with carprofen orally at 25 mg/kg/day for a year (Rôche Internal Data; Baruth and others, 1985). The low incidence of gastrointestinal intolerance may be due to tissue specific cyclooxygenase inhibition or to the pharmacokineticsand distribution of carprofen (Baruth and others, 1985). Carprofen appears to have a greater therapeutic index in the dog than most other NSAIDs (Teelman, 1983). A short tolerance study in dogs at 9 mg/kg/day is documented in Section 4.3.

Carprofen has shown no evidence of renal toxicity in the dog (Baruth and others, 1985). No central nervous, cardiovascular or respiratory side effects have been demonstrated in animal tests at doses far in excess of therapeutic doses. Mild dermatological effects were seen in some experimental dogs treated chronically (Maeda and others, 1977).

4.1.7 Contraindications and Drug Interactions

The recommendations from Hoffman-La Rôche are that active peptic ulceration or previous hypersensitivity to carprofen are contraindications to its use. Precautions included care in the use of carprofen in patients with a history of peptic ulceration, severe renal or hepatic insufficiency or previous sensitivity to aspirin or other NSAID. Since carprofen is highly protein-bound, it has been suggested that dosages of other highly protein-bound drugs such as anticoagulants, sulphonamides, phenytoin, certain potent diuretics and hypoglycaemic agents may require adjustment when administered concurrently. However, there are no known interactions between carprofen and anticoagulants. Co-administration of carprofen and antacids has no effect on carprofen bioavailability (Jeunet, 1982; Rôche Internal Data).

4.1.8 Summary

Carprofen is propionic acid derivative. It is a cyclooxygenase inhibitor and also has effects on cellular lipid release, neutrophil chemotaxis and on phospholipase which may be significant *in vivo*. It has no action on lipoxygenase. Carprofen has potent antiinflammatory activity and significant but less potent analgesic activity. It is rapidly absorbed after oral administration to give peak plasma concentrations in less than two hours. Carprofen is highly plasma protein bound. It is eliminated primarily by biotransformation and is mostly excreted in the bile and faeces. Enterohepatic recirculation occurs in man but has not been described in the dog. Elimination is biphasic or multiphasic according to some studies. In a study by the author it could be described in a monophasic fashion with an elimination half life of 6 to 13 hours. Rôche Internal Data reports an elimination half life of 12-24 hours.

Carprofen has relatively low ulcerogenic activity in animal tests. The dog is particularly resistant to ulcerogenic effects. Long term tolerance studies in dogs at 25 mg/kg/day did not cause any adverse effects. Gastrointestinal intolerance does occur at higher doses. Mild dermatological signs have been reported in some dogs treated chronically. No evidence of renal toxicity is reported. The therapeutic index for carprofen in the dog is superior to most other NSAIDs. Carprofen has less potential for interaction with anticoagulants and antacids than many NSAIDs. Carprofen has proven efficacy in the treatment of musculoskeletal disorders in man including osteoarthritis. The high therapeutic index of the drug in acute and chronic administration studies in the dog suggests that, at the appropriate dose rate, it may be the NSAID of choice for chronic therapy of osteoarthritis in dogs.

4.2 Study on the Pharmacokinetics of Carprofen 17.5 mg Tablets in Dogs when Administered as a Single 4 mg/kg Oral Dose

4.2.1 Objective

The objective of the investigation was to determine the plasma pharmacokinetics of a single oral dose of 4 mg/kg carprofen (Ro 20-5720/659) in beagle dogs.

4.2.2 Materials and Methods

(a) Animals:

The test animals were three male and three female beagle dogs aged between 2 and 3 years old. The animals received no medication in the 14 days before the experiment began. The dogs were fed a complete cereal based diet and water was available *ad libitum*. Details of the dogs are given in TABLE 10.

TABLE 10: Experimental Animal Details

Dog Number	Sex	Weight prior to drug administration (kg)	Calculated Dose (mg)	Actual dose Admin. (mg)	(mg/kg)
1	F	14.5	58.00	58.00	4.00
2	M	17.0	68.00	68.02	4.00
3	F	12.0	48.00	47.98	4.00
4	F	13.0	52.00	51.97	4.00
5	M	18.5	74.00	74.12	4.01
6	M	15.0	60.00	59.92	4.00

(b) Test Drug:

Carprofen ad us vet. (Rôche Ro 20-5720/659); Lot No. MZ 626 B 01;
Expiry date : 07/91.

Tablet formulation: 17.5 mg carprofen per tablet;
Supplied by Hoffman-La Rôche via Grampian Holdings Ltd.

(c) Reagents:

Diethyl ether:	unwashed analar grade (Rathburn Chemicals Ltd)
Methanol:	Redistilled analar grade (Rathburn Chemicals Ltd)
Water:	Permanganate distilled water. Impurities capable of degrading the HPLC column are present in undistilled water
pH 3 Buffer:	Citrate/phosphate buffer (pH 3); 20.5% M/5 Na_2HPO_4 :79.5% M/10 Citric acid

(d) Trial Design:

The six beagles were weighed on the day prior to the day of drug administration . The 17.5 mg tablets were weighed to establish the mean weight of one tablet. Tablets were shaved to obtain a dosage such that carprofen was administered to all dogs at 4 mg/kg body weight (TABLE 10). All six dogs were given the oral dosage at the same time on the same date.

Blood was collected from the left jugular vein with a 20 gauge needle and 10 ml syringe before drug administration ('Pre'), and at 15 minutes, 30 minutes, 1 , 1.5, 2, 4, 8, 12, 24, 48 and 96 hours after drug administration. Samples were placed in heparinised Sarstedt monovettes for plasma drug concentration estimations.

(e) Carprofen Analysis:

The heparinised blood sample from each dog was centrifuged and the plasma decanted and frozen. Each plasma sample was defrosted at room temperature and a 2 ml plasma aliquot was placed in a 50 ml stoppered tube. 0.6 ml of phosphate-citrate buffer (pH 3) and 20 ml of diethyl ether were added and the mixture was shaken for ten minutes on a rotary mixer. 15 ml of the upper ether layer was recovered and placed in a 50 ml thin walled glass boiling tube.

A further aliquot of 20 ml of diethyl ether was added to each stoppered tube. The tube was shaken for a further ten minutes and 20 ml of the upper ether fraction recovered and added to the 15 ml already obtained. The combined diethyl ether volumes were evaporated on a Dri-Block at 50°C under airstream until about 5 ml remained. The diethyl ether extract was transferred to a conical tube. The walls of the 50 ml tube were rinsed with 1 ml of ether three times and the washings combined with the extract. The extracts were evaporated to dryness in the Dri-Block at 50°C under airstream. Again, the walls were rinsed with about 1 ml of ether and evaporated to dryness.

Samples were reconstituted in methanol (minimum volume of methanol= 150 ul) prior to injection into an HPLC (High Pressure Liquid Chromatography) system (FIG 29 and 30). HPLC was performed using the materials listed below:

HPLC Apparatus:

Pump:	Gilson 302
Detector:	Cecil Instruments UV Detector CE 2012
Column:	100 x 5 mm Shandon Southern Ltd.
Packing:	ODS-Hypersil 5 µm Shandon Southern Ltd.
Wavelength:	254 nm
Absorbance:	0.05 a.u.f.s. units
Solvent:	70 Redistilled methanol : 30 Perchloric acid (50 ul of $^1/_{55}$ dilution of 70% solution)
Flow Rate:	1 ml/minute
Recorder:	Vitatron 2001R
Loop volume:	20 µl
Injection volume:	20 µl
Standard:	Carprofen 2 µg/l in methanol

The plasma concentration of carprofen in the test animals was determined by comparing the UV absorption of the sample with that of a 2 µg/l standard solution in methanol and adjusting the ratio for the expected 95% recovery.

(f) Drug Recovery and Calculations:

Known concentrations of carprofen were added to blank plasma. "Spiked" plasma samples with known concentrations of carprofen of 0.25, 1, 10, 20, and 50 µg/ml were extracted to find the mean recovery in every batch of extractions that were performed. The expected proportion of carprofen extracted in ether would be 0.95 since in the first extraction 15 of 20 ml were recovered (0.75) and in the second extract 0.2 was removed and the remaining 0.05 was discarded.

The concentration of carprofen recovered in the 'spikes' after extraction was calculated using the formula below:

$$\text{Recovery} = \frac{\text{concentration recovered}}{\text{actual concentration}}$$

$$= \frac{\text{UV absorp sample}}{\text{UV absorp standard}} \times [\text{standard}] \times \frac{\text{Analysis volume}}{\text{Plasma sample vol.}} \times \frac{100}{95} / \text{actual conc.}$$

$$= \frac{\text{Sample peak height*}}{\text{Standard peak height*}} \times [\text{standard}] \times \frac{\text{Analysis volume}}{\text{Plasma sample vol.}} \times \frac{100}{95} / \text{actual conc.}$$

(* = Chromatogram peak heights)

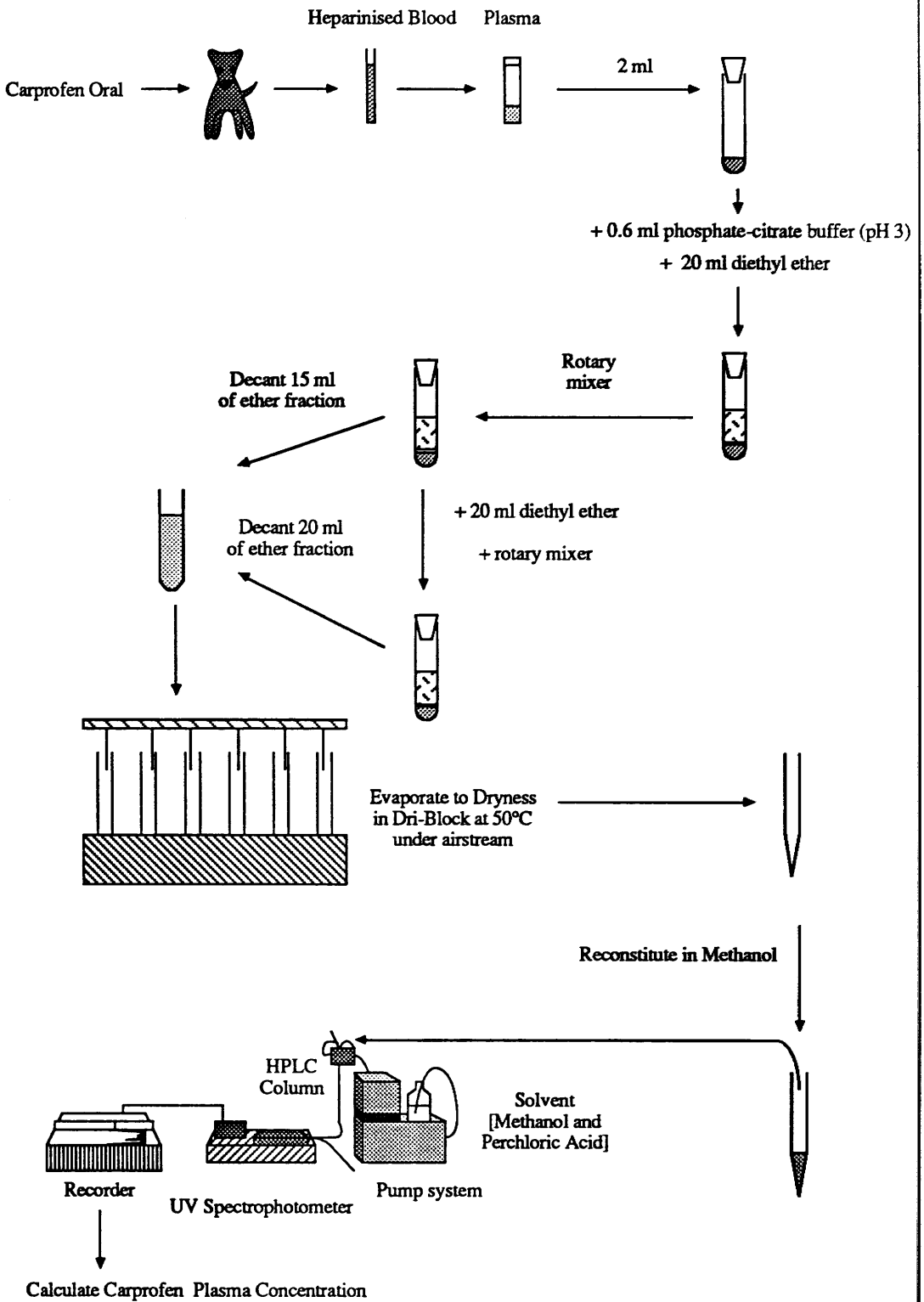


Fig 29: Simplified diagrammatic representation of plasma carprofen extraction and assay procedure

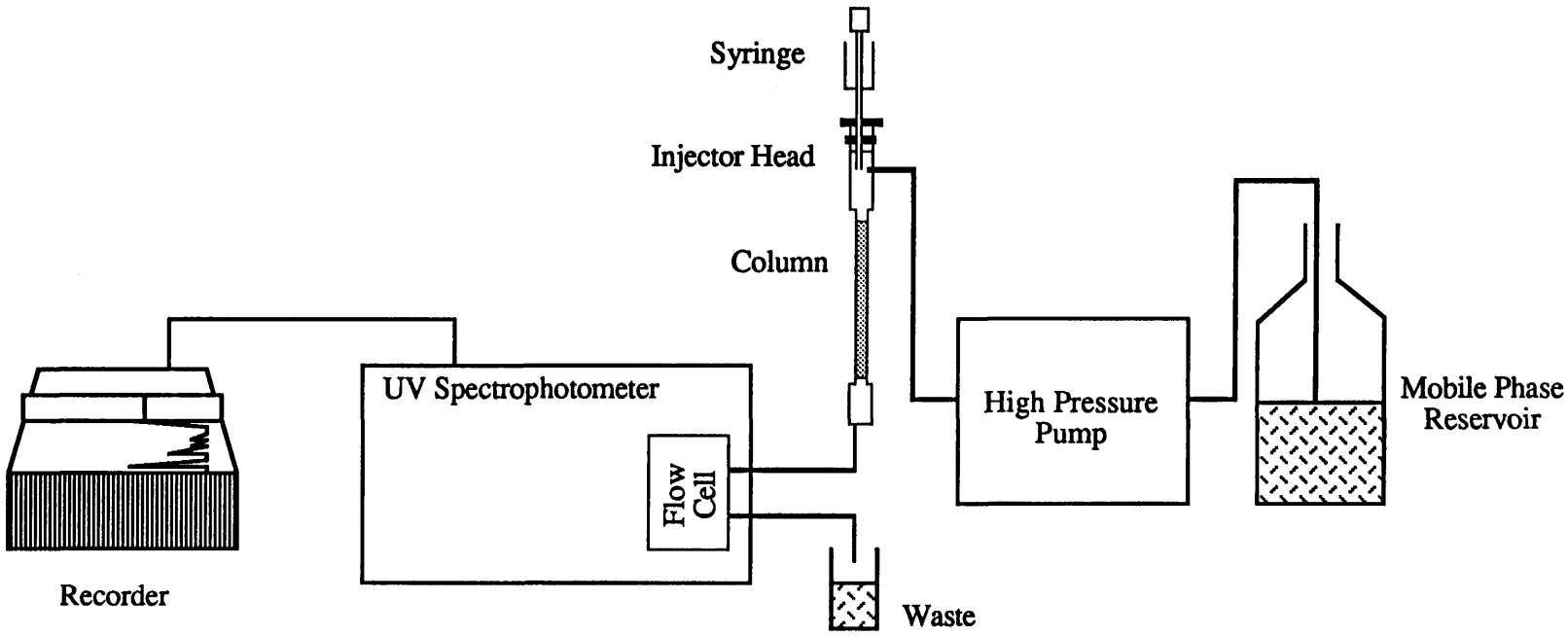


Fig 30: Diagrammatic representation of
High Pressure Liquid Chromatography (HPLC) system

The plasma concentration of carprofen in the test samples was calculated in a similar fashion. A conversion factor (the reciprocal of the recovery determined from the analysis of the 'spikes') was used to adjust the calculated concentration in the extracted sample to derive the actual plasma drug concentration:

$$\text{Plasma [carprofen]} = \frac{\text{UV absorp sample}}{\text{UV absorp standard}} \times [\text{standard}] \times \frac{\text{Analysis volume}}{\text{Plasma sample vol.}} \times \frac{100}{95} \times \frac{1}{\text{recovery}}$$

$$\text{Plasma [carprofen]} = \frac{\text{Sample peak height}}{\text{Standard peak height}} \times [\text{standard}] \times \frac{\text{Analysis volume}}{\text{Plasma sample vol.}} \times \frac{100}{95} \times \frac{1}{\text{recovery}}$$

Examples of 'spike' recoveries and calculations are given in TABLE 11 below.

TABLE 11: Examples of Spike Recoveries and Plasma Carprofen Concentrations

Examples of Carprofen Spike Sample Recovery Calculation

Sample	Sample Peak Height	Standard Peak Height	Sample Pk Ht / Standard Pk Ht x Standard Conc.	x Residual vol / Plasma vol	x 100/95	+ Actual Concentration [10 µg/ml]	RECOVERY
Spike S4 [10 µg/ml]	41.25	43.5	41.25 / 43..5 x 2 = 1.8965	10 ml / 2 ml = 9.4828	9.9819	0.9819	0.9982

Examples of Test Sample Carprofen Concentration Calculation

Sample	Sample Peak Height	Standard Peak Height	Sample Pk Ht / Standard Pk Ht x Standard Conc.	x Residual vol / Plasma vol	x 100/95	x Conversion Factor * [1.042]	PLASMA CARPROFEN CONCN.
DOG 4 8 hour sample	37.0	46.0	37.0 / 46.0 x 2 = 1.609	16 ml / 2 ml = 12.8696	9.9819	13.547	14.116 µg/ml

*Conversion Factor = 1 + Mean Spike Recovery

(g) Pharmacokinetics

Standard models and equations were used to calculate pharmacokinetic parameters (Sedman and Wagner, 1976; Baggot, 1977).

4.2.3 Results

All six dogs were clinically normal prior to the trial and remained healthy throughout. Food and water intake were normal.

Plasma Carprofen Concentrations

The concentrations of carprofen in the plasma of the individual dogs and the mean concentrations are given in Appendix A1. Pharmacokinetic parameters are listed in TABLE 12 below. Mean concentrations and standard errors from the mean for the six dogs are represented graphically in FIG 31 and FIG 32.

Carprofen was rapidly absorbed after oral administration in all dogs. Peak plasma concentrations ranging from 26.1 to 44.3 µg/ml (mean 35.3 ug/ml) were attained between 0.5 and 2 hours after administration (mean 1.25 hours). The elimination half life ($t^1/_2$ ß) ranged from 6.5 to 13.7 hours (mean 9.3 hours). The area under the curve (AUC observed) ranged from 171 to 460 (mean 310).

TABLE 12:

Pharmacokinetic Parameters for Carprofen After Oral Administration of a Single 4 mg/kg Dose

	Dog 1	Dog 2	Dog 3	Dog 4	Dog 5	Dog 6	**Mean**	±SEM
No. of exponentials	3	3	3	3	3	3		
$t^1/_{2\,(ab)}$ (hrs) (absorption)	0.4	0.5	0.6	0.3	0.2	0.3	**0.4**	**0.06**
$t^1/_{2\,(alpha)}$ (hrs) (distribution)	3.0	2.3	7.5	1.4	2.5	1.1	**3.0**	**1.0**
$t^1/_{2\,(ß)}$ (hrs) (excretion)	9.3	7.6	13.7	8.6	9.9	6.5	**9.3**	**1.0**
AUC (observed)	171	460	428	353	247	198	**310**	**50**
Cmax. [ug/ml]	31.8	44.3	26.1	31.6	40.7	37.4	**35.3**	**2.7**
Tmax. [hrs]	1	2	2	1	0.5	1	**1.25**	**0.25**

Key:

$t^1/_{2\,(ab)}$:	Absorption half-life (ie. 0.693/ apparent first-order absorption rate constant)
$t^1/_{2\,(alpha)}$:	Distribution half-life
$t^1/_{2\,(ß)}$:	Elimination half life (Biological /Plasma half life of drug)
AUC :	Total area under the plasma drug concentration vs. time curve from t=0 to t=∞ after administration of a single dose.
Cmax.:	Maximum plasma drug concentration after administration of a single dose.
Tmax.:	Time after oral administration when Cmax. was attained.
SEM:	Standard error from the mean

FIG 31: Mean Plasma Concentrations of Carprofen ±SEM After Single Oral Administration of 4mg/kg (up to 12 hours post administration)

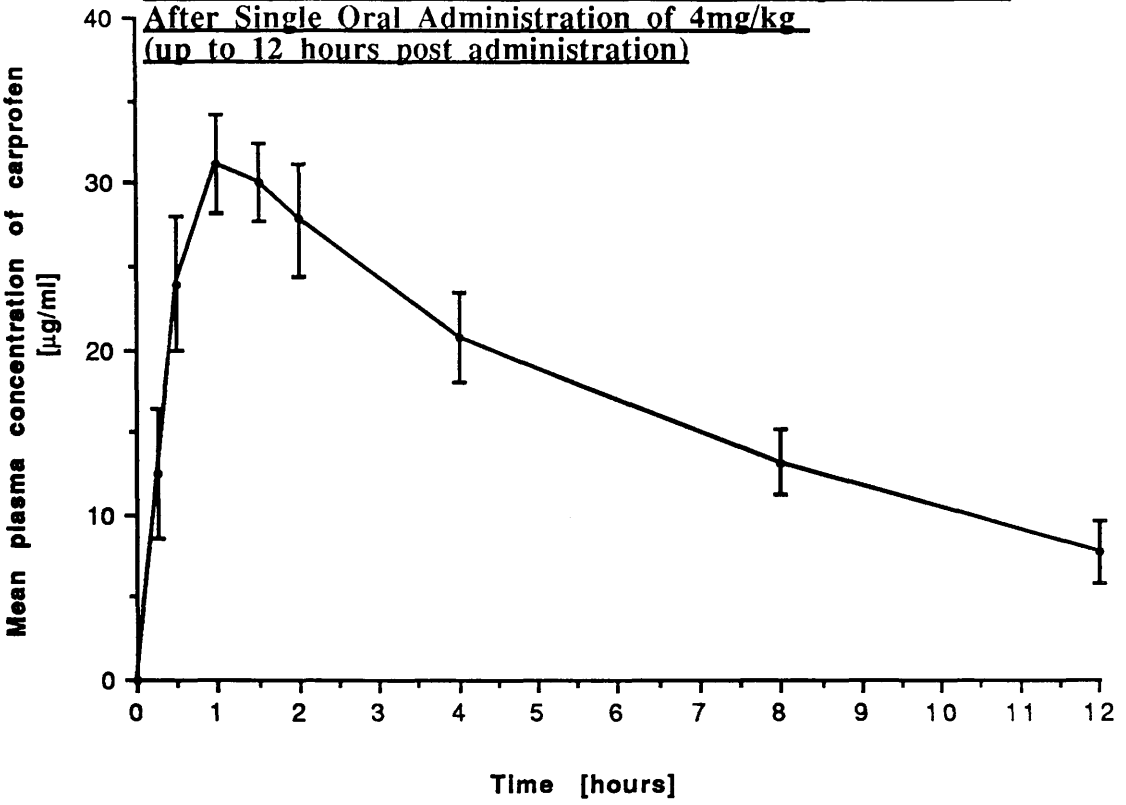
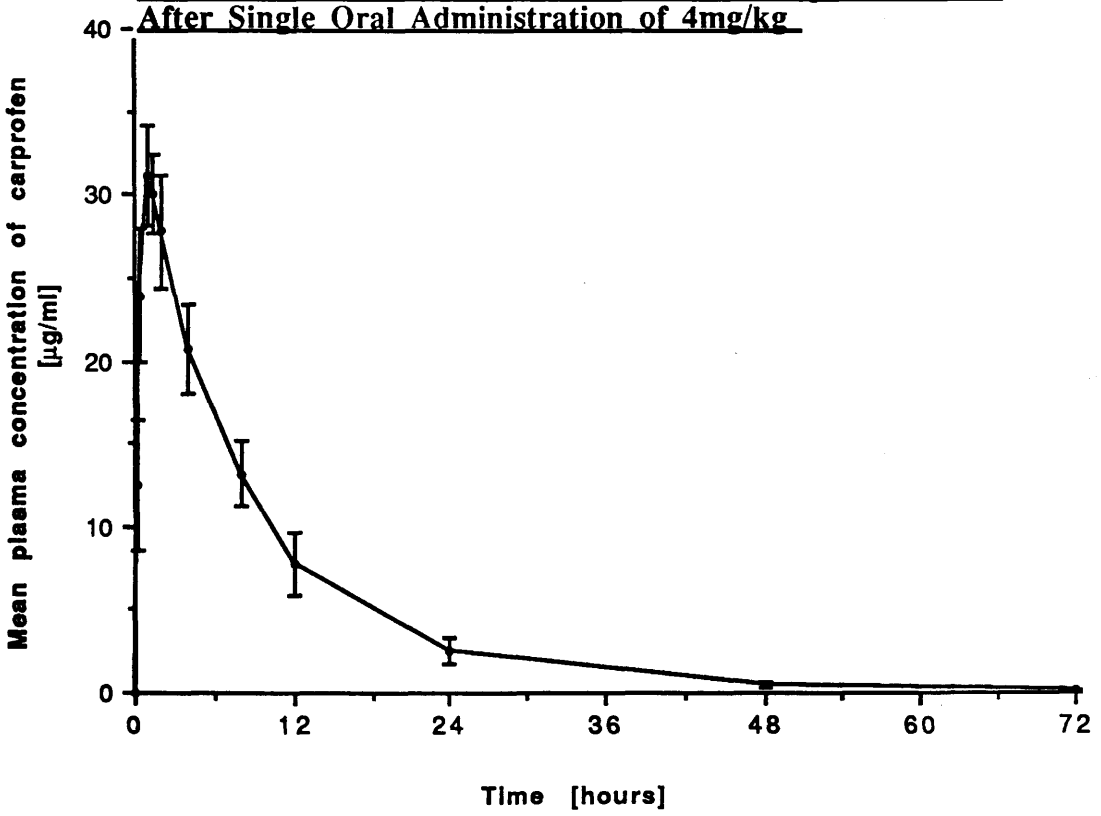


FIG 32: Mean Plasma Concentrations of Carprofen ±SEM After Single Oral Administration of 4mg/kg



4.2.4 Conclusions and Discussion

Oral absorption was more uniform than in studies at 0.7 mg/kg with a paste formulation (McKellar, 1989). Peak concentrations were attained in less than two hours. Peak plasma concentration and excretion rate showed some individual variation. Peak concentration were higher than those reported by some authors (Rôche Internal Data). Peak concentrations were in agreement with extrapolations of blood concentrations in radioimmunoassay studies at 1mg/kg in beagles (Rubio and others, 1980). Extrapolation was valid since plasma levels are directly proportional to dose in the range 1-10 mg/kg (Rubio and others, 1980).

No results for intravenous administration of carprofen at 4 mg/kg are available to estimate bioavailability. However, the AUC varied quite markedly between individuals. The elimination half life ($t^1/_2ß$) calculated was shorter than that estimated by other studies (Rubio and others, 1980) and by the manufacturer (12-24 hours: Rôche Internal Data). However, these authors describe two phases of excretion (Rubio and others, 1980; Rôche Internal Data). In this study there was good correlation with single exponential elimination kinetics. The elimination half life was similar to that calculated by other authors (McKellar, 1989). In dog 3, the absorption, distribution and elimination half lives were prolonged. The reason is not known. There was no evidence of enterohepatic recirculation. Plasma concentrations above 3.3 µg/ml were maintained in all dogs for 12 hours and in dogs 2, 3, and 4 for 24 hours after drug administration.

The disagreement with previous studies in the peak plasma concentrations attained may relate to the difference in the oral preparation used, differences in the assay method used and differences in the statement of the concentrations. In previous studies kinetics are expressed in "blood concentration" rather than the "plasma concentration". This will include the cellular component of blood. Since carprofen is highly plasma protein bound (Rubio and others, 1980), and assuming that cell binding is minimal, the concentration in plasma will be significantly greater than that in whole blood. There is also variation in peak concentrations in different dogs within the study. Variation is likely between dogs in different studies and under different management conditions.The dogs used in some previous studies had been fasted for shorter periods than the dogs in this study and were receiving a different feedstuff (Rôche Internal Data).

4.3 Tolerance Study in Dogs with Carprofen Administered Orally at a Dose Rate of 9 mg/kg Once Daily For Fourteen Days

4.3.1 Summary

The study indicated that at 9 mg/kg body weight carprofen is well tolerated by normal dogs when administered once daily for fourteen days. No dog showed any abnormal clinical signs. There were no biochemical changes suggestive of hepatic or renal toxicity. There were no biochemical or haematological signs suggestive of gastrointestinal ulceration and no blood was detected at consistent or significant levels in faeces. Typical haematological or biochemical signs of NSAID toxicity such as hypoproteinaemia, hypoalbuminaemia, or anaemia did not occur.

The aetiology of high C-reactive protein (CRP) concentrations and eosinophilia in Dog 5 remains obscure but on the evidence available the changes were not associated with carprofen administration or venipuncture. With the exception of increased numbers of Target Cells in all dogs of unknown pathogenesis and the eosinophilia in Dog 5, there were no significant variations in haematological parameters.

It was concluded that at a dose of 9 mg/kg body weight administered once daily over 14 consecutive days, carprofen was well tolerated by clinically healthy, young adult Beagle dogs.

4.3.2 Objective

To assess the tolerance of dogs to carprofen at a dose rate of 9 mg/kg body weight administered orally once daily for 14 consecutive days. Specifically, to determine any clinical, blood biochemical or haematological effects of carprofen at this dose.

4.3.3 Materials and Methods

(a) Test Animals

Six two year old beagle dogs, 3 male and 3 female, were used in the study. The dogs had not received any medication in the fourteen days before the trial commenced. The dogs were fed a complete cereal based diet.

(b) Test Drug

Carprofen [Ro 20-5720/ 659]; Lot No. GMZ 626 B 01; Expiry date: July 1991]

Tablet formulation: 17.5 mg carprofen per tablet;
Supplied by Hoffman-La Rôche via Grampian Holdings Ltd.

(c) Drug Administration

Carprofen was administered orally. The dose for each dog was calculated at 9 mg/kg based on the weight of the dogs on the day before the trial commenced. The number of whole and half tablets required to give a daily dose of 9 mg/kg or greater was calculated [Appendix B1]. The tablets were administered in a single daily dose. The dogs were fed at approximately 9 am each day and tablet administration and sampling carried out between 12 and 3 pm [ie. approx. 3 - 6 hours after feeding].

(d) Trial Design

The six dogs were weighed and a pretrial blood sample was taken at 2 pm on the day before the trial commenced. Blood samples were subsequently taken on days 3, 5, 8, 11, 14, and 17 [the first day of drug administration was considered day 0]. Sampling by venipuncture was performed between 12 and 3 pm, just prior to carprofen administration.

Blood was placed in Lithium-Heparin biochemistry tubes which were centrifuged for 15 minutes and the plasma supernatant decanted for biochemical assay including C-reactive protein estimations. Urea, creatinine, cholesterol, alkaline phosphatase, aspartate transaminase, and alanine transaminase concentrations were measured using a Cobas Mira Discrete Analyser. Sodium and potassium concentrations were measured using flame photometry. Chloride concentration was measured using a chloride meter. Calcium and magnesium concentrations were measured by atomic absorption. Total protein concentration was measured by a standard biuret method using an autoanalyser. Albumin was measured by a standard Bromopresil Green method using an autoanalyser. CRP estimations were performed using a specific enzyme-linked immunoadsorbant assay (ELISA). The analyses were carried out by Glasgow University Veterinary Biochemistry Department.

Blood was placed in potassium-EDTA haematology tubes and was submitted for full haematological profile including differential leucocyte count and film analysis. White and red blood cell counts and haemoglobin estimations were performed using a Coulter Counter S-Plus IV. Differential white blood cell counts were performed microscopically. Analyses took place at University of Glasgow Veterinary Pathology Department.

Clotting times were assessed on sampling days. Free flowing blood was collected from the venipuncture needle using three capillary tubes. These tubes were placed in a tray with a warm water sleeve at 37 C. The time taken for the blood in each tube to clot was noted. The mean clotting time for each dog was calculated, as was the mean clotting time for the six dogs. Faecal samples were taken on sample days and tested for the presence of occult blood using a Colo-Rectal Test kit [Rôche]. The dogs were kept in pens in pairs. Two samples were taken from each pen. Results were recorded for each sample in each of the three pens.

4.3.4 Results

Clinical Observations

At no time during the trial did clinical examination of the six dogs demonstrate any signs of illness. Appetite remained good and faeces of normal consistency were passed. None of the dogs was seen to vomit at any time and water intake remained normal.

Biochemistry

Blood biochemical parameters were measured on the day before the trial began and on days 3, 5, 8, 11, 14, and 17. Dogs 5 and 6 were also sampled on day 47 when results of the C-reactive protein assays during the trial period were returned. Appendix B2 gives the normal value ranges for healthy young adult dogs. Individual results are shown in Appendices B3-B5 and mean blood biochemical values are given in Appendix B5. Mean values for most biochemical parameters were within the normal range on all occasions with the following exceptions:

Mean urea concentrations [normal 0 -7.47 mmol/l] were raised on days 3, 5, 11, and 17. However, this range of normal values is for fasted animals and since sampling occurred 3-6 hours after feeding the levels of urea can be considered normal.

Mean serum inorganic phosphate [normal 1.29 - 2.9 mmol/l] was low in the pretrial sample and on day 14. The mean phosphate was low in the pre sample because all dogs except Dog 4 had serum phosphate levels below 1.29 mmol/l. On day 14, Dogs 1, 5, and 6 showed low levels. Dog 6 had sub-normal phosphate levels in the Pre, and day 3, 5, 11, 14, and 47 samples. Concentrations were particularly low in the Pre sample [0.81 mmol/l n= 1.29 - 2.9 mmol/l] , on day 5 [0.92 mmol/l n= 1.29 - 2.9 mmol/l] and on day 47 [0.88 mmol/l n=1.29 -2.9 mmol/l]. On days 8 and 17, Dog 6 had normal serum phosphate concentrations.

In most cases, the disparate mean values were the result of high or low values in a number of animals rather than extremes in a particular individual. However, Dog 5 and Dog 6 showed more particular changes. Mean C-reactive protein values were raised on days 5, 8, and 14 [normal <10 mg/l]. These values were due to high levels in samples from Dog 5. In Dog 5, CRP values were consistently above normal and on days 5 and 14 exceeded 100 mg/l indicating extensive tissue damage [normal= < 10 mg/l, Dog 5 range 16.5 to >100 mg/l]. The Pre sample also had high CRP levels. At no time did Dog 5 show any clinical signs of illness. The CRP on Day 47 was back in the normal range, indicating that there was not an active inflammatory process occurring at this date. Dog 6 had a high CRP titre on Day 8 [49.1 mg/l, n=<10 mg/l] but all other values of CRP were within the normal range. Total plasma protein was low [normal 50-77 g/l] in Dog 5 on days 5, 11, 14, and 17, mainly due to a hypoglobulinaemia [globulin = 13 g/l on day 5, normal 18-35].

Other results outwith the normal expected limits in individual animals were minor and transitory, generally returning to normal range values on subsequent sampling occasions.

Haematology

Blood samples were taken for haematological examination on the day before the first day of carprofen administration and subsequently on Days 3, 5, 8, 11, 14, and 17. Individual results are given in Appendices B6-B9, mean values in Appendix B9 and ranges of expected normal values in Appendix B2.

Mean haematological parameters measured were within the expected normal limits except for slightly depressed percentage of neutrophils in the differential leucocyte counts on Day 3 and Day 11 [normal =60-77 %]. These values were due to a number of individuals with lower neutrophil percentages and not to a very low level in any individual. The reduction was slight. Individual results were on occasion outwith the expected normal range of values but these were generally marginal and transitory.

Dog 5 had a relative eosinophilia on days 3, 5 and 17 [normal <10%] and an absolute eosinophilia on days 3, 5, 8 and 17 [normal 0.1-1.25 x 10 /l]. All dogs were reported as having increased numbers of Codocytes ["Target Cells"] on film examination on Days 5, 8, 11, 14 and 17.

Clotting Times

Clotting times were measured on the day before the first administration of carprofen and on days 3, 5, 8, 11, 14 and 17. Individual mean results and the mean clotting time for the six dogs on each of the sample days is recorded in Appendix B10. All mean clotting times were within the range of expected normal values and there was no significant increase in clotting time between the Pre sample and samples taken during the administration of carprofen.

Occult Faecal Blood

Occult faecal blood was assessed on the day before the first administration of carprofen and on Days 3, 5, 8, 11, 14, and 17. Results are given for each of the pairs of dogs on test days in Appendix B10. Occult blood in faeces was only detected in one of the two samples from Pen 3 [Dogs 5 & 6] on Day 14. Occasional positive results can be expected in normal dogs not receiving NSAIDs (McKellar, 1989).

4.3.5 Discussion and Conclusions

Carprofen tablets were well accepted orally by all the dogs. At the dose rate of 9 mg/kg body weight once daily for 14 days, no adverse clinical signs were shown by any of the dogs.

Marginal elevations in urea levels in many of the dogs at various sampling times were almost certainly a result of feeding. The low serum phosphate concentrations were transitory in all dogs except Dog 6 where they were low in a number of samples. Consistent low levels of serum phosphate can occur in Rickets, Osteomalacia and Primary Hyperparathyroidism. However, Alkaline Phosphatase levels were not raised and phosphate levels were within expected normal values on Day 8 and Day 17. These conditions are very rare and no clinical signs were shown by Dog 6 at any time. Whatever the aetiological or physiological basis of the low serum phosphate in Dog 6, it appears unrelated to and unaffected by carprofen administration since pretrial and Day 47 (33 days after the last dose of carprofen) samples also have depressed levels of serum phosphate. Mild hypophosphataemia may have been related to the cereal based diet.

The raised C-reactive protein (CRP) values in Dog 5 on all days before and during the trial could have a number of causes. CRP is virtually absent from serum before tissue damage and is only produced as part of the Acute Phase Reaction in response to tissue damage events such as vasodilation, inflammation, and movement of leucocytes to the area of damage. CRP has been shown to be present at high concentrations in serum for about 4 days following surgery and in a variety of inflammatory conditions including Systemic lupus erythematosus, polyarthritis, Pemphigus, Thrombocytop enia, osteoarthritis and acute orthopaedic injuries and in response to the administration of endotoxin. The levels of CRP rapidly decline when the inflammatory response abates (Eckersall and others, 1985; Caspi and others, 1987). Thus, Dog 5 had an unidentified inflammatory condition on the day before the start of carprofen administration and during the trial but not on day 47, 33 days after the last dose of carprofen. The levels of CRP were over 100 mg/l on Days 5 and 14 which is indicative of extensive tissue damage. However, at no time did Dog 5 show any clinical signs of pathology. There were no other significant changes in the blood biochemistry of Dog 5 except the low total protein and Globulin levels. Dog 5 also had an eosinophilia in a number of haematology samples. These findings may or may not have been related to the inflammatory process elucidated by the CRP assay.

Whatever the aetiology of the condition, it does not appear to have involved hepatic, renal or gastrointestinal pathology which would have caused changes in biochemical parameters other than CRP. Neither carprofen nor venipuncture initiated the inflammatory process since elevated pretrial CRP levels indicated that tissue damage was present on the day before the first administration of carprofen. The rises in CRP on days 5 and 14 to over 100 mg/l [normal= <10 mg/l] may have been precipitated by carprofen or venipuncture or may have been part of the progression of the inflammatory process. The process had apparently resolved by Day 47 when CRP levels were within normal expected values. The single high CRP value in Dog 6 on Day 8 was transient, all other samples having normal values. It could have been due to any mild acute inflammatory response.

Most of the haematological values outwith the normal range of expected figures were marginal and transitory. The two findings of concern were the elevated numbers of Codocytes or Target Cells in all the Dogs' blood films on Days 5, 11, and 17 and the eosinophilia shown by Dog 5 on Days 3, 5, 8 and 17. Codocytes or Target Cells are thin, cup-shaped erythrocytes with a dense central area of haemoglobin that is separated partially or completely by a colourless or pale zone from the peripheral haemoglobinised region. This is a result of the redistribution of haemoglobin within the cell, probably as a consequence of excessive cell membrane or a decrease in haemoglobin content, or both. In man, Codocytes are found in hypochromic anaemias, liver disease with cholestasis, a rare deficiency of the enzyme lecithin-cholesterol acyltransferase (LCAT), certain haemoglobinopathies and after splenectomy. In hypertonic plasma they may be seen as an artefact. Target Cells have been found in dogs with conditions similar to humans except for haemoglobinopathies and LCAT-deficiency which have not been described in animal species. In this case, a possible cause of increased numbers of Target Cells associated with NSAID administration would be liver damage. However, there was no consistent or significant rise in enzymes associated with hepatic damage or cholestasis, or in bilirubin or CRP. There was no consistent hypoproteinaemia or hypoalbuminaemia and no anaemia. It seems very unlikely that liver damage could cause Target Cell formation in isolation.

The absolute and relative eosinophilia in Dog 5 could have a number of causes. Eosinophilia is most often associated with disease involving antigen, IgE antibody and Mast Cell response. Diseases which may be included in this are parasitic infections eg. gastrointestinal parasitism, flea bite allergy/dermatitis, allergic respiratory disease, dermatoses, allergic responses to drugs and any disease condition involving the continuous degranulation of Mast Cells such as eosinophilic enteritis. The cause in this case is uncertain. No other indications of any possible allergic reaction to the carprofen were apparent during the trial. Whether the eosinophilia and high CRP in Dog 5 were linked is conjecture.

The clotting time studies during the period of carprofen administration demonstrated no increase in mean clotting time outwith the normal range expected in untreated dogs [normal range 1.53-4.03 minutes (mean +/-2 S.D.)]. The negative faecal blood results provide some evidence against gastrointestinal haemorrhage during carprofen administration at 9 mg/kg body weight.

In this study, carprofen was well tolerated by normal dogs when administered orally at 9 mg/kg once daily for fourteen days. No dog showed any abnormal clinical signs and there were no biochemical changes suggestive of hepatic or renal toxicity. There were no biochemical or haematological signs suggestive of gastrointestinal ulceration and blood was not detected at significant levels in faeces.Typical haematological or biochemical signs of NSAID toxicity such as hypoproteinaemia, hypoalbuminaemia, or anaemia did not occur.

4.4 Clinical Trial of the Efficacy of Carprofen 17.5 mg Tablets in the Therapy of Canine Osteoarthritis

4.4.1 Summary

The aim of the trial was to establish the clinical efficacy of carprofen tablets in the therapy of clinical osteoarthritis in the dog. This was under taken by comparing the effect of carprofen tablets with the effect of a previous treatment for the condition in the same animal and by comparing the effect of treatment in a group of carprofen treated dogs with the effect of treatment in a group of phenylbutazone treated dogs. Ten dogs received one drug and then the other in a form of cross-over trial.

Carprofen tablets were efficacious in the therapy of 49 of 74 cases of clinical osteoarthritis (66%). Carprofen was as efficacious or superior to previous treatment in 32 of 46 cases (70%) where the veterinarian stated comparative efficacy. Phenylbutazone treatment was considered satisfactory in only 10 of 21 dogs treated (48%). However, there was no significant difference between efficacy of treatment in the carprofen treated and phenylbutazone treated groups or in the effect of carprofen and phenylbutazone in the ten cases which received both drugs. In carprofen treated cases there were reported side effects such as vomiting, diarrhoea, constipation and inappetance which may have been associated with gastrointestinal disturbance. There was no evidence of increased toxicity in a limited number of dogs with concurrent cardiac or renal disease.

From the limited numbers of dogs treated during the trial, carprofen appears to be effective in the therapy of many cases of clinical osteoarthritis when used at 0.71 to 3.50 mg/kg/day. There was a correlation between the treatment dose and effect within this dose range. Carprofen seemed to be very much more effective when used at over 2 mg/kg/day sid or bid than when used at lower dose rates. For the duration of treatment, carprofen was well tolerated in most dogs. The incidence of side effects and treatment withdrawal were comparable with other non-steroidal anti-inflammatory drugs (NSAIDs). Treatment was withdrawn because of side effects in only 2 dogs. In many cases the reported side effects were thought to be coincidental and unconnected to carprofen therapy.

4.4.2 Objective

1) To compare carprofen tablets:
   (a) with previous medical treatment in existing cases
   (b) with the standard drug phenylbutazone in new cases
in the control of the signs of clinical osteoarthritis in the dog.

2) To determine and record the incidence and nature of any unwanted side effects.

4.4.3 Materials and Method

Test Drugs

Carprofen tablets
[Ro 20-5720/659; Lot No. G MZ 626 B 01; Expiry date: July 1991]
(each tablet containing 17.5 mg Carprofen)

Flexazone Tablets® 100 mg [Batch No. 80302A-1; Expiry Date: April 1993]
(each tablet containing 100 mg Phenylbutazone BP)

Trial Design

The aim of the trial was to establish the clinical efficacy of carprofen tablets in the therapy of osteoarthritis in the dog. This was undertaken by comparing the effect of carprofen tablets with the effect of a previous treatment for the condition in the same animal and by comparing the effect of treatment in a group of carprofen treated dogs with the effect of treatment in a group of phenylbutazone treated dogs. Thus the trial was based on a form of Positive Control design. A Placebo Control design would not have been acceptable to owners or veterinary practitioners and would also have been ethically unsound. It was not considered practical to perform a "cross-over" type trial because of the possible lack of compliance of veterinary practitioners and owners. However, veterinarians were encouraged to use both drugs in the same dog where possible. It was hoped that the carprofen and phenylbutazone treated groups would be large enough to be comparable.

The number of cases required to assess the efficacy of the drug was greater than would be seen in a reasonable period of time at Glasgow University Veterinary Hospital and veterinarians in general practice were asked to use carprofen and phenylbutazone in cases requiring NSAID treatment for osteoarthritis. No financial or other inducements were offered or given to veterinarians or practices involved in the trial.

Investigator Selection

Veterinary practitioners who were known personally by the authors, by Dr. Q. McKellar, of the Department of Veterinary Pharmacology, or by Mr. S. Carmichael of the Department of Veterinary Surgery, University of Glasgow were contacted by letter and asked to participate in the clinical trial. Further correspondence and telephone conversations led to the recruitment of 26 practices, 16 of which returned results information sheets. Each practice was supplied with information on the product, and instructions on case selection, dose recommendation and condition scoring [Appendices C1; C2; C3]. Approximately 20 sets of results information sheets ["Patient Information", "Efficacy Assessment" and "Clinical Assessment" sheets; Appendices C4; C5; C6] were also delivered to each practice. Carprofen 17.5 mg tablets and Flexazone Tablets® 100 mg (each tablet containing 100 mg Phenylbutazone BP) were supplied.

Dose Recommendations

The Dose Recommendations sheet supplied to practitioners [Appendix C2] recommended that carprofen tablets be administered orally based on a theoretical minimum of 0.7 mg per kilogram bodyweight per day in a single daily dose. Due to the set quantity per tablet the recommendations would give a daily dosage of between 0.7 and 1.75 mg carprofen per kilogram bodyweight (minimum bodyweight 5 kg). The initial treatment period was to be 5 to 7 days, subject to clinical response.

After two months, the author wrote to participating veterinarians advising that the dose rate of carprofen was adjusted such that dogs would receive a theoretical minimum of 2 mg/kg/day. Due to the set quantity per tablet, the recommendations would give a daily dosage of between 2 and 5.25 mg carprofen per kilogram bodyweight (minimum bodyweight 5 kg).

With the 100 mg tablets provided, a dose rate in tablets was calculated such that phenylbutazone would be administered at a suggested dose rate of between 8 and 16 mg/kg bodyweight/day in two divided doses. It was stated that phenylbutazone should not be used in animals with cardiac, renal or hepatic insufficiency or in animals showing signs of or with a history of anaemia, as recommended in the Data Sheet for the product.

Case Selection and Protocol

Carprofen tablets were to be assessed for therapeutic effect in cases of clinical osteoarthritis. Diagnosis was made by the history and clinical presentation. In some cases radiography was performed and radiographic findings consistent with a clinical diagnosis of osteoarthritis reported. Since no financial incentives or remuneration were offered to any veterinarian it was not possible to insist that diagnostic radiography was performed in all cases.

Cases were of two groups:

- existing cases (dogs already receiving medical therapy for osteoarthritis);
- new cases (dogs at first presentation to the practitioner or for which the previous history was not known).

The protocol for the trial was as follows:

1. Existing Cases:

i) Information on the owner and the dog was recorded. The joints affected were noted. In most cases, a brief summary of the clinical history was given. The dose, regime, duration and effect of the previous treatment was noted and the previous treatment was withdrawn.

ii) Where possible, dependent upon the wishes of the owner and the veterinary surgeon, the time taken for the signs of the painful condition to reappear was monitored.

iii) The clinical condition was scored for lameness [0 to 4], weightbearing [0 to 2] and joint mobility [0 to 2] according to the condition scoring sheet [Appendix C3].

iv) Therapy was instituted with carprofen tablets at the recommended dose rate.

v) The effect of treatment was monitored, i.e. the dog was re-examined after a period of treatment (5 to 7 days was the recommendation) and the clinical condition was rescored. Where possible, the owner was to be questioned as to the efficacy of the treatment and the time taken for the treatment to have an effect, if any.

vi) At the end of the treatment period, the "Clinical Assessment" sheet was to be completed with the veterinary practitioners' subjective opinion on whether the treatment had been satisfactory and how the treatment compared to the previous treatment. Any side effects could also be noted on the "Clinical Assessment" sheet. Provision was made on the first sheet ["Patient Information"] for noting premature withdrawal and its cause or any change of dose rate.

2. New Cases:

i) Osteoarthritis was confirmed clinically and in some cases radiographically. Patient information and the joint(s) affected were noted. A brief summary of the history was also to be given.

ii) The clinical condition was scored for lameness [0 to 4], weightbearing [0 to 2], and joint mobility [0 to 2] according to the condition scoring sheet [Appendix C3].

iv) Therapy was instituted with carprofen tablets or phenylbutazone (Flexazone Tablets) at the recommended dose rate on an "alternate case" basis. i.e. treating dog 1 with carprofen tablets, dog 2 with phenylbutazone, dog 3 with carprofen tablets etc.

v) The effect of treatment was monitored, ie. the dog was re-examined after a period of treatment (5 to 7 days was the recommendation) and the clinical condition was rescored. Where possible, the owner was to be questioned as to the efficacy of the treatment and the time taken for the treatment to have an effect, if any.

vi) At the end of the treatment period, the "Clinical Assessment" sheet was to be completed with the veterinary practitioners' subjective opinion on whether the treatment was satisfactory. Any side effects could also be noted on the "Clinical Assessment" sheet. Provision was made on the first sheet ["Patient Information"] for noting premature withdrawal and its cause or any change of dose rate.

It was suggested that, where possible, new cases should be treated firstly with one of the two test drugs and then, after an interval, the drug used could be switched to the second drug. This would allow comparison of the effects of carprofen and phenylbutazone tablets in the same animal.

Exclusions

Dogs which were concurrently receiving treatment with a drug with antiinflammatory or analgesic effect were excluded from the results analysis. Incomplete or totally illegible results forms were also excluded. Dogs which were not diagnosed as having osteoarthritis or with a history not consistent with such a diagnosis were not included in the results analysis. It was considered reasonable to consider results valid in cases where the full address of the owner or the dog name was omitted from the "Patient Information" form.

Results Analysis

Five statistical analysis methods were used: unpaired "Students" *t* -test; paired *t*-test; Wilcoxon Signed Rank test; Chi squared (X^2) test; Kendall Correlation (Weisbrot, 1985; Wardlaw, 1985).

The Student's *t*-test or *t*-independent test compares the means and standard deviations of two independent samples; each standard deviation is presumed to be from the same population. This test was used to compare the differences in the total condition scores in the phenylbutazone and carprofen treated groups.

The paired *t*-test analyses the average differences between a series of paired observations. It is considered more rigorous and useful than the unpaired "Students" *t*-test since it allows isolation of the effects of manipulation on otherwise identical samples. However, the paired *t*-test, like the Student's *t*-test, does assume a parametric or normal distribution of data which could not be guaranteed for the parameters measured during the trial (lameness, weightbearing, joint mobility, and total condition scores), especially when the sample size was so small.

The Wilcoxon Signed Rank test is the non-parametric homologue of the parametric *t*-test. Thus, if the data was non-parametric, any statistical significance in differences between pre and post-treatment condition scores would still be assessed.

The Chi squared (X^2) test is frequently used in epidemiology and therapeutics to compare categorical data (lived/died, improved/not improved). It was used in this trial to compare the response rates to carprofen and previous treatment or phenylbutazone treatment, and to compare groups with or without advice to reduce exercise.

Kendall Correlation is a non-parametric rank-order correlation. This test was used to assess whether there was any statistically significant linear correlation between the dose rate of carprofen administered and the improvement in the overall condition of the patient.

The effect of treatment in carprofen and phenylbutazone groups was assessed by the comparison of pretreatment and post-treatment condition scores for lameness, weightbearing, joint mobility, and the total condition score (Lameness + weightbearing + joint mobility). The condition scores before and after treatment were compared using a paired *t*-test and by a Wilcoxon Signed Rank test.

Treatment with carprofen and phenylbutazone was compared by the differences in pre and post-treatment condition score within the two treatment groups. The differences in pre and post condition scores between carprofen tablet and phenylbutazone treatment were compared using a Student's *t* -test and the overall effect of treatment (Improved / Not Improved) compared with a X^2 test. The veterinary practitioner gave a subjective opinion of whether Carprofen Tablets were more or less efficacious than the previous treatment.

4.4.4 Results

One hundred and four sets of case results sheets were returned. Nineteen sets of results were completely excluded. In 5 cases the results were incomplete. In 8 cases the dog had received concurrent treatment with a drug preparation with possible anti-inflammatory or analgesic activity and which therefore might interfere with the results obtained for the test drugs. A further 6 cases were treated which were not diagnosed as suffering from clinical osteoarthritis.

After the exclusion of these results, there were a total of 85 dogs reported. The mean number of case reports per practitioner was 5. However, the number of usable results per practitioner ranged from 1 to 18 cases (Appendix C8).

Seventy four dogs were treated with carprofen tablets; twenty one dogs were treated with phenylbutazone (Flexazone® 100 mg Tablets); ten dogs were treated with carprofen tablets and phenylbutazone consecutively: 8 dogs were treated with carprofen and then phenylbutazone; 2 dogs were treated with phenylbutazone and then carprofen.

Trial Animal Details

Animal details are tabulated in Appendices C9 & C10.

Age Distribution [Appendix C11]

Most dogs clinically affected were in the 7 to 12 years old range (Mean age = 8.3 years; Standard deviation [S.D.] = 4.4 years). The age of one dog was not specified. The mean age of the phenylbutazone treated dogs was 7.8 years (S.D.= 3.5 years). The mean age of the carprofen treated dogs was 8.3 years (S.D. 4.6 years). These findings were similar to those for the PLT ® Tablet clinical trial in Section 5.2.4.

Breed Distribution [Appendix C12]

The breed distribution was similar to that seen in the PLT clinical trial (see 5.2.4) with a high proportion of the dogs being Labrador Retrievers (26 of 85 dogs, 31%). There were also more German Shepherd Dogs and Golden Retriever and Border Collies than other breeds. Breed distribution was similar in the carprofen and phenylbutazone treated groups, although there were relatively fewer Golden Retrievers, Border Collies and German Shepherd Dogs in the phenylbutazone treated group.

Sex Distribution [Appendix C13]

There was no significant sex predeliction for clinical osteoarthritis although slightly greater numbers of males than females were present in the sample population (47 of 85 dogs; 55 %). The sex distribution in the carprofen and phenylbutazone treated groups was similar.

Bodyweight Distribution [Appendix C14]

The body weight of cases ranged from 1.5 kg to 75 kg (Mean 26.3 kg; S.D. 12.1 kg). Most dogs (56 of 85; 66%) were between 16 and 35 kg in weight. The bodyweight of the dogs treated with phenylbutazone ranged from 6 kg to 45 kg with a mean of 26.6 kg (S.D. 11.3 kg). The bodyweight of the carprofen treated dogs varied from 1.5 kg to 75 kg with a mean of 26.1 kg (S.D. 12.4 kg).

Joint(s) Affected [Appendices C15; C16; C17]

The joint(s) affected and a brief history as recorded by the veterinary practitioner are listed for each case in Appendices C15 & C16. Thirty four dogs (40 %) had osteoarthritis of one or more often of both hips. In addition, 5 dogs had "hind limb" problems. Thirty three dogs had osteoarthritis affecting one or both elbows (39 %). Twenty eight dogs had osteoarthritis of one or both stifles (33 %). Sixteen dogs had shoulder osteoarthritis (19 %). In 21 dogs (25 %) more than one joint type was stated to be affected (eg. both hips, one stifle).

The joints affected in the carprofen treated dogs are similar to the total trial sample. There were no bilateral stifle, carpal or tarsal osteoarthritis cases in the phenylbutazone treated group.

Case History [Summary: Appendix C17]

No history was given in 26 cases. In most cases little history was given. Seven dogs had had previous surgery. One dog received a femoral head excision 5 weeks before the trial. Two dogs had elbow arthrotomies to remove osteochondrosis lesions two months before the trial period. Two dogs had a trochleoplasty of one or both stifles to correct a patellar subluxation in one case 2 months and in the other 19 months before the trial period. One dog had an elbow arthrotomy to remove ununited anconeal processes 5 months before the trial period. In 18 dogs the history gave firm evidence that the osteoarthritis had developed secondary to injury, developmental or conformational abnormalities. In twelve new cases, it was stated that the diagnosis had been confirmed by radiography. Where the duration of the clinical problem was stated it was months or years.

Previous Treatment

Details of previous treatments administered, dose rates, durations of treatment and effect of treatment is given in Appendices C34 - C36.

Fifty dogs had been previously treated. A total of 60 previous treatments had been given. One dog was treated with antimicrobials post-operatively with a reported "marked improvement". In the remaining 59 cases, NSAIDs or steroids were used in therapy. Previous treatment had no effect on the painful condition in 9 cases (9 of 60; 15%). In 30 cases the previous treatment had some effect (50%). In 18 cases, treatment had a marked effect (30%). In one case treated with Predno-Leucotropin Tablets, the dog was said to be "sound" whilst on treatment. In one case the effect of treatment was not stated.

The time for signs of the painful condition to reappear after the withdrawal of the previous treatment was stated in 28 cases. The period ranged from 2 days in a number of cases to one dog which had not been treated for 2 or 3 months. Where the time taken for the recurrence of painful signs was stated, the mean period was 7 days (S.D. 12 days). However, in the majority of cases, the period was 2 to 7 days. In one case it was stated that treatment was not withdrawn between the previous treatment and Carprofen treatment. In 18 cases, the "Time taken for return of painful condition" was not completed.

Carprofen Treatment

Dose Rates and Regimes:[Appendices C18-20]

The *initial* dose rate used by the practitioners ranged from 0.71 to 2.85 mg/kg/day. Overall, the minimum daily dosage administered was 0.39 mg/kg/day and the maximum dosage administered was 3.50 mg/kg/day. [Details Appendices C18-C20 and represented graphically in Appendix C20].

The treatment regime was once a day dosing (s.i.d.) in 62 of 99 treatments (63%). A divided daily dose (b.i.d.) was the regime in 32 of 99 treatments (32%). The initial treatment dose was divided into three administrations per day (t.i.d.) in 4 cases (4%). In one dog, the regime was reduced from s.i.d. to every other day treatment. The total duration of treatment ranged from a maximum of 70 days to a minimum of one day in a dog which vomited when treated with Carprofen. The mean treatment period before reexamination was 16 days (S.D. 12 days). For details see Appendices C18-20.

Other advice was reported as given to the owners in 38 cases (51%). In 30 cases the owner was advised to reduce the exercise which the dog received or change the exercise to frequent short walks or lead exercise. In two cases normal exercise was recommended. It was stated in only 6 cases that weight reduction was advised (Details in Appendices C18-20).

Twenty dogs were reported to be receiving other treatment or be suffering from other disease. Eight dogs were receiving treatments for cardiac disease, including the diuretic Frusemide in 5 cases. Five dogs were being treated with Millophyline-V (Etamiphyline camsylate). Three dogs were receiving treatment with digoxin. Case 21 suffered from incontinence but was not receiving any treatment. Case 23 had a femoral head excision 7 days before treatment. Case 26 had skin disease, conjunctivitis, and rhinitis. Case 34 had an abscess and was treated with antimicrobials; the antimicrobial was not stated. Case 36 was reported to suffer occasional bouts of colitis which were controlled by dietary changes. Case 52 was treated with Ampicillin after the surgical removal of a superficial growth. Case 54 had polydipsia for which Hills k/d® had been prescribed. Case 60 was treated with the anthelmintic Piperazine on the first day of trial treatment. Case 110 had a chronic nephritis. Case 201 had a conjunctivitis and lymphadenopathy and was treated with Ampicillin. Case 202 had a chronic nephritis and was treated with Ceporex® tablets.

It was hoped that none of the preexisting diseases would interfere with the actions of carprofen therapy. Since none of the concurrent treatments have any significant known direct anti-inflammatory or analgesic actions, it was not thought that these treatments would affect the efficacy of the carprofen treatment.

No specific information on the interaction of carprofen and diuretics such as frusemide, or the effect of carprofen in dogs with preexisting cardiac or renal disease was previously known to the author.

Palatability was reported as "Good" in 47 cases (47 of 66; 71 %), "Average" in 19 cases (19 of 66; 29 %) and "Poor" in no cases [66 cases Palatability reported].

Condition Scores:

The pretreatment, post-treatment and difference in condition scores for lameness, weightbearing, and joint mobility are given for each case in Appendices C21 & 22. A graphical representation is given in Appendices C23-26.

Lameness [Appendices C21; 22; 23]

One dog was not lame before treatment. Carprofen treated dogs demonstrated a reduction in lameness score of between 1 and 3 units in 49 of the 73 cases which were lame before treatment (67%). In three cases (4%) the lameness score was worse at reexamination. In 22 cases (30%) there was no change in lameness score at reexamination. Eleven dogs (15%) were not lame after treatment and a further 35 dogs (47%) were normal when standing and walking (score 1). The mean pre treatment lameness score was 2.4 (S.D. 0.8). The mean post treatment lameness score was 1.5 (S.D. 1.0). The mean reduction in lameness score between the pre and post treatment examinations was 0.92 units (S.D. 0.90). The pre and post treatment lameness scores are represented graphically in Appendix C23.

A paired *t* -test showed a significant improvement in lameness score between the pre and post treatment examinations ($p < 0.001$). A Wilcoxon Signed Rank Test showed a significant improvement in lameness score between the pre and post treatment examinations ($p < 0.001$).

Weightbearing [Appendices C21; C22; C24]

Weightbearing was reduced in 44 cases (44 of 74; 59%) before treatment. In 30 dogs weightbearing was not reduced (41%). Carprofen treated dogs showed an improvement in weightbearing score in 18 cases where weightbearing had been affected (18 of 44; 41%). In one case, the weightbearing score after treatment was worse than before treatment. The mean pre treatment weightbearing score was 0.7 (S.D. 0.6). The mean post treatment weightbearing score was 0.5 (S.D. 0.6). The mean reduction in weightbearing score between the pre and post treatment examinations where weightbearing was affected was 0.4 units (S.D. 0.5). The pre and post treatment weightbearing scores are represented graphically in Appendix C24.

A paired t-test showed a significant improvement in weightbearing score between the pre and post treatment examinations ($p < 0.001$). A Wilcoxon Signed Rank Test showed a significant improvement in weightbearing score between the pre and post treatment examinations ($p < 0.001$).

Joint Mobility [Appendices C21; C22; C25]

Joint mobility was reduced in 62 cases (62 of 74; 84%) before treatment. In 12 dogs joint mobility was not reduced (16%). Carprofen treated dogs showed an improvement in joint mobility score in 13 cases where joint mobility had been affected (13 of 62; 21%). In three cases, the joint mobility score was worse after treatment than before treatment. The mean pre treatment joint mobility score was 1.0 (S.D. 0.6). The mean post treatment joint mobility score was 0.8 (S.D. 0.6). The mean reduction in joint mobility score between the pre and post treatment examinations where joint mobility was affected was 0.2 units (S.D. 0.6). The pre and post treatment joint mobility scores are represented graphically in Appendix C25.

A paired *t* -test showed a significant improvement in joint mobility score between the pre and post treatment examinations ($p < 0.01$). A Wilcoxon Signed Rank Test showed a significant improvement in joint mobility score between the pre and post treatment examinations ($p < 0.01$).

Total Condition Score [Appendices C21; C22; C26]

Seven dogs had a zero score after carprofen treatment (7 of 74; 9%). Fifty one dogs showed an improvement in condition score at reexamination after treatment with carprofen (51 of 74; 69%). In twenty dogs, the condition score was unchanged by carprofen treatment. In 3 dogs, the condition score was worse at reexamination. The mean total condition score before treatment was 4.1 (S.D. 1.5). The mean post treatment total condition score was 2.8 (S.D. 1.7). The mean reduction in total condition score between the pre and post treatment examinations was 1.4 units (S.D. 1.5). Pre and post treatment total condition score is represented graphically in Appendix C26.

A paired *t* -test showed a significant improvement in total condition score between the pre and post treatment examinations ($p < 0.001$). A Wilcoxon Signed Rank Test showed a significant improvement in total condition score between the pre and post treatment examinations ($p < 0.001$).

To try to assess whether advice on exercise had made a difference, the improvement in the total condition scores of dogs where the owner was told to reduce exercise was compared with the scores from dogs where no exercise advice was stated. The difference between the two groups was not significant when the Reduced Exercise and No Advice Groups were analysed by a X^2 test or Students *t*-test. The improvement in total condition score between dogs which were judged to be overweight by the veterinarians was less than that in dogs which were not considered overweight. However, because the number of dogs which were of "ideal weight" was small and the difference in mean improvement was also small, the difference between the two groups was not statistically significant. No significant differences in treatment response were found for different breeds or for different affected joints.

Veterinarian Satisfaction:

The effect of carprofen treatment was considered satisfactory by the veterinary practitioner in 49 of the 74 cases (66%) and to have been unsatisfactory in 25 cases (34%).

Reported Side Effects and Treatment Withdrawals

Case 1 John: 8 month old Golden Retriever Male 30 kg. Bilateral elbow osteoarthritis.
Carprofen 2 x 17.5 mg b.i.d. [2.33 mg/kg/day]
After two days, good analgesia caused the dog to over-exercise and lameness increased. Treatment was temporarily withdrawn.

Case 2 John: 8 month old Golden Retriever Male; 30 kg. Bilateral elbow osteoarthritis. secondary to osteochondrosis lesions. Also hip dysplasia. Littermate of Case 1.
Carprofen 2 x 17.5 mg b.i.d. [2.33 mg/kg/day]
After two days, good analgesia caused the dog to over-exercise and lameness increased. Treatment was temporarily withdrawn.

Case 6 Cornelius: 4 year old Collie Spayed Female; 23 kg. Bilateral elbow osteoarthritis.
Carprofen 17.5 mg s.i.d. [0.76 mg/kg/day]
Veterinary surgeon reported: " Owner thought drug caused excessive drowsiness and was distressed by this". However, treatment was continued.

Case 15 Glass: 12 year old Chihuahua Male; 6.5 kg (Ideal weight approximately 4 kg). Bilateral elbow O.A. Previous treatment with Phenylbutazone at 15.4 mg/kg/day and Prednisolone at 0.15 mg/kg/day.
Carprofen 0.75 x 17.5 mg s.i.d. [2.02 mg/kg/day]
Veterinary surgeon reported " Slight inappetance". However, treatment was more effective than previous treatment and was continued without any further adverse effects.

Case 23 Knowles: 9 month old Jack Russell Terrier Male; 6 kg. Left hip: Avascular Necrosis of the Femoral Head; Femoral head excision performed 5 weeks before treatment with phenylbutazone. Later cross-over treatment with carprofen.
Carprofen 0.5 x 17.5 mg b.i.d. [2.92 mg/kg/day]
Veterinarian reported: Vomited on second and third days of treatment. Treatment withdrawn. Vomiting stopped. No time-scale or indication of severity was given.

Case 24 Miller: 14 year old Labrador Retriever F/N; 27 kg. Stiff on all legs but lame left fore when examined. Previously treated with Phenylbutazone at 11.1 mg/kg/day for 18 months. Also suffering from mild renal failure and proteinuria.
Carprofen 1.5 x 17.5 mg s.i.d. [0.97 mg/kg/day]
Veterinarian reported: Slight increase in thirst ? However, previous renal failure/proteinuria was already causing polydipsia. Treatment was continued.

Case 27 Gadsby: 6 year old Bearded Collie F/N; 30 kg. Right shoulder and elbow osteoarthritis.
Carprofen 1.5 x 17.5 mg s.i.d. [0.875 mg/kg/day]
Owner reported that the dog "smelt funny" for the first ten days of treatment. Treatment was continued.

Case 36 Flanagan: 12.5 year old Golden Retriever Male; 34 kg (Ideal weight ≈ 30 kg). Bilateral stifle secondary osteoarthritis. Previously treated with Phenylbutazone at 17.6 mg/kg/day and Predno-Leucotropin Tablets.
Carprofen 3 x 17.5 mg s.i.d. [1.54 mg/kg/day]
Veterinarian reported that after two days the dog had diarrhoea containing mucus. The dog had had previous bouts of colitis controlled by dietary changes. The veterinarian considered it doubtful that the mucoid diarrhoea was a true side effect and was more probably coincidental with treatment. However, treatment was withdrawn.

Case 48 Molloy: 7 year old German Shepherd Dog Female; 35 kg. Elbow osteoarthritis
Carprofen 1.5 x 17.5 mg daily [0.75 mg/kg/day]
Veterinarian reported that the dog showed inappetance on days 5 to 7 of treatment and increased salivation whilst on treatment. Treatment had little effect and the dog had two painful episodes during the treatment period. Treatment was not withdrawn.

Case 59 Walls: 10 year old German Shepherd Dog Male; 45 kg (Ideal weight ≈ 35 kg). Bilateral hip osteoarthritis. Previously treated with Phenylbutazone at 8.89 mg/kg/day.
Carprofen 1 x 17.5 mg b.i.d. [0.77 mg/kg/day]
Veterinarian reported that the dog had diarrhoea on days 2 to 5 of treatment. Owner thought that the diarrhoea might have been dietary in origin. Dietary control was advised and the carprofen dosage was reduced by one half and later increased. Treatment was not withdrawn.

Case 64 Jagielko: 13 month old Mastiff Male; 75 kg. Bilateral elbow osteoarthritis secondary to ununited anconeal processes.

Carprofen 8 x 17.5 mg daily [1.86 mg/kg/day]

Veterinarian reported that the dog vomited three times. Thought that this may have been related to an Upper Respiratory Tract infection. Treatment was not withdrawn. Vomiting ceased.

Case 65 Jack: 8 year old Golden Retriever Male; 35 kg. Stifle osteoarthritis. Previously treated with Phenylbutazone at 17.1 mg/kg/day.

Carprofen 1.5 x 17.5 mg s.i.d. [0.75 mg/kg/day]

Veterinarian reported: Diarrhoea from 7 to 14 days. Reported that the dog was "prone to diarrhoea". Treatment was not withdrawn.

Case 67 Osbourne: 2 year old Labrador Retriever Female; 23 kg. Elbow/Shoulder.

Carprofen 1.5 x 17.5 mg b.i.d. [2.28 mg/kg/day]

"Vomiting" reported. No details given. Treatment not withdrawn.

Case 110 Barker: 14 year old Crossbred Male; 17 kg. All joints affected. Previously treated with Predno-Leucotropin Tablets and Phenylbutazone. Concurrent "chronic nephritis".

Carprofen 17.5 mg b.i.d. [2.06 mg/kg/day]

Variable thirst reported. Treatment not withdrawn.

Case 203 Edwards: 12 year old Pekinese Male; 5 kg. Stifle osteoarthritis. Previously treated with Predno-Leucotropin Tablets. Also on Digitalis.

Carprofen 0.25 x 17.5 mg b.i.d. [1.75 mg/kg/day]

Veterinarian reported increased thirst and constipation. Peridale granules prescribed for constipation. Carprofen was stated to be more effective and to cause less nausea and polyphagia than the previous treatment. Treatment was not withdrawn.

Case 211 Stalker: 8 year old Shetland Sheepdog Male; 10 kg. Right hind leg affected. Previously treated with Opticorten Tablets. Concurrent therapy with "Heart Tonic and Stimulant" and Frusemide.

Carprofen 0.5 x 17.5 mg daily [0.88 mg/kg/day]

Veterinarian reported thirst. Thought to be due to diuretic therapy. Treatment not withdrawn.

Case 212 Scott: 16 year old Standard Poodle; 23 kg. Hip osteoarthritis. Concurrent therapy with Millophyline.

Carprofen 3 x 17.5 mg s.i.d. [2.28 mg/kg/day]

Veterinarian reported dog suffered from constipation and restlessness. However, dog said to be much happier and livelier on treatment and treatment was not withdrawn.

Phenylbutazone Treatment

Dose Rates and Regimes [Appendix C27]

The initial dose rate used by the practitioners ranged from 5.7 to 33.3 mg phenylbutazone/kg/day with a mean of 12.4 mg/kg/day (S.D. 5.7). The regime was s.i.d. in two phenylbutazone treatments, b.i.d. in 13 treatments and t.i.d. in 4 cases. In two cases the regime was not stated. The duration of treatment before the dog was re-presented ranged from 4 to 50 days (mean = 16.5 days; S.D. 10.9). Other advice was reported as given to the owners in 5 cases. In five cases the owner was advised to reduce the dogs' exercise and in two cases weight loss was advised.

Two dogs were reported to be receiving other treatment or to be suffering from other disease. Case 204 was receiving treatment with Heart Tonic and Stimulant Tablets® and Case 205 was receiving treatment with Lasix® during the trial. Presumably both of these dogs had cardiac disease. It was not thought that these diseases or treatments would affect the efficacy of the treatment. However, the use of phenylbutazone in animals suffering from cardiac disease increases the risks of nephrotoxicity. Phenylbutazone is reported to cause fluid retention in man. It is also known that the concurrent administration of NSAIDs with frusemide reduces the diuretic action of the latter.

Palatability of the sugar-coated Flexazone 100 mg Tablets® was reported as "good" in 8 cases and "average" in 10 cases. In 3 cases the palatability of the tablets was not stated.

Condition Scores

The phenylbutazone group pretreatment, post-treatment and difference in condition scores for lameness, weightbearing, and joint mobility are given for each case in Appendix C28. A graphical representation is given in Appendices C29-32.

Lameness [Appendices C28 & C29]

Phenylbutazone treated dogs showed a reduction in lameness score of between 1 and 3 units in 8 of the 21 cases which were lame before treatment (38%). In 13 cases (62%) there was no change in lameness score at reexamination. Three dogs (14%) were not lame after treatment and a further 8 dogs (38%) were normal when standing and walking (score 1). The mean pre treatment lameness score was 2.6 (S.D. 0.9). The mean post treatment lameness score was 1.8 (S.D. 1.1). The mean reduction in lameness score between the pre and post treatment examinations was 0.77 units (S.D. 0.91). The pre and post treatment lameness scores are represented graphically in Appendix C29.

A paired *t* -test showed a significant improvement in lameness score between the pre and post treatment examinations ($p < 0.01$). A Wilcoxon Signed Rank Test showed a significant improvement in lameness score between the pre and post treatment examinations ($p < 0.02$).

Weightbearing [Appendices C28 & C30]

Weightbearing was reduced in 13 cases (13 of 21; 62%) before treatment. In 8 dogs weightbearing was not reduced (38%). Phenylbutazone treated dogs showed an improvement in weightbearing score in 2 cases where weightbearing had been affected (2 of 13; 15%). In two cases, the weightbearing score after treatment was worse than before treatment. The mean pre treatment weightbearing score was 0.8 (S.D. 0.7). The mean post treatment weightbearing score was 0.8 (S.D. 0.6). The mean reduction in weightbearing score between the pre and post treatment examinations where weightbearing was affected was zero (S.D. 0.5). The pre and post treatment weightbearing scores are represented graphically in Appendix C30.

A paired *t* -test demonstrated no statistically significant improvement in weightbearing score between the pre and post treatment examinations ($p = 1.0$). A Wilcoxon Signed Rank Test showed no statistically significant improvement in weightbearing score between the pre and post treatment examinations ($p = 0.5$).

Joint Mobility [Appendices C28 & 31]

Joint mobility was reduced in 18 cases (18 of 21; 86%) before treatment. In 3 dogs joint mobility was not reduced (14%). Phenylbutazone treated dogs showed an improvement in joint mobility score in one case where joint mobility had been affected (1 of 18; 6%). In two cases, the joint mobility score was worse after treatment than before treatment. The mean pre treatment joint mobility score was 1.0 (S.D. 0.5). The mean post treatment joint mobility score was also 1.0 (S.D. 0.6). There was a mean *increase* in joint mobility score between the pre and post treatment examinations where joint mobility was affected of 0.05 units (S.D. 0.08). The pre and post treatment joint mobility scores are represented graphically in Appendix C31.

A paired *t* -test showed no significant improvement in joint mobility score between the pre and post treatment examinations ($p = 0.6$). A Wilcoxon Signed Rank Test showed no significant improvement in joint mobility score between the pre and post treatment examinations ($p = 0.5$).

Total Condition Score [Appendices C28 & C32]

One dog had a zero score after phenylbutazone treatment (1 of 21; 5%). Nine dogs showed an improvement in condition score at reexamination after treatment with Phenylbutazone (9 of 21; 43%). In nine dogs, the condition score was unchanged by Phenylbutazone treatment (9 of 21; 43%). In 3 dogs (3 of 21; 14%), the condition score was worse at reexamination. The mean total condition score before treatment was 4.3 (S.D. 1.5). The mean post treatment total condition score was 3.6 (S.D. 1.8). The mean reduction in total condition score between the pre and post treatment examinations was 0.7 units (S.D. 1.3). Pre and post treatment total condition score is represented graphically in Appendix C32.

A paired *t* -test showed a significant improvement in total condition score between the pre and post treatment examinations ($p < 0.02$). A Wilcoxon Signed Rank Test showed a significant improvement in total condition score between the pre and post treatment examinations ($p < 0.02$).

Veterinarian Satisfaction:

The effect of treatment with phenylbutazone was considered to have been satisfactory by the veterinary practitioner in only 10 of the 21 cases (48%), to have been unsatisfactory in 8 cases (38%). In 3 cases (14%), the veterinarian said that the effect of treatment was not completely satisfactory but there was an effect on the condition.

Reported Side Effects

Case 204 Sharples; 9 year old Crossbred Male; 12 kg. Stifle/hip osteoarthritis. Concurrent therapy with Heart Tonic and Stimulant Tablets.
Phenylbutazone 100 mg b.i.d. [16.7 mg/kg/day]
Vomiting and inappetance after 12 days treatment. Treatment not withdrawn.

Comparison Between Treatments

Carprofen Tablet Treatment and Previous Treatment

Fifty dogs had been previously treated with a total of 60 treatments. In four cases, these previously treated dogs were treated with phenylbutazone during the trial period. The remaining 56 dogs were treated with carprofen during the trial [Appendices 34-36]. The investigating veterinarian stated the relative effectiveness of carprofen and the previous treatment on the Clinical Assessment Form for 46 of the 56 previous treatments. The stated comparison with all previous analgesic and anti-inflammatory therapy is represented in tabular form in Appendices C37 & C38.

Carprofen was judged to be superior to the previous treatment in 26 cases (26 of 46; 57%), to be equivalent to the previous treatment in 6 cases (13%) and to be inferior to the previous treatment in 14 cases (30%). Compared to previous treatment of 21 dogs with phenylbutazone at 6 to 27 mg/kg/day, where a comparative efficacy was stated, carprofen treatment was stated to be more effective in 12 cases (57%), equivalent in 3 cases (14%) and inferior in 6 cases (29%). Compared to previous treatment of 11 dogs with Predno-Leucotropin® Tablets at 5-40 mg cinchophen and 0.03-0.20 mg prednisolone/kg/day, where the comparative efficacy was stated, in five cases (5 of 11; 45%) carprofen was considered more efficacious, and in 6 cases (55%) Predno-Leucotropin® Tablets were considered more efficacious.

Seven previous treatments had no effect on clinical presentation (Score 0). Five of these cases improved when treated with carprofen. In two of these cases carprofen did not have any effect. Twenty one previous treatments had "some effect" (Score 1) on the clinical condition. In fifteen cases the efficacy of Carprofen was considered superior to the previous treatment and in a further two cases was considered of equivalent effect. In four cases where the previous treatment had some effect, the efficacy of carprofen was considered inferior. Eighteen previous treatments gave a "marked improvement" (Score 2) in the clinical condition. In six cases the efficacy of carprofen was considered superior to the previous treatment and in a further two cases was considered of equivalent effect. In nine cases where the previous treatment had a marked effect, the efficacy of carprofen was considered inferior. One case was considered "sound" whilst on treatment with Predno-Leucotropin Tablets® and in this case carprofen was considered to be less beneficial.

The above findings are tabulated fully in Appendices C34-36 and are summarised below:

Previous Treatment Effect	Subjective Comparative Effect of Carprofen Treatment		
	Worse	Same	Better
No Effect	0	2 (29%)	5 (71%)
Some Effect	4 (19%)	2 (10%)	15 (71%)
Marked Improvement	9 (53%)	2 (12%)	6 (35%)
Sound	1 (100%)	0	0
Carprofen efficacy cf : all previous treatments	14 (30%)	6 (13%)	26 (57%)

Carprofen Tablet Treatment and Phenylbutazone Treatment

The pre treatment condition scores for lameness, weightbearing, joint mobility and total condition score for the carprofen treated and phenylbutazone treated groups were not significantly different when analysed by a Students t-test. There was no statistically significant difference in the reduction in lameness score or in the post treatment lameness scores between the carprofen and phenylbutazone treated groups when the scores were compared by a Students *t* -test.

The improvement in weightbearing score was significantly greater in the carprofen treated group than in the phenylbutazone treated group when the differences in pre and post treatment scores were compared by a Students *t* -test ($p < 0.01$).

The improvement in joint mobility score was significantly greater in the carprofen treated group than in the phenylbutazone treated group when the differences in joint mobility scores pre and post treatment were compared by a Students *t*-test ($p < 0.05$).

There was no statistically significant difference between the improvement in total condition score for the carprofen and phenylbutazone treated groups when the scores were compared by a Students *t*-test. However, the post treatment total condition scores for the carprofen treated group were significantly lower than those for the phenylbutazone treated group when compared by a Students *t*-test ($p < 0.05$).

Both carprofen and phenylbutazone were used in ten cases. Eight cases were treated with carprofen at 0.92 to 2.92 mg/kg/day for between 7 and 21 days followed by phenylbutazone at 8.26 to 15.4 mg/kg/day for between 7 and 21 days. In two cases, the dogs were treated with phenylbutazone at 10.5 mg/kg/day in one case and at 33.3 mg/kg/day in the other, both for 7 days, followed by carprofen at 0.92 mg/kg/day for 14 days in Case 22 and at 2.92 mg/kg/day on one day in Case 23 (dog vomited on second and third days of treatment and carprofen was withdrawn). In four cases neither treatment was considered satisfactory. In four cases carprofen was considered the more efficacious of the two treatments. In two cases phenylbutazone was considered the more efficacious treatment. When the difference in total condition score pre and post treatment for the two treatments was compared by a paired *t*-test and Wilcoxon Signed Rank test there was no statistically significant difference between the two treatments in these ten dogs.

Carprofen Dose and Effect

The recommended range of treatment doses was changed to 2 to 4 mg/kg/day after 2 months of the trial period because a number of the investigating veterinarians stated that the effect of carprofen at the 0.7 mg/kg/day recommended was disappointing. When a Kendall Rank Order Correlation test was applied to the data, there was a significant positive correlation between the dose rate of carprofen and the improvement in total condition score ($p < 0.05$). The effect of treatment was compared for the group of dogs treated at less than 2 mg/kg/day to those treated at 2 mg/kg/day or over by expressing the improvement in total condition score as a percentage of the pre treatment total condition score, as below:

$$\frac{\text{Post treatment total condition score - Pre treatment total condition score}}{\text{Pre treatment condition score}} \times 100\ \%$$

The percentage improvement in total condition score is represented graphically for the two dose ranges in Appendix C33. The number of dogs with a zero improvement or worse on carprofen is 11 of 46 (28%) for the <2 mg/kg/day group but only 5 of 28 (18%) for the ≥2 mg/kg/day group. Also, the number of dogs with a 50-100% improvement in total condition score is only 14 of 46 (30%) for the lower dose range but is 13 of 28 (46%) for the higher dose rate. However, these differences are not *statistically* significant when compared by a X^2 test.

Eighteen dogs were treated at a higher dose rate when treatment with carprofen at a lower rate failed to have a satisfactory effect. The dose rates and effects are tabulated in Appendix C37. The effect of treatment with the two dose rates on the difference in pre and post treatment total condition score is represented graphically in Appendix C33. In seven cases when the low dose rate had failed to improve the condition, the higher dose rate was also ineffective (7 of 18; 39%). In two cases the increased dose rate had the same effect as the lower dose rate (11%). In the remaining nine cases (50%) the higher dose rate was considered appreciably more efficacious. The lower treatment doses ranged from 0.71 to 1.84 mg/kg/day (mean 1.1 mg/kg/day; S.D. 0.36). The higher treatment doses ranged from 1.46 to 3.50 mg/kg/day (mean 2.11 mg/kg/day; S.D. 0.54). The lower dose rate gave a mean improvement in total condition score of 0.3 units (S.D. 0.8). The higher dose rate gave a mean improvement in total condition score of 1.2 units (S.D. 1.0). When the differences in pre and post treatment total condition scores for the two doses were compared by a paired *t*-test, the improvement in total condition score at the higher dose rate was significantly greater than for the lower dose rate ($p < 0.001$). The number of dogs showing improvement was significantly greater at the higher dosage range when an X^2 test was performed.

4.4.5 Conclusions

Efficacy of Treatment

The efficacy of carprofen in the therapy of dogs with clinical osteoarthritis was judged to have been satisfactory in 49 of 74 treated dogs (66%). The post carprofen treatment examination showed statistically significant improvements in subjective scores for lameness, weightbearing and joint mobility.

The efficacy of phenylbutazone in the therapy of dogs with clinical osteoarthritis was judged to have been satisfactory in 10 of 21 treated dogs (48%). The post phenylbutazone treatment examination showed statistically significant improvements in subjective scores for lameness but not for weightbearing or joint mobility.

Carprofen had a satisfactory effect in 49 of 74 cases treated (66%) whilst phenylbutazone had a satisfactory effect in only 10 of 21 (48%). Improvements in condition score parameters were seen in more cases treated with carprofen than in dogs treated with phenylbutazone. However, there was no significant difference between the mean improvements in total condition scores for the carprofen and phenylbutazone treated groups. In the ten cases where a form of cross-over trial was undertaken there was no statistically significant difference between improvement in total condition scores for the two treatments when compared by a paired *t*-test. No statistically significant differences in efficacy were found for different joints or under different reported management changes.

Carprofen was considered more effective than previous treatment in 26 (57%) and of equivalent efficacy in 6 (13%) of 46 cases where the veterinarian stated the comparative efficacy.

There was a correlation between the improvement in total condition score and dose rate of carprofen administered. The number of dogs which had improved after carprofen therapy was greater for dogs treated at over 2 mg/kg/day than at less than 2 mg/kg/day. Also, a larger number of dogs improved by a greater amount when treated at the higher dose range.

Adverse Reactions

The veterinarian entered details in the "Side Effects" section for fifteen dogs treated with carprofen (15 of 74 cases; 20%). In seven cases there was another likely cause of the observed signs. In eight cases an adverse reaction was suspected (8 of 74 cases; 11%). However, it was unclear whether the reports of side effects were volunteered or were elicited by questioning.

Treatment was withdrawn because of suspected adverse reactions in only 2 cases (2 of 74 cases; 3%). In Case 23, treatment was withdrawn because the dog vomited on the second and third days of carprofen treatment. Vomiting could have been due to gastritis or nausea.

In Case 36 treatment was withdrawn when the dog developed diarrhoea. However, this dog had a previous history of colitis and diarrhoea. The veterinarian believed that the bout of diarrhoea was probably coincidental. In two cases, Cases 1 and 2, treatment was withdrawn because analgesia was causing the dogs to over-use their damaged joints.

Gastrointestinal disturbances were reported in a further six cases. Two dogs vomited but treatment was not withdrawn. Case 64 had a coincidental upper respiratory tract infection. Two dogs became diarrhoeic. In case 59 the diarrhoea was thought to be dietary in origin. Treatment was maintained at a lower dose rate and the diarrhoea resolved. Case 65 had a previous history of diarrhoeic episodes. Constipation was reported in two cases. Inappetance was reported in case 15, and inappetance and increased salivation in case 48. These signs may have been due to nausea. Polydipsia was reported in 4 cases. However, in 2 cases concurrent renal disease was thought to be responsible; in one case concurrent diuretic therapy was thought responsible. Drowsiness was reported in Case 6.

Side effects were reported for carprofen at a range of doses from 0.75 to 2.92 mg/kg/day. No relationship between dose rate and side effects was apparent although the three dogs which vomited whilst on treatment were all treated at over 1.86 mg/kg/day. The trial sample is too small to assess whether the incidence of vomiting or diarrhoea are related to dose rate. Concurrent renal or cardiac disease was not apparently associated with increased drug toxicity or with an increased incidence of suspected adverse reactions.

One dog treated with phenylbutazone had reported side effects (1 of 21; 5%). Case 204 vomited after 12 days of phenylbutazone treatment but treatment was continued. Vomiting could have been due to nausea, gastritis, or gastrointestinal ulceration. The trial sample is too small to be an accurate prediction of the incidence of adverse reactions in dogs treated with phenylbutazone.

The clinical trial was limited by practical constraints and the absence of any form of remuneration for participating veterinarians. This led to the unblinded, positive control trial design, no radiological confirmation of the diagnosis in all cases, and a limited number of cases. The subjective nature of condition assessment and variation between veterinarians in scoring the condition and in other advice given on exercise undoubtedly affects the validity of the trial results. However, with the exception of flexion and extension angle measurement, there are no objective measurable parameters of the severity of osteoarthritis or of any improvement with analgesic or antiinflammatory treatment. Little relationship has been detected between objective indicators and the degree of pain and functional loss experienced in human osteoarthritis patients (Berry, 1983; Kramer, 1983; Harkness, 1984). Summers reported that radiographic assessment was poorly correlated with the degree of pain or of functional impairment in osteoarthritis of the knee or hip in man (Summers, 1988).

There were differences in the carprofen and phenylbutazone treated groups in age distribution, breed distribution and joint affected. The differences were partly due to the limited size of the trial population. However, for a disease like osteoarthritis variance within and between groups is inevitable unless the sample population is very large. Although the two groupsare not completely comparable, the trends indicated in the trial are probably valid.

Carprofen appears to be efficacious in the therapy of many cases of osteoarthritis when used at a dose rate of 0.71 to 3.50 mg/kg/day. There was a correlation between dose rate and effect within this dose range. A dosage range of 2.00 to 3.50 mg/kg/day improved efficacy without an apparent increase in toxicity or adverse reactions.

Carprofen was well tolerated in most dogs. The incidence of suspected adverse reactions was comparable to that of other non-steroidal anti-inflammatory drugs. The subjectively assessed improvement in the clinical condition in carprofen treated dogs was equivalent or superior to that in phenylbutazone treated dogs and carprofen compared favourably with the treatments previously prescribed.

Results Summary:

	Carprofen	Phenylbutazone
Total number of dogs treated	74	21
Dose rate (mg/kg/day)	0.39 - 3.5	5.7 - 33.3
Reported side effects (all)	15 (20%)	1 (5%)
Probable adverse reaction	8 (11%)	1 (5%)
Treatment withdrawn because of adverse reaction	2 (3%)	0
Lameness reduced	49/73 (67%)	8/21 (38%)
Weightbearing increased	18/44 (41%)	2/13 (15%)
Joint mobility increased	13/62 (21%)	1/18 (6%)
50-100% improvement:		
< 2 mg/kg/day	14/46 (30%)	-
≥ 2 mg/kg/day	13/46 (46%)	-
Treatment considered satisfactory	49/74 (66%)	10/21 (48%)

Chapter 5

The NSAID-Steroid Combination PLT ® Tablet and its Use in the Therapy of Canine Osteoarthritis

The NSAID-Steroid Combination Preparation PLT® Tablet and its Use in the Therapy of Canine Osteoarthritis

5.1 General Available Data on PLT® Tablets and Related Preparations

5.1.1 Preparation

PLT ® Tablets are a fixed combination product containing:

Cinchophen	200 mg	
Prednisolone BP	1 mg	per tablet.

The product has been developed by BK Veterinary Products to replace Predno-Leucotropin Tablets® which have been available for veterinary use in the United Kingdom for 22 years. Predno-Leucotropin Tablets contain 100 mg Hexamine per tablet in addition to cinchophen and prednisolone BP.

Hexamine is a surface acting urinary antiseptic. It is believed that antibacterial activity of the compound is due to its conversion to formaldehyde in a slightly acidic environment. Hexamine was removed from the product because at the suggested dose rate of approximately 10 mg/kg in Predno-Leucotropin Tablets, hexamine has little anti-inflammatory activity.

The effect of urinary acidification on the excretion of cinchophen or its metabolites is not documented. *If* the excretion of cinchophen depends upon urinary excretion of the active drug, the low pKa of cinchophen may mean that acidification of the urine could delay excretion and prolong plasma concentrations (La Du and others, 1972).

5.1.2 Active Ingredients, Properties and Mechanisms of Activity

Cinchophen

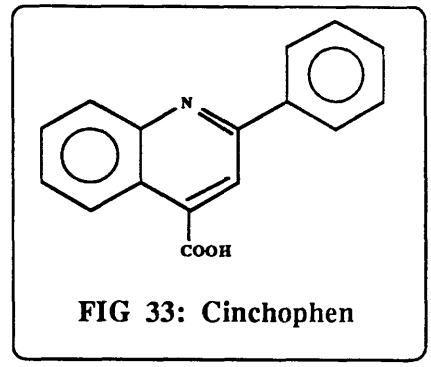


FIG 33: Cinchophen

Cinchophen (chemical name: 2-phenylquinolone-4-carboxylic acid or 2-phenylcinchoninic acid) is a non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic and uricosuric properties (Hueper, 1948). The anti-inflammatory and analgesic actions of cinchophen are thought to be due to reversible inhibition of the enzyme complex cyclooxygenase which reduces the tissue production of the inflammatory prostanoids (McKellar, 1989). Little is known about the pharmacology of cinchophen since it has not been used in man for many years. Other quinolones have antimicrobial and inhibitory effects on DNA transcription (Booth, 1982).

Unpublished studies in beagles carried out in the Department of Veterinary Pharmacology, University of Glasgow have indicated that cinchophen administered at 12.5 mg/kg in a single dose has an elimination half life of about 8-9 hours and an average oral availability of 85 to 90%. Cinchophen was generally rapidly absorbed. Maximum plasma concentrations of between 44.7 and 99.5 ug/ml were attained between 45 minutes and eight hours after administration. However, since effective plasma concentrations are not documented, the significance of kinetic data cannot be determined.

No LD50 values are documented for cinchophen in the dog. Oral toxicity studies have been limited because cinchophen consistently causes vomiting at oral doses over 500 mg/kg. 620 mg/kg by subcutaneous injection is lethal (Risi, 1932). 500 mg/kg for 2-3 days is fatal (Starkenstein, 1924). In man, dermatological, cardiovascular, hepatic, and renal toxicity have been described (Biberfeld, 1913; Hanzlik, 1921; 1927; Sutton, 1928; Chen, 1936; Stalker and others, 1937; Hueper, 1948). Doses of 50-400 mg/kg have caused renal and liver pathology (Hueper, 1948). Cinchophen was withdrawn from use in man because of a high incidence of hepatotoxicity, which is thought to be much less common in the dog.

Cinchophen causes gastrointestinal ulceration (Bollman and others, 1937; Stewart and others, 1980). The mechanisms of gastrointestinal pathology may be local although some authors have demonstrated hypothalamic effects (Nagamichi, 1977). At higher than therapeutic doses, gastric mucosal inflammation is apparent by 24 hours after the ingestion of the first dose of cinchophen. Gastritis is reversible if treatment is withdrawn. Gastric ulceration appears to be dose related and the incidence increases with the number of treatments given. Even at relatively low doses such as 22 mg/kg it is thought that gastrointestinal ulceration will develop with chronic use (Van Wagoner and Churchill, 1931). At 50 mg/kg bid, protein losing gastroenteropathy will probably develop. It is thought that 25 mg/kg/day is well tolerated for the proposed 14 day treatment period. It has been advised that a maximum dose of 25 mg/kg/day for up to 14 days is not exceeded (McKellar, 1989).

Cinchophen can cause tinnitus, dizziness and vertigo in man (Hanzlik, 1929). No effect has been demonstrated on prothrombin clotting time in dogs fed a normal diet (Hueper, 1946) but cinchophen could affect the platelet component of the clotting mechanism which may be important in animals with preexisting clotting deficiencies or where gastrointestinal haemorrhage occurs.

Prednisolone

Prednisolone is a synthetic corticosteroid with an intermediate duration of activity. The double bond in the steroid 'A' ring protects the ring from metabolic deactivation and increases the drug half life. It has 0.8 times the mineralocorticoid activity and 4 times the glucocorticoid activity of cortisol (Haynes and Murad, 1980; McDonald, 1982). Prednisolone is less expensive than more derivatised steroids and has good antiinflammatory, antiallergic and immunosuppressive activity. The increased therapeutic ratio of prednisolone/prednisone and their usefulness in alternate day therapy makes them the steroids of choice for chronic oral use (Green and Lutsky, 1986).

The antiinflammatory action of steroids may be partly due to the induction of translation of a protein (macrocortin or lipomodulin) which inhibits phospholipase A2, the enzyme responsible for catalysis of the conversion of membrane or free phospholipid into arachidonic acid. This may reduce the substrate available for the lipoxygenase and cyclooxygenase pathways and reduce the synthesis of inflammatory mediators (Flower and Blackwell, 1979). However, recent experiments have cast doubt on the *in vivo* importance of this mechanism (Lees, 1989). Other mechanisms of steroid activity are believed to be important but have not been elucidated (Green and Lutsky, 1985).

The side effects of chronic exogenous steroid administration have been widely reported and include: accelerated carbohydrate, protein and fat catabolism; immunosuppression; reversible hepatopathy; iatrogenic hyperadrenocorticism (Cushing's Syndrome); and iatrogenic secondary adrenocortical insufficiency (Liddle, 1971; Irvine and Barnes, 1972; Scott and Greene, 1974; Chastain and Graham, 1979; Haynes and Murad, 1980; McDonald, 1982). It is believed that the minimum dose required to suppress the hypothalamic-pituitary-adrenal axis is approximately 0.3 mg/kg/day which is equivalent to 1 mg/kg/day of hydrocortisone (Mulnix, 1979). This is greater than the dose of prednisolone available at the proposed dose rate of PLT Tablets. Corticosteroids decrease gastric mucus secretion and viscosity and increase secretion of acid and pepsin. Used alone corticosteroids can occasionally cause gastrointestinal ulceration (Rogers and Ruebner, 1977) but they may potentiate the effects of NSAIDs on the gastric mucosa (Cosenza, 1984). Prednisolone at higher dose rates has been shown to enhance the ulcerogenic activity of cinchophen (Hamori and others, 1968). Side effects to steroid administration show a marked variation in individual response to the same dosage.

High doses of corticosteroids have adverse effects on the joint. However, a number of studies have demonstrated a cartilage protective and disease inhibiting effect of corticosteroids at lower doses similar to those in PLT Tablets.

Cinchophen and Prednisolone Combination

There are a number of satisfactory arguments for the potential advantages for a cinchophen-prednisolone combination. The prednisolone may promote absorption of cinchophen, may compete for plasma protein binding sites, or may prolong plasma concentration of cinchophen by antagonising excretion. Because cinchophen and prednisolone act by different antiinflammatory mechanisms, synergy may exist between the two drugs. However, the dose of prednisolone in PLT Tablets is lower than doses usually considered to have therapeutic antiinflammatory activity (Haynes and Murad, 1980; McDonald, 1982). At the higher limits of the dose range, the dosage of prednisolone *is* similar to dosages which inhibit early articular cartilage degenerative changes in experimental osteoarthritis in dogs.

5.1.3 Clinical Efficacy Data on PLT Tablets and Related Drugs

Unfortunately, neither cinchophen nor the drug preparations of which it is a constituent are included in standard veterinary or human pharmacology and therapeutics texts (eg. Alexander, 1969; Goodman, 1980; Booth, 1982; Chandler, 1984). Most reports on cinchophen which have appeared in medical journals in the last 35 years concern its use at high doses to induce the formation of gastric ulceration. Recent texts mention the anti-inflammatory and uricosuric activity of cinchophen (Shen, 1979).

In the last 40 years, the only published data on the veterinary use of cinchophen containing products are two anecdotal reports on the use of "Leucotropin", an injectable fixed-combination of cinchophen and hexamine or of cinchophen, hexamine and sodium salicylate and caffeine (Lustig-Lendva, 1949; Frost, 1949). The only data available on cinchophen and prednisolone in fixed combination is the data on Predno-Leucotropin Tablets® and the clinical trial documented in section 5.2.

5.1.4 Efficacy of Predno-Leucotropin in the Therapy of Canine Musculoskeletal Pain

There are no documented studies on the clinical efficacy of Predno-Leucotropin Tablets® in the dog or other species. However, it is unlikely that Predno-Leucotropin Tablets would have continued to be such a popular veterinary product if they were not efficacious in the therapy of osteoarthritis in the dog. Between January 1984 and June 1988, 51 million Predno-Leucotropin Tablets were sold in the UK.

5.1.5 Adverse Reactions to Predno-Leucotropin Tablets

No serious adverse reactions have been reported in man when hexamine has been used at doses much greater than those in Predno-Leucotropin Tablets. Nausea, vomiting, rashes and urinary irritation have occasionally occurred. However, reported adverse reactions to Predno-Leucotropin Tablets are probably attributable to cinchophen or prednisolone. It is probable that a similar spectrum and incidence of side effects will occur for PLT Tablets.

In the period January 1984 to June 1988, sixteen adverse reactions and 10 deaths in dogs receiving Predno-Leucotropin Tablets were reported by veterinarians. Unfortunately, all the details of the animals or treatments in all cases (eg. ages, dose rates, treatment period before reaction/death) are unavailable.

Where the age of the dog was stated, in both fatal and non-fatal adverse reaction cases it was between 4 and 11 years. There was no obvious breed or sex predisposition except that 3 Dachshunds and 2 Chows were among the total. Calculating daily dosages based on estimated breed weight, daily dose rates ranged from 23 to 50 mg/kg/day. Both adverse reactions and deaths occurred in dogs treated at dosages within the proposed range. Suspected adverse reactions began between 1 day and 4 months after treatment started. However, in the majority of cases, clinical signs were seen within 2-4 days of the start of treatment. Where mortality was reported, death occurred between a few hours and ten days after the first clinical signs.

Adverse reactions included vomiting, gastritis, gastric ulceration, abdominal pain, diarrhoea and melaena in cases which subsequently recovered and vomiting, melaena, haemorrhagic enteritis, diarrhoea, lethargy, collapse, seizures, bilirubinuria and proteinuria, and haemorrhage from the nares and gingiva in animals which died. Necropsy findings included a perforated gastric ulcer, gastrointestinal ulceration, and findings consistent with a diagnosis of "post-anaesthetic death".

In summary, suspected adverse reactions (SARs) occurred in a range of breeds and ages of dogs. The dose rate was within the recommended dosage range in most cases. SARs and deaths occurred mostly in the first week of treatment. The most common clinical signs could be attributed to gastrointestinal irritation or ulceration although some cases showed evidence of nephropathy or a defective clotting mechanism.

The number of reported adverse reactions and deaths in dogs receiving treatment with Predno-Leucotropin Tablets is small when compared to the number of dogs treated with the preparation. However, the number of reported adverse reactions is certainly very much lower than the actual incidence of side effects since veterinarians seldom report non-fatal SARs. It is also possible that adverse reactions in dogs treated chronically with Predno-Leucotropin Tablets are not always correctly attributed to the drug preparation. Weight loss and subclinical anaemia may be consequences of chronic gastrointestinal ulceration and protein losing enteropathy although the loss of blood and protein may not be sufficient to cause acute distress. Such reactions may not be diagnosed.

5.1.6 Dose Recommendations:

Proposed Dose Rate

Bodyweight [kg]	Suggested dosage [tablets]	Daily Dose[mg/kg/day]			
		Minimum		Maximum	
		Cinc.	Predn.	Cinc.	Predn.
8	1/2 bid	25	0.125	25	0.125
9-16	1 bid	25	0.125	44.4	0.222
17-24	1.5 bid	25	0.125	35.3	0.176
25-32	2 bid	25	0.125	32	0.160

5.1.7 Conclusions

To determine what oral dose rate and regime is appropriate for PLT ® Tablets, efficacy data and minimum effective plasma concentrations are required. This will require *in vitro* and *in vivo* measurement of antiinflammatory effects and inhibition of prostanoid synthesis. There are arguments for a combination product containing NSAID and steroid. The most convincing is that the two drugs act synergistically by exerting complementary activities on inflammatory mechanisms. However, it is possible that the analgesic or antiinflammatory efficacy of PLT Tablets is entirely due to their cinchophen content. Further studies are required to assess the effect of prednisolone on cinchophen pharmacokinetics, and the effect of the component drugs compared with the effect of their combination.

From data available, PLT Tablets are probably well tolerated for up to 14 days at 20-30 mg/kg/day divided. Longer term treatment at the recommended dose rates may cause gastrointestinal inflammation and ulceration. The spectrum and incidence of side effects to cinchophen are similar to those of other NSAIDs, principally gastrointestinal intolerance. Clinical efficacy data was required and a clinical trial of the efficacy of PLT Tablets in the therapy of canine osteoarthritis was instigated (see section 5.2).

5.2 Clinical Trial of the Efficacy of PLT Tablets in the Therapy of Canine Osteoarthritis

5.2.1 Summary

The aim of the trial was to establish the clinical efficacy of PLT Tablets in the therapy of clinical osteoarthritis in the dog. This was under-taken by comparing the effect of PLT Tablets with the effect of a previous treatment for the condition in the same animal and by comparing the effect of treatment in a group of PLT treated dogs with the effect of treatment in a group of phenylbutazone treated dogs.

PLT Tablets were efficacious in the therapy of 31 of 36 (86%) cases of clinical osteoarthritis. Phenylbutazone was efficacious in the therapy of 12 of 15 cases treated (80%). PLT was generally as efficacious or superior to previous treatment and there was no significant difference between the PLT treated and Phenylbutazone treated groups. In the thirty-six PLT treated cases there were mild reported side effects such as dullness, increased thirst and mild diarrhoea in 6 cases (17%). In two cases vomiting was a side effect and treatment was withdrawn (6%). Of the fifteen phenylbutazone treated cases, there was dullness for the first few days of treatment in one case (7%). Vomiting was a side effect in one case and treatment was withdrawn (7%).

From the limited numbers of dogs treated during the trial, PLT appears to be effective in the therapy of many cases of clinical osteoarthritis when used at 8-46 mg cinchophen/kg bodyweight/day [0.04-0.23 mg prednisolone/kg bodyweight/day]. There was correlation between treatment dose and effect within this dose range. For the duration of treatment, PLT was well tolerated in most dogs. The incidence of adverse reactions and treatment withdrawal were comparable with other non-steroidal anti-inflammatory drugs.

5.2.2 Objective

i) To compare PLT Tablets, a fixed combination preparation containing 200 mg cinchophen and 1 mg prednisolone per tablet:

(a) with previous medical treatment in existing cases
(b) with the standard drug phenylbutazone in new cases

in the control of the signs of clinical osteoarthritis in the dog.

ii) To determine and record the incidence and nature of any unwanted side effects.

5.2.3 Method and Materials

Test Drugs

1. PLT Tablets: cinchophen 200 mg
prednisolone BP 1 mg per tablet

[Batch No. 88T2918; Expiry Date: January 1991]

2. Flexazone® Tablets: phenylbutazone BP 100 mg per tablet

[Batch No. 80302A-1; Expiry Date: December 1990]

Trial Design

The aim of the trial was to establish the clinical efficacy of PLT Tablets in the therapy of clinical osteoarthritis in the dog. This was undertaken by comparing the effect of PLT Tablets with the effect of a previous treatment for the condition in the same animal and by comparing the effect of treatment in a group of PLT treated dogs with the effect of treatment in a group of phenylbutazone treated dogs. Thus the trial was based on a form of positive control design. It was not considered practical to perform a "cross-over" type trial because of the possible lack of compliance of veterinary practitioners and owners. A blind placebo control design would not have been acceptable to owners or veterinary practitioners and would also have been ethically unsound. It was hoped that the PLT and phenylbutazone treated groups would be comparable. No financial or other inducements were offered to any participating veterinary surgeon.

Investigator Selection

Veterinary practitioners who were known personally by the author, by Dr. Q. McKellar of the Department of Veterinary Pharmacology, or by Mr. S. Carmichael of the Department of Veterinary Surgery, University of Glasgow, or by Mr. Graeme Bell of C-Vet Limited were contacted by letter and asked to participate in the clinical trial. Further correspondence and telephone conversations led to the recruitment of 20 practices, 14 of which returned results information sheets. Each practice was supplied with information on the product, and instructions on case selection, dose recommendation and condition scoring [Appendices D1-3]. Approximately 15 sets of results information sheets ["Patient Information", "Efficacy Assessment" and "Clinical Assessment" sheets] were also posted to each practice. These sheets were similar to those used in the previous clinical trial on the efficacy of carprofen [Appendices C4-6] except that a fourth parameter "stiffness" was added to those of lameness, weightbearing and joint mobility. This category was included because a number of practitioners involved in the previous trial commented that stiffness had markedly improved in a number of cases where lameness was still apparent. It was hoped that, by distinguishing between lameness and stiffness, scoring the condition would be simpler. PLT Tablets and Flexazone® 100 mg tablets were supplied.

Dose Recommendations

The Dose Recommendations sheet supplied to practitioners [Appendix D2] recommended that PLT Tablets be administered orally in a divided dose based on a theoretical minimum of 25 mg cinchophen and 0.125 mg prednisolone per kilogram bodyweight per day. Due to the fixed combination and set quantity per tablet the recommendations would give a daily dosage of between 25 and 44 mg/kg/day cinchophen and between 0.125 and 0.22 mg/kg/day prednisolone. The initial treatment period was to be 14 days, subject to clinical response.

With the 100 mg tablets provided, a dose rate in tablets was calculated such that phenylbutazone would be administered at a suggested dose rate of between 8 and 16 mg/kg bodyweight/day divided into two doses daily. It was stated that phenylbutazone should not be used in animals with cardiac, renal or hepatic insufficiency or in animals showing signs of or with a history of anaemia, as recommended in the Data Sheet for the product.

Case Selection and Protocol

PLT Tablets were to be assessed for therapeutic effect in cases of clinical osteoarthritis. Diagnosis was made by the history and clinical presentation. Confirmation of the clinical diagnosis with radiographic diagnosis would have been preferable but since no payment or inducements were offered to participating veterinarians, it was not considered reasonable or practical to insist on radiographic confirmation of diagnosis. Cases were of two groups:

1. existing cases (dogs already receiving medical therapy for osteoarthritis);

2. new cases (dogs at first presentation to the practitioner or for which the previous history was not known).

The protocol for the trial was as follows:

1. Existing Cases:

i) Information on the owner and the dog was recorded. The joints affected were noted. In most cases, a brief summary of the clinical history was taken. The dose, regime, duration and effect of the previous treatment was noted and the previous treatment was withdrawn.

ii) Where possible, dependent upon the wishes of the owner and the veterinary surgeon, the time taken for the signs of the painful condition to reappear was monitored.

iii) The clinical condition was scored for lameness [0 to 4], weightbearing [0 to 2], joint mobility [0 to 2], and stiffness [0 to 4] according to the condition scoring sheet [Appendix D3].

iv) Therapy was instituted with PLT Tablets at the recommended dose rate [Appendix D2].

v) The effect of treatment was monitored, i.e. the dog was re-examined after a period of treatment (14 days was the recommendation) and the clinical condition was re-scored. Where possible, the owner was to be questioned as to the efficacy of the treatment and the time taken for the treatment to have an effect, if any.

vi) At the end of the treatment period, the "Clinical Assessment" sheet was to be completed with the veterinary practitioners' subjective opinion on whether the treatment had been satisfactory and how PLT treatment compared to the previous treatment. Any adverse reactions could be noted on the "Clinical Assessment" sheet. Provision was made on the first sheet ["Patient Information"] for noting premature treatment withdrawal and its cause or any change of dose rate.

2. New Cases:

i) Osteoarthritis was confirmed clinically and in four cases radiographically. Patient information and the joint(s) affected were noted. A brief summary of the history was taken.

ii) The clinical condition was scored for lameness [0 to 4], weightbearing [0 to 2], joint mobility [0 to 2], and stiffness [0 to 4] according to the condition scoring sheet [Appendix D3].

iv) Therapy was instituted with PLT Tablets or phenylbutazone (Flexazone® Tablets) at the recommended dose rate [Appendix D2] on an "alternate case" basis. i.e. treating dog 1 with PLT Tablets, dog 2 with Flexazone Tablets, dog 3 with PLT Tablets etc.

v) The effect of treatment was monitored, i.e. the dog was re-examined after a period of treatment (14 days was the recommendation) and the clinical condition was re-scored. Where possible, the owner was to be questioned as to the efficacy of the treatment and the time taken for the treatment to have an effect, if any.

vi) At the end of the treatment period, the "Clinical Assessment" sheet was completed with the veterinary practitioners' subjective opinion on whether the treatment was satisfactory. Any adverse reactions could be noted on the "Clinical Assessment" sheet. Provision was made on the first sheet ["Patient Information"] for noting premature withdrawal and its cause or any change of dose rate.

It was suggested that, where possible, new cases should be treated firstly with one of the two test drugs and then, after an interval, the drug used could be switched to the second drug. This would allow comparison of the effects of PLT and phenylbutazone in the same animal.

Exclusions

Dogs which were concurrently receiving treatment with a drug with anti-inflammatory or analgesic effect were excluded from the results analysis. Incomplete or totally illegible results forms were also excluded. Dogs which were not diagnosed as having osteoarthritis or with a history not consistent with such a diagnosis were not included in the results analysis. It was considered reasonable to consider results valid in cases where the full address of the owner or the dog's name was omitted from the "Patient Information" form. Dogs treated with PLT Tablets or phenylbutazone outwith the recommended dose rate were included.

Results Analysis

The case results were divided by the treatment received into PLT Tablet treated and phenylbutazone treated groups. The PLT treated group was further divided into previously treated/ existing cases and non-treated/ new cases.

Five statistical analysis methods were used: unpaired "Students" *t*-test; paired *t*-test; Wilcoxon Signed Rank test; Chi squared (X^2) test; Kendall Correlation (Weisbrot, 1985).

The Student's *t*-test or *t*-independent test compares the means and standard deviations of two independent samples; each standard deviation is presumed to be from the same population. This test was used to compare the differences in the total condition scores in the phenylbutazone and PLT treated groups.

The paired *t*-test analyses the average differences between a series of paired observations. It is considered more rigorous and useful than the unpaired "Students" *t*-test since it allows isolation of the effects of manipulation on otherwise identical samples. However, the paired *t*-test, like the Student's *t*-test, does assume a parametric or normal distribution of data which could not be guaranteed for the parameters measured during the trial (lameness, weightbearing, joint mobility, stiffness and total condition scores), especially when the sample size was so small.

The Wilcoxon Signed Rank test is the non-parametric homologue of the parametric *t*-test. Thus, if the data was non-parametric, any statistical significance in differences between pre and post-treatment condition scores would still be assessed.

The Chi squared (X^2) test is frequently used in epidemiology and therapeutics to compare categorical data (lived/died, improved/not improved). It was used in this trial to compare the response rates to PLT and previous treatment or phenylbutazone treatment, and to compare groups with or without advice to reduce exercise.

Kendall Correlation is a non-parametric rank-order correlation. This test was used to assess whether there was any statistically significant linear correlation between the dose rate of PLT administered and the improvement in the overall condition of the patient.

The effect of treatment in PLT and phenylbutazone groups was assessed by the comparison of pretreatment and post-treatment condition scores for lameness, weightbearing, joint mobility and stiffness, and the total condition score (Lameness + weightbearing + joint mobility + stiffness). The condition scores before and after treatment were compared using a paired *t*-test and by a Wilcoxon Signed Rank test.

Treatment with PLT and phenylbutazone was compared by the differences in pre and post-treatment condition score within the two treatment groups, and by the assignment of "Improvement" scores based on the improvement in condition score, the comments of the veterinary practitioner and the comparison of the effect of treatment with any previous treatment (see below). The overall effect of treatment was rated as:

0 = No Effect
1 = Some Effect
2 = Marked Improvement
3 = Sound

The differences in pre and post condition scores between PLT Tablet and phenylbutazone treatment were compared using a Student's *t*-test and the overall effect of treatment compared with a X^2 test.

The effect of PLT Tablets was compared with the effect of previous treatment using the same system of "Improvement" scores. The "Improvement" scores for the PLT treatment and the previous treatment were compared using a paired *t*-test and X^2 test. In addition, the veterinary practitioner gave a subjective opinion of whether PLT Tablets were more or less efficacious than the previous treatment.

5.2.4 Results

Sixty-nine sets of case results sheets were returned. Twenty cases were completely excluded. In 4 cases the results were incomplete. In 3 cases the dog had received concurrent treatment with a drug preparation with possible anti-inflammatory or analgesic activity and which therefore might interfere with the results obtained for the test drugs. One dog was concurrently receiving prednisolone 5 mg bid for eczema. One dog was receiving treatment with Oterna ® Ear Drops which contain betamethasone. One dog was receiving treatment with Sesoral ® tablets which contain ethinyloestradiol and methyltestosterone. A further 13 cases were treated which were not diagnosed as suffering from clinical osteoarthritis.

After excluding these results, there were a total of 49 dogs which were diagnosed as suffering from clinical osteoarthritis. The mean number of case reports per practitioner was 3.5. However, the number of usable results per practitioner ranged from 1 to 9 cases (Appendix D4).

Thirty-four dogs were treated with PLT Tablets only; thirteen dogs were treated with phenylbutazone only; two dogs were treated with PLT Tablets and phenylbutazone consecutively: one dog received PLT for 14 days then phenylbutazone for 14 days; one dog received phenylbutazone for 14 days and then received PLT for a similar period.

Trial Animal Details

Animal details are summarised in Appendices D5 & D6.

Age Distribution [Appendix D7]

The age distribution of the cases of osteoarthritis was similar to that seen in the carprofen clinical trial with most dogs clinically affected in the 7 to 12 years old range. The age of three dogs was not specified. The mean age of all the osteoarthritic dogs was 8.5 years (standard deviation (S.D.) 3.8 years). The mean age of the Phenylbutazone treated dogs was 8.4 years (S.D 2.4 years). The mean age of the PLT treated dogs was 8.6 years (S.D. 4.2 years).

Breed Distribution [Appendix D8]

The breed distribution was similar to that seen in the carprofen trial with a high proportion of the dogs being Labrador Retrievers (16 of 49 dogs, 33%). There were also more German Shepherd Dogs, Golden Retriever and Border Collies than other breeds.

Sex Distribution [Appendix D9]

There were slightly more bitches than dogs with clinical osteoarthritis in the trial sample (22 male:27 female (45%: 55%)). In the PLT treated group, the ratio was 50:50 but in the phenylbutazone treated group it was 33% male: 66% female. It was not thought likely that there would be sex differences in the efficacy of treatment.

Bodyweight Distribution [Appendix D10]

The body weight of cases ranged from 13 kg to 52 kg. Most dogs (34 of 49: 69%) were between 25 and 40 kg in weight. The mean body weight was 31.6 kg (S.D. 9.2 kg). The animal weight was mostly associated with the breed. However, twenty five dogs were considered to be greater than their "ideal" weight by the veterinary practitioner (25 of 49: 51%). The bodyweight distribution of dogs treated with PLT Tablets and phenylbutazone were similar to those of the whole trial group.

Joint(s) Affected [Appendices D11-13]

The joint(s) affected and a brief history as recorded by the veterinary practitioner are listed for each case in Appendices D12 & D13.

Osteoarthritis of one or both hips was most prevalent (21 of 49 dogs: 43%). The stifle (15 of 49: 31%) and elbow (6 0f 49: 12%) were the other joints more often affected. In 5 cases (10%) more than one joint type is affected (eg. Case 1 both hips, one stifle). The joints affected in dogs receiving PLT or phenylbutazone is represented graphically in Appendix D11. There are differences between the two treatment groups because of the small sample size.

Case History [Summary: Appendices D12 & D13]

In seven cases the veterinary practitioner provided almost no history. In general, there was little history given. In 5 cases, osteoarthritis was thought to have developed secondary to previous surgical repair of ruptured anterior (cranial) cruciate ligament(s). Where stated, the history duration was months or years in most cases. In Cases 10, 16, 21, 46, 48, 55 and 56 radiography was performed and radiographic findings consistent with a clinical diagnosis of osteoarthritis were reported.

Previous Treatment

Details of previous treatments administered, dose rates, durations of treatment and effect of treatment is given in Appendix D31. The effect of treatment is also represented graphically in Appendix D32.

Twenty-two dogs were treated with a total of twenty-four treatments. In Cases 36 and 54 previous Predno-Leucotropin® treatment had no effect. In case 56, phenylbutazone had no effect. Seven (of 16) treatments had some effect.Twelve (of 22) previous treatments had a marked effect. Cases 36, 48, 54 and 58 were treated with phenylbutazone during the trial. Case 10 was treated with both phenylbutazone and PLT Tablets consecutively. The remaining 17 dogs were treated with PLT Tablets.

The time for signs of the painful condition to reappear after the withdrawal of the previous treatment was stated in only 5 cases. The period ranged from "a few days" or "several days" to 10 days, 6 weeks and 6 to 8 weeks. In 3 cases it was stated that treatment was not withdrawn between the previous treatment and PLT treatment. In 14 cases, the "Time taken for return of painful condition" was not completed.

PLT Treatment

Dose Rates and Regimes [Appendices D14 & D15]

The initial dose rate used by the practitioners ranged from 8 to 46.2 mg cinchophen/kg/day (0.04 to 0.23 mg prednisolone/kg/day)[Graph: Appendix D17] and are summarised below:

Initial Treatment Dose (mg/kg/day)		Number of dogs:
Cinchophen	Prednisolone	
8.0 - 46.2	0.04 - 0.23	36
8 - 20	0.04 - 0.10	12 [33%]
20 - 30	0.10 - 0.15	22 [61%]
30 - 47	0.15 - 0.23	2 [6%]

The initial regime was once a day dosing in two cases only (Case 6 and case 49). A divided daily dose (bid) was the initial regime in 26 cases (72%). The initial treatment dose was divided into three administrations per day in 7 cases (19%). Four times a day dosing was prescribed initially in one case (case 45).

In only five cases was the recommendation to reduce the treatment dose gradually followed by the veterinary practitioner. However, in 13 cases the treatment was not discontinued and the practitioner reported that treatment with PLT Tablets was to continue indefinitely. In other cases treatment stopped abruptly. The duration of PLT Tablet treatment before the dog was re-presented ranged from 5 to 28 days. The mean treatment period before reexamination was 13 days (S.D. 6 days). The *total* duration of trial PLT treatment with monitoring and result completion ranged from less than a week in cases where vomiting occurred to 90 days in case 49 (mean=19 days S.D. 17 days).

Other advice was reported as given to the owners in 28 cases. In 17 cases the owner was advised to reduce the exercise which the dog received or change the exercise to frequent short walks or lead exercise. In 4 cases normal exercise was recommended. In one case, a gradual increase in exercise was advised. In 10 of the 25 cases which the veterinarian considered overweight, it was reported that weight reduction was advised.

Five dogs were reported to be receiving other treatment or to be suffering from other disease. Case 21 was pruritic. PLT was said to benefit the condition. Case 30 had a dermatitis and was being treated with Pevidine baths. Case 32 had a history of a mild "stroke" four weeks previously. True "strokes" or intracranial vascular accidents are believed to be rare in the dog. The term "stroke" in veterinary usage is usually applied to cases of spontaneous "Vestibular Syndrome". In addition this dog also had bilateral cataracts. Case 37 had gingivitis and was on treatment with Metronidazole. Case 42 was being treated with Theocardin®(Diprophylline) and presumably had cardiac disease but unfortunately this was not stated. Case 44 was treated with Kaobiotic and Buscopan® for diarrhoea after 6 weeks of PLT treatment. The effect of the antacids in kaolin and of hyoscine N-butylbromide in Buscopan® on gastrointestinal absorption of cinchophen, and the effect of the NSAID dipyrone in Buscopan® in case 44 was not known. However, treatment was only administered once with these drugs and the remainder of the treatment period would be unaffected. It was not thought that the other diseases or treatments would affect the efficacy of the treatment. [Details Appendices D14 & D15].

Palatability was reported as "Good" in 14 cases, "Average" in 17 cases and "Poor" in 3 cases [Palatability reported in 34 cases].

Condition Scores

The pretreatment, post-treatment and difference in condition scores for lameness, weightbearing, joint mobility and stiffness are given for each case in Appendix D18. A graphical representation is given in Appendices D20-23. One dog was not reassessed because treatment was withdrawn and therapy with aspirin instituted.

Lameness [Appendices D18 & D20]

In four cases, the dog was not lame before treatment. PLT Tablets caused a reduction in lameness score of between 1 and 4 units in 25 of the 31 cases which were lame before treatment (81%). In 6 of these 31 lame cases (19%) there was no reduction in the lameness score. In 13 of the dogs lame before treatment, there was no detectable lameness after treatment (13 of 31: 42%). The mean lameness score before treatment was 2.2 (S.D. 1.3). The mean score after treatment was 0.7(S.D. 0.9). A paired *t*-test showed a significant improvement in lameness score ($p < 0.001$). A Wilcoxon Signed Rank Test showed a significant post PLT treatment improvement in lameness score ($p < 0.001$).

Weightbearing [Appendices D18 & D21]

Weightbearing was not reduced in 19 dogs (54%). Of the 16 dogs with reduced weightbearing, 13 had normal weightbearing at the post treatment reexamination (81%), whilst 3 dogs did not improve (19%). The mean pretreatment weightbearing score was 0.5 (S.D. 0.5). The mean score after treatment was 0.1 (S.D. 0.3). A paired *t*-test indicated a significant reduction in weightbearing score after treatment ($p<0.001$). A Wilcoxon Signed Rank Test showed a difference in weightbearing score post treatment which was significant despite the small sample size ($p<0.005$).

Joint Mobility [Appendices D18 & D22]

Joint mobility was reduced before treatment in 24 of 35 dogs (69%). Treatment with PLT Tablets was associated with an improvement in joint mobility in 8 of these 24 dogs (33%). The mean joint mobility score before PLT treatment was 0.9 (S.D. 0.7) and after treatment was 0.6 (S.D. 0.6). There was a statistically significant change in joint mobility after PLT treatment when the scores were compared by paired *t*-test ($p < 0.01$). Though the sample size was small there was a statistically significant difference in joint mobility score between the pre and post treatment examinations when analysed by a Wilcoxon Signed Rank Test ($p<0.01$).

Stiffness [Appendices D18 & D23]

Thirty-two dogs had stiffness before PLT treatment. In 27 of these 32, there was a reduction in stiffness score at the post treatment reexamination (84%).The mean stiffness score before PLT treatment was 2.4 (S.D. 1.2) and after treatment was 1.0 (S.D. 1.0). There was a significant decrease in stiffness score after PLT treatment by analysis using a paired *t*-test ($p < 0.001$) and when analysed by a Wilcoxon Signed Rank Test ($p < 0.001$).

Total Condition Score [Appendices D19 & D24]

Appendix D19 gives the pre and post PLT treatment and difference in total condition scores ie. the sums of the lameness, weightbearing, joint mobility and stiffness scores. Appendix D24 shows the pre and post PLT total condition scores and the change in total score between the pre and post treatment examination. In one dog (Case 21)the total score was zero before PLT treatment. This dog was receiving treatment (Predno-Leucotropin®) when the first examination took place. In 29 of 35 dogs (83%), PLT treatment was associated with a reduction in total condition score of between 1 and 9 units. Twenty-three dogs (23 of 36: 64%) had a 50 to 100% improvement in total condition score.

The mean total condition score before PLT treatment was 5.9 (S.D. 2.6) and after treatment was 2.5 (S.D. 2.0). There was a significant decrease in the total condition score after treatment with PLT when the scores were analysed by paired *t*-test ($p < 0.001$). A Wilcoxon Signed Rank Test also revealed a significant decrease in the total condition score post treatment ($p < 0.001$)

Improvement Rating [Appendices D19 & D33]

The improvement rating was assigned to each case result based upon the improvements in condition score but also considering the veterinary practitioners comments on the effect of treatment and the relative efficacy of PLT treatment compared with the previous treatment, for which the veterinary practitioner had assigned an improvement score (0=No effect, 1=Some Effect, 2=Marked Improvement, 3=Sound).

In Case 2, the dogs' condition deteriorated during treatment with PLT. The dog was euthanased because of the severity of the condition. In case 19, treatment with PLT gave no improvement and side effects were reported (see below). Case 43 did not improve on treatment. In case 50 treatment was withdrawn because of vomiting.

In 6 cases (17%) PLT treatment had some effect. In 21 of 36 cases (58%) PLT treatment had a marked effect. In 4 cases (11%) PLT treatment made the dog sound according to the veterinary practitioner.

Treatment was considered satisfactory by the veterinary practitioner in 31 cases (86%). The exceptions were Cases 2, 19, 43, 50, and 57.

Reported Side Effects

Case 12

Gooch: 3.5 year old M/N Golden Retriever; 52.5 kg (Ideal 40 kg). Left hock.
No previous treatment.
PLT Tablets: 22.9 mg cinchophen/kg/day; 0.11 mg prednisolone/kg/day
Veterinary surgeon reported: "Both polydipsia and polyphagia were noticed by the owner after a few days treatment; neither were severe enough to cause owner concern". The dog was also on a strict diet.

Case 19

Fowler: 9 year old M/N Labrador Crossbred; 35 kg (Ideal 25 kg). Hips, especially left. No previous treatment.
PLT Tablets: 22.9 mg cinchophen/kg/day; 0.11 mg prednisolone/kg/day.
Veterinary surgeon reported vomiting after 3 days. The dose rate was halved to 11.4 mg cinchophen/kg/day; 0.06 mg prednisolone/kg/day but the dog vomited after 4 days on this lower dose rate. Treatment was then withdrawn.

Case 24

Lomas: 11 year old M Labrador; 30 kg. Hips; concurrent pruritis.
Previously treated with phenylbutazone long term (20 mg/kg/day).
PLT Tablets: 20 mg cinchophen/kg/day; 0.1 mg prednisolone/kg/day.
Veterinary surgeon reported the dog had slightly increased thirst whilst on treatment.

Case 26

Giles: 14 year old M Collie; 18 kg. "Pain in back legs and spine".
No previous treatment.
PLT Tablets: 22.2 mg cinchophen/kg/day; 0.11 mg prednisolone/kg/day.
Veterinary surgeon reported: "Slight dullness for few days, then O.K.".

Case 34

Love: 8 year old F Labrador; 25-30 kg. Hips. No previous treatment.
PLT Tablets: 14.8 mg cinchophen/kg/day; 0.07 mg prednisolone/kg/day.
Veterinary surgeon reported: "Slight diarrhoea problem which cleared up once off PLT". Occasional diarrhoea, from about 18 days of treatment. Treatment not continued after veterinary surgeon re-examined the dog.

Case 38

Duncan: 10 year old F/N Corgi; 13 kg (Ideal 11 kg). Shoulder.
PLT Tablets: 46.2 mg cinchophen/kg/day; 0.23 mg prednisolone/kg/day
Veterinary surgeon reported: "Polyuric. Wets in house at night. Previously clean". Thirst reported at 7 day reexamination. Dose reduced to 30.8 mg cinchophen; 0.15 mg prednisolone/kg/day.

Case 44

Young: 12 year old M Bearded Collie; 33 kg. Shoulder, carpal and spinal problems.
PLT Tablets: 12.1 mg cinchophen/kg/day; 0.06 mg prednisolone/kg/day
Treated previously with phenylbutazone 12 mg/kg/day for 1 month.
Veterinary surgeon reported that the dog was presented with diarrhoea after 41 days on PLT Tablets. Treated with Kaobiotic and Buscopan. Diarrhoea not thought connected to PLT. PLT therapy continued.

Case 50

Campbell: 11 year old M Border Collie; 35 kg (Ideal 25 kg). Bilateral stifle.
PLT Tablets: 17.1 mg cinchophen/kg/day; 0.09 mg prednisolone/kg/day
Veterinary surgeon reported that dog had vomited and treatment withdrawn. Neither the number of treatments nor the severity or frequency of vomiting were reported.

There were no adverse reactions reported on abrupt withdrawal of PLT treatment.

Phenylbutazone Treatment

Dose Rates and Regimes [Appendix D16]

The initial dose rate used by the practitioners ranged from 5.0 to 11.4 mg phenylbutazone/kg/day with a mean of 8.4 mg/kg/day. The regime was sid in two cases, bid in 10 cases and tid in 3 cases. The duration of treatment before the dog was re-presented was 14 days in most dogs but ranged from 7 to 18 days. The duration of trial treatment with phenylbutazone ranged from 3 to 60 days. In case 16 an adverse reaction caused treatment to be withdrawn after three days.

Other advice was reported as given to the owners in 13 cases. In 10 cases the owner was advised to reduce the exercise which the dog received or change the exercise to frequent short walks or lead exercise. In 6 cases, weight reduction was advised.

Three dogs were reported to be receiving other treatment or be suffering from other disease. Case 3 was diagnosed as suffering from Chronic Degenerative Radiculo-Myelopathy and the associated ataxia was said to confuse the gait abnormality due to hip dysplasia and osteoarthritis. During the first seven days of phenylbutazone treatment, Case 4 was receiving treatment with a trimethoprim-sulphonamide preparation for a urinary tract infection. Case 54 was treated at ten day intervals with an insecticidal spray to reduce flea dermatitis. It was not thought that these diseases or treatments would affect the efficacy of the treatment.

Palatability of the sugar-coated Flexazone 100 mg Tablets® was reported as "Good" in 13 and "Average" in two cases.

Condition Scores

The phenylbutazone group pretreatment, post-treatment and difference in condition scores for lameness, weightbearing, joint mobility and stiffness are given for each case in Appendix D25. A graphical representation is given in Appendices D26-30.

Lameness [Appendices D25 & D26]

Thirteen of the 15 dogs treated were lame before treatment. In case 16, the dog was more severely lame after treatment with phenylbutazone: in this case treatment had been withdrawn because of vomiting. Two of the thirteen lame dogs did not improve with treatment (13%). Ten dogs had reduced lameness after treatment (67%).

The mean lameness score before phenylbutazone treatment was 2.2 (S.D. 1.3) and after treatment was 1.1 (S.D. 1.2). There was a statistically significant improvement in lameness score after treatment when assessed using a paired *t*-test ($p < 0.005$). By a Wilcoxon Signed Rank Test, the post treatment lameness score was significantly different from the pretreatment score ($p<0.005$) despite the small sample size.

Weightbearing [Appendices D25 & D27]

Eleven of the fifteen treated dogs had reduced weightbearing before treatment. In 9 of the 11, there was an improvement in weightbearing score after treatment (82%).

The mean weightbearing score was 0.9 (S.D. 0.6) before treatment and 0.3 (S.D. 0.5)after treatment. There was statistical significance in the improvement between pretreatment and post-treatment weightbearing scores with a paired *t*-test ($p<0.001$). By a Wilcoxon Signed Rank Test, there was a statistically significant improvement in weightbearing score after treatment ($p<0.005$) despite the small sample size.

Joint Mobility [Appendices D25 & D28]

Joint mobility pre treatment was reduced in 14 of the 15 dogs. In 7 of the 14, there was an improvement in joint mobility at the post treatment reexamination (50%).

The mean joint mobility score was 1.4 (S.D. 0.6) before and 0.9 (S.D. 0.8) after treatment. There was a statistically significant improvement in joint mobility score after treatment with a paired *t*-test ($p<0.005$) and by a Wilcoxon Signed Rank Test ($p<0.01$) despite the small sample size.

Stiffness [Appendices D25 & D29]

Stiffness was a feature in 14 of the 15 dogs before treatment. In 12 of these 14 dogs, stiffness score had improved at the post treatment reexamination (86%).

The mean stiffness score was 2.6 (S.D. 1.0) before treatment and 1.1 (S.D. 1.1) after treatment. There was a statistically significant reduction in the stiffness score after treatment when the data was analysed by a paired *t*-test ($p<0.001$) and a Wilcoxon Signed Rank Test ($p<0.002$) despite the small sample size.

Total Condition Score [Appendices D25 & D30]

In case 16 the total condition score was worse at reexamination than before treatment. This was the dog which had treatment withdrawn because of a suspected adverse reaction. In case 3 there was no change in the condition score after treatment. The condition of this dog deteriorated during the trial period and it was later euthanased. In 13 of 15 treated dogs there was a reduction in total condition score of between 1 and 7 units (87%). The percentage improvement in total condition score is shown graphically in Appendix 7(ii). In 9 cases (9 of 15: 60%) there was a 50 to 100% improvement in total condition score.

The mean total score before treatment was 7.0 (S.D. 2.5) and after treatment was 3.5 (S.D. 2.9). There was a statistically significant reduction in total condition scores between the pre and post phenylbutazone treatment examinations when they were submitted to a paired *t*-test ($p<0.001$)and a Wilcoxon Signed Rank Test ($p <0.002$). Despite the small sample size there was a very low probability that this could have occurred by chance.

Improvement Rating [Appendices D25 & D33]

The improvement rating was assigned to each case result subjectively based upon the improvements in condition score but also considering the veterinary practitioners comments on the effect of treatment. In two cases, Cases 3 and 16, the condition was assessed as being worse after treatment than before (13%). In Case 3 the dog was later euthanased. In Case 16 treatment was withdrawn after three days because of a suspected adverse reaction. In six cases treatment was stated to have had some effect (40%). In six cases treatment was said to have had a marked effect (40%). In one case the dog was said to be sound after treatment (7%).

Treatment was considered satisfactory by the veterinary practitioner in 12 of the 15 cases treated (80%).

Reported Side Effects

Case 14

Avernell: 4 year old F/N Labrador; 30 kg. Bad hip dysplasia, especially right hip.
No previous treatment.
Phenylbutazone: 10 mg/kg/day for 10 days.
Veterinary surgeon reported dullness: "Dog seemed rather quiet".

Case 16

Edmunds: 8 year old M German Shepherd Dog.; 40 kg. Left hip. Previously treated with Predno-Leucotropin at 15 mg cinchophen/kg/day. Marked improvement. Phenylbutazone: 10 mg/kg/day.
Veterinary surgeon reported:" Within 12 hours of first tablets: Vomiting++; would not eat or get up. Stopped PBZ after 3 days. Better in 24 hours. Reinstituted therapy with Predno-Leucotropin®".

Comparison Between Treatments

PLT Tablet Treatment and Previous Treatment

There was no statistically significant difference in the "improvement scores" for PLT and the previous treatments when compared by either paired or Student's *t*-test. However, when the number of dogs showing a "Marked Improvement" or "Sound" score (+2 or +3) was compared with dogs showing no effect or only some effect (-1,0, or +1), there were significantly more dogs with the +2 or +3 scores in the PLT treatment than in the previous treatment group when the data was analysed by a X^2 test. In addition, the veterinary surgeon was required to state how the PLT treatment compared to the previous treatment. This was stated for 18 previous treatments in 17 dogs. In the 5 dogs which had previously received Predno-Leucotropin®, the PLT treatment was said to be of equivalent efficacy. In one case, a previous treatment with Predno-Leucotropin® had been more effective. The PLT treatment was said to be superior to 11 previous treatments and equivalent to phenylbutazone in one case [Appendix D32].

PLT Tablet Treatment and Phenylbutazone Treatment

Both drugs were used at separate times in the same case in only 2 dogs. In one, PLT and phenylbutazone were said to be of equivalent efficacy. In the other case, PLT was said to give a better effect and reduced the condition scores more than phenylbutazone. When the effect of treatment on condition scores and the percentage improvement in total condition score were compared for the PLT and phenylbutazone groups, there was no statistically significant difference between the two groups by X^2 test or by Student's *t*-test.

PLT Dose and Effect

Analysis of the PLT Tablet treatment dose and the effect of treatment by Kendall Correlation Test revealed a significant correlation between dose and percentage reduction in total condition score within the treatment dose range of 8 to 47 mg cinchophen:0.04 to 0.23 mg prednisolone/kg/day ($p<0.002$).

5.2.5 Conclusions

There were differences in the PLT and phenylbutazone treated groups in sex distribution, breed distribution, joint affected and the severity of the disease. The differences were partly due to the small size of the trial population. However, variance within and between the groups was inevitable. Although the two groups are not truly comparable, the trends indicated in the trial are probably valid.

Eight cases had reported adverse reactions whilst receiving PLT treatment (22%). It is not clear whether all these effects were volunteered or were elicited by questioning. The reported polyphagia was more likely a consequence of a weight reducing diet than the low dose prednisolone treatment. The slight increase in thirst reported in 2 cases was unlikely to have been due to the low dose of prednisolone. It may have been suggested by questioning or might be indicative of nausea. In one case receiving a higher dose of PLT polyuria was reported. The "slight dullness" reported in case 26 may have been due to nausea or gastric irritation.

Vomiting, inappetance and depression from 3 to 9 days on 22.9 mg cinchophen: 0.11 mg prednisolone/kg/day in case 19 and after a "few days" on 17.1 mg cinchophen/kg/day: 0.09 mg prednisolone/kg/day in case 50 were reported. Treatment was withdrawn in both cases and the dogs recovered. These signs may have been due to nausea, gastric irritation or ulceration. In case 34 mild diarrhoea was a side effect after 18 days of treatment. Treatment was discontinued at the next veterinary examination. Diarrhoea after six weeks of treatment in case 44 was thought by the veterinarian to be coincidental. Treatment was continued and the diarrhoea resolved. Adverse reactions were apparently unrelated to higher PLT Tablet dose rates.

Adverse reactions were reported in two phenylbutazone treated dogs (13%). Dullness was reported in case 14 and may have indicated nausea. Vomiting , inappetance and depression were side effects in case 16. These signs may have been due to nausea, gastric irritation or ulceration. Treatment was withdrawn.

From the limited numbers of dogs treated during the trial, PLT appears to be effective in the therapy of many cases of clinical osteoarthritis when used at 8-46 mg cinchophen/kg bodyweight/day [0.04-0.23 mg prednisolone/kg bodyweight/day] for between 5 and 90 days. There was correlation between treatment dose and effect within this dose range. For the duration of treatment, PLT was well tolerated in most dogs. The incidence and type of reported adverse reactions and treatment withdrawal were comparable with other non-steroidal anti-inflammatory drugs. No correlation between dose rate or treatment duration and the incidence or severity of adverse reactions was apparent.

The clinical trial suggested that PLT Tablets may be effective at lower dose rates or less frequent dosing than is recommended by the manufacturer. It appears that the dosage recommendations from the manufacturer for Predno-Leucotropin Tablets and for PLT Tablets are not followed by veterinary practitioners.

On the basis of currently available information, including the clinical trial described in this section, PLT Tablets appear to have a good therapeutic effect in cases of canine osteoarthritis. From the clinical trial, PLT Tablets are probably equivalent to or of greater efficacy than phenylbutazone. Based upon the SAR information reported for the closely related combination Predno-Leucotropin Tablets, and the clinical trial data, the available evidence suggests that the proposed 25-44 mg cinchophen and 0.125-0.22 mg prednisolone/kg/day as two divided daily doses is effective and well tolerated for at least 14 days with an incidence of adverse reactions similar to that of other NSAIDs.

The trial design was limited by practical constraints. This led to the use of a positive control design. Unfortunately, the limited time available and a poor response by some veterinarians has meant that only 49 cases of clinical osteoarthritis were treated during the trial. The small size of the phenylbutazone treated group limits the comparability of the two groups. In addition, the use of subjective measurements and the lack of blinding at the level of the practitioner also reduce the significance that can be attributed to the results. Performing a cross-over design and insisting on radiographic confirmation of osteoarthritic changes would have severely affected recruitment of practices, investigator compliance and the number of results returned.

It would have been more useful to have a smaller number of dogs which were diagnosed osteoarthritic radiographically in addition to clinically, treated blind with both test drug and positive control in a cross-over type design. The two drugs could then be compared in therapy of the same condition in the same animal and a preference stated by the owner. This approach would reduce the potential errors involved in the present trial due to the possibility of incorrect diagnosis and inappropriate treatment, lack of group comparability and bias in favour of one of the treatments by the veterinarian (Harris and Fitzgerald, 1970). However, the extra requirements in time and materials would necessitate the use of financial compensation for the veterinarians involved.

Results Summary:

	PLT		PBZ	
Total no. of dogs treated	36		15	
Dose rate (mg/kg/day)	8 - 46 cinchophen 0.04 - 0.23 predn.		5 - 11.4	
Reported adverse reactions	8	(22%)	2	(13%)
Treatment withdrawal	2	(5.5%)	1	(6.7%)
Lameness reduced	25/31	(81%)	10/13	(67%)
Weightbearing increased	13/16	(81%)	9/11	(82%)
Joint mobility increased	8/24	(33%)	7/14	(50%)
Total condition score improved	31/36	(86%)	13/15	(87%)
50-100% Improvement in total score	23/36	(64%)	9/15	(60%)
Treatment considered satisfactory	31/36	(86%)	12/15	(80%)

APPENDIX
A

TABLE A1: Plasma Carprofen Concentration [ug/ml] measured after oral administration of a single 4 mg/kg dose

Plasma Carprofen Concentration [ug/ml]

Time (hours)	Dog 1	Dog 2	Dog 3	Dog 4	Dog 5	Dog 6	Mean	±SEM
Pre	0	0	0	0	0	0	0	0
0.25	2.02	9.25	NS	8.65	24.71	17.97	12.52	3.96
0.5	19.57	17.17	13.63	24.11	40.74	28.39	23.94	3.97
1	31.84	33.57	16.69	31.58	35.41	37.38	31.08	3.01
1.5	29.73	38.28	20.44	29.13	31.75	30.80	30.02	2.34
2	25.93	44.30	26.13	24.98	25.19	20.02	27.76	3.43
4	17.33	32.02	21.61	21.94	19.49	11.89	20.71	2.71
8	7.27	19.85	17.82	14.12	11.16	8.93	13.19	2.03
12	3.33	13.94	11.42	10.40	3.85	3.74	7.78	1.91
24	0.42	3.33	5.78	3.35	1.18	1.10	2.53	0.82
48	0.07	0.49	1.26	0.48	0.22	0.09	0.44	0.18
72	0	0.05	0.30	0.10	0.05	0	0.083	0.046
96	0	0	0.11	0	0	0	0.018	0.018

APPENDIX
B

Calculations of Dosage Schedule

Each dog was weighed on the day previous to the start of the trial. The number of tablets and half tablets [17.5mg] required to give a dose of 9mg/kg/day or greater was calculated as below:

Dog Number	Weight [kg]	x 9mg/kg	tabs req.	Admin.
1	13.5	121.5	6.9	7
2	16.3	146.7	8.4	8.5
3	12.3	110.7	6.3	6.5
4	13.5	121.5	6.9	7
5	16.5	148.5	8.5	8.5
6	15.5	139.5	8.0	8.0

Thus the actual daily doses were as follows:

DOG 1: 9.07 mg/kg orally once a day for fourteen days

DOG 2: 9.13 mg/kg "

DOG 3: 9.25 mg/kg "

DOG 4: 9.07 mg/kg "

DOG 5: 9.02 mg/kg "

DOG 6: 9.03 mg/kg "

BIOCHEMISTRY PROFILES:

	NORMAL CANINE VALUES [S.I. units]
UREA (mmol/l)	0-7.47
SODIUM "	136-160
POTASSIUM "	3.4-5.8
CHLORIDE "	95-115
CALCIUM "	2.34-3.03
MAGNESIUM "	0.61-1.19
PHOSPHATE "	1.29-2.9
CHOLESTEROL "	1.8-6.96
CREATININE "	44-132
BILIRUBIN (umol/l)	0-10.26
ALK PHOS (I.U.)	0 - 130
AS T (I.U.)	0 - 40
AL T (I.U.)	0 - 50
TOTAL PROTEIN (g/l)	50-78
ALBUMIN (g/l)	36
GLOBULIN (g/l)	27
C R P (mg/l)	0-10 [10-100 reflects degree of tissue damage, >100= extensive tissue damage]

HAEMATOLOGY PROFILES:

		NORMAL CANINE VALUES
WBC	($x10^9$/l)	6.0 -17.0
RBC	($x10^{12}$/l)	5.5 -8.5
Hb	(g/dl)	12 -18
Hct	(l/l)	0.370 - 0.550
MCV	(fl)	60 - 70
NEUTROPHILS	(%)	60 -77
LYMPHOCYTES	"	12 - 30
MONOCYTES	"	3 - 10
EOSINOPHILS	"	2 - 10
NORMOBLASTS	"	< 1
PLATELETS	(x 10^9/l)	100 - 350

BIOCHEMISTRY PROFILES: **DAY: Pre**

DOG NUMBER:

	1	2	3	4	5	6
UREA (mmol/l)	7.9	7.0	5.5	8.6	6.7	3.9
SODIUM "	146	146	144	145	147	146
POTASSIUM "	3.8	3.9	3.9	4.0	4.1	3.9
CHLORIDE "	103	108	108	101	102	104
CALCIUM "	2.61	2.63	2.58	2.79	2.63	2.58
MAGNESIUM "	0.76	0.72	0.75	0.69	0.66	0.60
PHOSPHATE "	1.17	1.12	1.12	1.34	1.15	0.81
CHOLESTEROL "	4.82	3.02	3.54	4.64	2.48	4.04
CREATININE "	96	80	89	93	96	83
BILIRUBIN (umol/l)	1	0	1	1	1	1
ALK PHOS (I.U.)	55	59	71	76	52	70
AS T (I.U.)	22	34	24	25	41	20
AL T (I.U.)	29	66	35	51	84	35
TOTAL PROTEIN (g/l)	54	54	57	59	51	59
ALBUMIN (g/l)	38	34	32	33	34	28
GLOBULIN (g/l)	16	20	25	26	17	31
C R P (mg/l)	5.6	3.8	6.5	0	24.8	2

BIOCHEMISTRY PROFILES: **DAY:3**

DOG NUMBER:

	1	2	3	4	5	6
UREA (mmol/l)	11.6	10.8	8.3	11.1	11.8	9.4
SODIUM "	146	142	147	149	150	146
POTASSIUM "	4.4	4.2	5.1	4.7	4.5	4.2
CHLORIDE "	101	107	109	104	108	104
CALCIUM "	2.69	2.65	2.78	2.78	2.80	2.64
MAGNESIUM "	0.85	0.71	0.81	0.84	0.81	0.76
PHOSPHATE "	1.51	1.22	1.78	1.88	1.63	1.24
CHOLESTEROL "	5.19	3.08	3.53	4.89	2.46	4.15
CREATININE "	94	82	90	92	89	80
BILIRUBIN (umol/l)	1	0	1	0	0	0
ALK PHOS (I.U.)	63	76	70	75	60	68
AS T (I.U.)	23	32	24	26	30	17
AL T (I.U.)	26	61	34	53	46	33
TOTAL PROTEIN (g/l)	57	58	58	63	54	62
ALBUMIN (g/l)	34	34	32	37	36	28
GLOBULIN (g/l)	22	24	26	26	18	34
C R P (mg/l)	0	0	2.8	0	31.6	2

BIOCHEMISTRY PROFILES: **DAY:5**

DOG NUMBER:

	1	2	3	4	5	6
UREA (mmol/l)	9.4	8.8	8.6	9.1	9.1	7.3
SODIUM "	146	150	145	145	147	148
POTASSIUM "	4.4	3.9	4.8	4.7	4.5	4.3
CHLORIDE "	106	109	104	108	109	106
CALCIUM "	2.63	2.60	2.51	2.66	2.46	2.68
MAGNESIUM "	0.85	0.79	0.76	0.74	0.74	0.72
PHOSPHATE "	1.68	1.39	1.30	1.61	1.36	0.92
CHOLESTEROL "	4.97	3.43	3.68	4.46	2.61	4.20
CREATININE "	89	82	84	82	97	81
BILIRUBIN (umol/l)	1	0	1	0	0	1
ALK PHOS (I.U.)	59	56	62	70	46	67
AS T (I.U.)	22	34	27	34	24	19
AL T (I.U.)	28	63	34	50	37	37
TOTAL PROTEIN (g/l)	54	58	58	58	47	63
ALBUMIN (g/l)	36	33	32	34	34	26
GLOBULIN (g/l)	28	25	26	24	13	37
C R P (mg/l)	3.6	0	0	0	>100	6.1

BIOCHEMISTRY PROFILES: **DAY:8**

	DOG NUMBER:					
	1	2	3	4	5	6
UREA (mmol/l)	7.3	6.7	6.3	7.5	8.5	4.7
SODIUM "	151	152	149	149	148	148
POTASSIUM "	4.2	4.1	4.0	4.2	4.4	3.9
CHLORIDE "	109	113	112	109	109	109
CALCIUM "	2.60	2.60	2.65	2.70	2.68	2.70
MAGNESIUM "	0.70	0.76	0.82	0.68	0.76	0.79
PHOSPHATE "	1.66	1.43	1.26	1.31	1.59	1.48
CHOLESTEROL "	5.06	3.44	3.79	4.62	2.32	5.21
CREATININE "	79	63	81	86	89	67
BILIRUBIN (umol/l)	1	0	1	2	0	1
ALK PHOS (I.U.)	53	45	62	65	52	115
AS T (I.U.)	27	30	26	31	32	16
AL T (I.U.)	27	57	35	54	31	32
TOTAL PROTEIN (g/l)	53	56	57	56	51	64
ALBUMIN (g/l)	31	30	32	32	25	35
GLOBULIN (g/l)	22	26	35	24	26	29
C R P (mg/l)	0	0	0	0	67.9	49.1

BIOCHEMISTRY PROFILES: **DAY:11**

	DOG NUMBER:					
	1	2	3	4	5	6
UREA (mmol/l)	11.9	9.0	7.0	9.4	9.2	7.5
SODIUM "	143	146	144	146	144	145
POTASSIUM "	4.4	4.2	4.6	4.4	4.6	4.0
CHLORIDE "	103	109	108	108	107	105
CALCIUM "	2.62	2.59	2.68	2.65	2.54	2.69
MAGNESIUM "	0.85	0.74	0.74	0.72	0.74	0.74
PHOSPHATE "	1.73	1.61	1.73	1.86	1.38	1.23
CHOLESTEROL "	4.92	3.22	3.61	4.85	2.72	4.87
CREATININE "	88	70	73	77	82	74
BILIRUBIN (umol/l)	0	0	1	0	0	0
ALK PHOS (I.U.)	67	51	67	64	46	96
AS T (I.U.)	27	36	27	27	37	20
AL T (I.U.)	24	54	34	49	37	33
TOTAL PROTEIN (g/l)	52	54	55	59	49	61
ALBUMIN (g/l)	31	30	32	32	25	34
GLOBULIN (g/l)	21	24	23	23	24	27
C R P (mg/l)	0	0	0	0	16.5	9.1

BIOCHEMISTRY PROFILES: **DAY:14**

	DOG NUMBER:					
	1	2	3	4	5	6
UREA (mmol/l)	7.4	5.7	4.3	5.3	5.1	2.8
SODIUM "	145	148	144	145	141	144
POTASSIUM "	3.9	3.7	4.8	4.2	4.4	3.9
CHLORIDE "	102	105	105	103	104	104
CALCIUM "	2.62	2.55	2.72	2.70	2.32	2.64
MAGNESIUM "	0.66	0.60	0.76	0.66	0.80	0.69
PHOSPHATE "	1.21	1.33	1.38	1.49	1.22	1.07
CHOLESTEROL "	4.72	3.28	4.04	5.08	2.74	4.83
CREATININE "	85	82	83	90	83	73
BILIRUBIN (umol/l)	1	1	1	2	1	1
ALK PHOS (I.U.)	50	51	78	78	66	100
AS T (I.U.)	24	30	29	32	28	14
AL T (I.U.)	31	58	40	55	33	33
TOTAL PROTEIN (g/l)	50	50	58	59	44	61
ALBUMIN (g/l)	30	28	32	33	23	33
GLOBULIN (g/l)	20	22	26	26	21	28
C R P (mg/l)	5.5	0	0	5.4	>100	7.3

BIOCHEMISTRY PROFILES: **DAY:17**

	DOG NUMBER:					
	1	2	3	4	5	6
UREA (mmol/l)	11.6	9.5	8.5	11.2	8.4	8.4
SODIUM "	149	148	145	146	143	146
POTASSIUM "	4.3	3.9	4.8	4.5	4.4	4.0
CHLORIDE "	104	107	107	102	103	104
CALCIUM "	2.68	2.58	2.61	2.67	2.50	2.71
MAGNESIUM "	0.62	0.76	0.68	0.74	0.72	0.68
PHOSPHATE "	1.70	1.25	1.39	1.72	1.54	1.67
CHOLESTEROL "	5.05	3.36	3.71	4.76	2.14	4.56
CREATININE "	96	80	86	90	94	73
BILIRUBIN (umol/l)	1	0	1	0	0	0
ALK PHOS (I.U.)	60	52	82	74	42	105
AS T (I.U.)	22	26	23	22	35	24
AL T (I.U.)	31	72	38	53	35	34
TOTAL PROTEIN (g/l)	54	55	58	57	47	63
ALBUMIN (g/l)	32	31	33	31	24	34
GLOBULIN (g/l)	22	24	25	26	23	29
C R P (mg/l)	3.8	5.8	0	3.3	34.1	0

BIOCHEMISTRY PROFILES: **MEAN VALUES**

	PRE	3	5	8	11	14	17
UREA (mmol/l)	6.6	10.5	8.7	6.8	9.0	5.1	9.6
SODIUM "	146	147	147	150	145	145	146
POTASSIUM "	3.93	4.52	4.43	4.13	4.37	4.15	4.32
CHLORIDE "	104	106	107	110	107	104	105
CALCIUM "	2.64	2.72	2.59	2.66	2.63	2.59	2.63
MAGNESIUM "	0.70	0.80	0.77	0.76	0.76	0.70	0.70
PHOSPHATE "	1.12	1.54	1.38	1.46	1.59	1.28	1.55
CHOLESTEROL "	3.76	3.88	3.89	4.07	4.03	4.12	3.93
CREATININE "	90	88	86	78	77	83	87
BILIRUBIN (umol/l)	0.8	0.3	0.5	0.8	0.2	1.2	0.3
ALK PHOS (I.U.)	64	69	60	65	65	70	69
AS T (I.U.)	28	25	27	27	29	26	25
AL T (I.U.)	50	42	42	39	39	42	44
TOTAL PROTEIN (g/l)	56	59	56	56	55	54	56
ALBUMIN (g/l)	33	29	32	31	31	30	31
GLOBULIN (g/l)	23	25	25	27	24	24	25
C R P (mg/l)	7.1	6.1	18.3	>19.5	4.3	>19.7	7.8

Haematology Results: **PRE**

		Dog 1	Dog 2	Dog 3	Dog 4	Dog 5	Dog 6
WBC	($x10^9$/l)	13.2	15.0	12.6	12.5	18.0	14.5
RBC	(x 10^{12}/l)	7.0	6.8	6.2	7.3	6.7	7.0
Hb	(g/dl)	15.6	16.9	15.4	18.1	14.0	17.0
Hct	(l/l)	0.475	0.496	0.452	0.540	0.425	0.498
MCV	(fl)	68	73	73	74	64	71
Neutrophils	(%)	68	61	57	72	78	71
Lymphocytes	"	26	33	35	22	14	26
Monocytes	"	0	1	2	4	1	0
Eosinophils	"	6	5	6	2	7	3
Platelets	($x10^9$/l)	510	450	380	270	510	380

Haematology Results: **Day 3**

		Dog 1	Dog 2	Dog 3	Dog 4	Dog 5	Dog 6
WBC	($x10^9$/l)	14.6	18.8	13.1	14.2	18.0	13.5
RBC	(x 10^{12}/l)	7.0	6.9	6.3	7.7	6.6	7.4
Hb	(g/dl)	15.2	16.9	15.4	19.0	14.2	17.7
Hct	(l/l)	0.480	0.506	0.406	0.573	0.417	0.535
MCV	(fl)	69	73	73	74	63	72
Neutrophils	(%)	59	62	43	57	52	59
Lymphocytes	"	28	32	52	35	21	33
Monocytes	"	1	1	0	3	2	3
Eosinophils	"	12	5	5	5	25	5
Platelets	($x10^9$/l)	420	460	280	250	450	400

Haematology Results: **Day 5**

		Dog 1	Dog 2	Dog 3	Dog 4	Dog 5	Dog 6
WBC	($x10^9$/l)	11.6	14.3	12.4	11.5	16.6	12.2
RBC	(x 10^{12}/l)	6.8	6.9	6.3	7.2	6.5	7.5
Hb	(g/dl)	14.7	16.8	15.7	18.1	14.2	18.6
Hct	(l/l)	0.462	0.501	0.459	0.530	0.408	0.534
MCV	(fl)	68	73	73	74	63	71
Neutrophils	(%)	64	55	61	55	65	61.5
Lymphocytes	"	26	27	31.5	38	15.5	25
Monocytes	"	2	7	2.5	4	7	6.5
Eosinophils	"	8	11	5	3	12	6
Platelets	($x10^9$/l)	410	400	370	250	470	320

Film Report:
Increased numbers of target cells in all dogs in this batch.

Haematology Results: **Day 8**

		Dog 1	Dog 2	Dog 3	Dog 4	Dog 5	Dog 6
WBC	($x10^9$/l)	13.3	15.7	12.8	10.9	19.2	18.2
RBC	(x 10^{12}/l)	6.6	6.6	6.3	7.0	6.5	7.9
Hb	(g/dl)	15.5	16.4	16.1	17.8	14.2	19.7
Hct	(l/l)	0.445	0.474	0.450	0.517	0.405	0.559
MCV	(fl)	67	72	72	74	62	71
Neutrophils	(%)	67	73	75	80	77	87
Lymphocytes	"	27	15	18	14	11	10
Monocytes	"	2	3	1	3	2	1
Eosinophils	"	4	9	6	3	10	2
Platelets	($x10^9$/l)	400	390	300	210	490	310

Haematology Results: **Day 11**

		Dog 1	Dog 2	Dog 3	Dog 4	Dog 5	Dog 6
WBC	($x10^9$/l)	15.2	20.0	C	C	C	13.6
RBC	($x\ 10^{12}$/l)	6.5	6.6	L	L	L	7.7
Hb	(g/dl)	14.8	16.4	O	O	O	18.6
Hct	(l/l)	0.441	0.480	T	T	T	0.554
MCV	(fl)	68	73	T	T	T	72
Neutrophils	(%)	52	52.5	E	E	E	53
Lymphocytes	"	40	35	D	D	D	36
Monocytes	"	3	6	-	-	-	7
Eosinophils	"	5	6	-	-	-	3
Normoblasts	"	0	0.5	-	-	-	1
Platelets	($x10^9$/l)	370	350	-	-	-	330

Film Report:
Films from 1, 2, and 6 show target cells

Haematology Results: **Day 14**

		Dog 1	Dog 2	Dog 3	Dog 4	Dog 5	Dog 6
WBC	($x10^9$/l)	11.7	15.3	12.3	11.1	15.8	12.4
RBC	($x\ 10^{12}$/l)	6.4	6.3	7.3	6.5	6.8	7.1
Hb	(g/dl)	15.0	16.0	19.0	16.5	14.5	18.1
Hct	(l/l)	0.419	0.449	0.531	0.462	0.411	0.493
MCV	(fl)	66	71	73	71	60	69
Neutrophils	(%)	58	64	69	61	74	64
Lymphocytes	"	31	24	25.5	29	16	28
Monocytes	"	7	4	4	2	6	1
Eosinophils	"	4	7	1	8	4	6
Normoblasts	"	0	0	0	0	0	1
Platelets	($x10^9$/l)	430	420	260	380	510	340

Haematology Results: **Day 17**

		Dog 1	Dog 2	Dog 3	Dog 4	Dog 5	Dog 6
WBC	($x10^9$/l)	15.4	19.3	13.1	14.7	20.4	10.2
RBC	(x 10^{12}/l)	6.8	6.8	6.3	7.4	6.7	6.7
Hb	(g/dl)	15.5	16.8	15.5	18.6	13.7	16.1
Hct	(l/l)	0.462	0.494	0.459	0.542	0.409	0.475
MCV	(fl)	68	73	73	73	61	71
Neutrophils	(%)	57	58	64	65	55.5	66
Lymphocytes	"	34.5	31	28	26.5	10.5	24.5
Monocytes	"	5.5	6.5	4	6.5	2	3
Eosinophils	"	2.5	4	4	2	32	3.5
Platelets	($x10^9$/l)	386	450	350	240	490	220

Film Report:
All dogs still have increased numbers of Target Cells.

Haematology Results: **Mean values**

		Pre	**d3**	**d5**	**d8**	**d11**	**d14**	**d17**
WBC	($x10^9$/l)	14.3	15.4	13.1	15.0	16.3	13.1	15.5
RBC	($x10^{12}$/l)	6.8	7.0	6.9	6.8	6.9	6.7	6.8
Hb	(g/dl)	16.2	16.4	16.4	16.6	16.6	16.5	16.0
Hct	(l/l)	.481	.495	.482	.475	.492	.461	.474
MCV	(fl)	71	71	70	70	71	68	70
Neutophils	(%)	68	55	60	77	53	65	61
Lymphocytes	"	26	34	27	16	37	26	26
Monocytes	"	1.3	1.7	4.8	2.0	5.3	4.0	4.6
Eosinophils	"	4.8	9.5	7.5	5.7	4.7	5.0	8.0
Normoblasts	"	0	0	0.25	0	0.5	0.17	0.17
Platelets	($x10^9$/l)	417	377	370	350	350	390	356

Clotting Times[minutes]

	PRE	Day 3	Day 5	Day 8	Day 11	Day 14	Day 17
DOG 1	2.50	2.13	3.00	2.79	3.33	2.55	3.42
DOG 2	3.47	2.18	3.50	2.74	2.93	2.61	3.50
DOG 3	1.88	4.02	2.50	3.33	3.38	3.92	2.33
DOG 4	3.15	1.23	2.83	2.28	3.18	2.17	2.58
DOG 5	2.60	3.22	2.33	4.03	2.35	3.08	1.50
DOG 6	3.12	3.08	2.58	3.48	3.80	1.83	3.00
MEAN:	**2.79**	**2.64**	**2.79**	**3.11**	**3.16**	**2.69**	**2.72**
SEM +/- :	**0.23**	**0.40**	**0.17**	**0.26**	**0.20**	**0.30**	**0.31**

Normal range [Mean ± 2x S.D] = 1.53 to 4.03 minutes (mean = 2.78 minutes)

Faecal Blood Test [Colo-Rectal Test Kits: Roche]

	PRE	Day 3	5	8	11	14	17
DOG 1	-	-	-	-	-	-	-
+							
DOG 2	-	-	-	-	-	-	-
DOG 3	-	-	-	-	-	-	-
+							
DOG 4	-	-	-	-	-	-	-
DOG 5	-	-	-	-	-	+	-
+							
DOG 6	-	-	-	-	-	-	-

APPENDIX
C

CARPROFEN

Carprofen is a non-steroidal anti-inflammatory compound registered for use in humans in several countries but not so far registered for veterinary use. Pharmacokinetic studies in Beagles treated at 0.7mg/kg have shown that Carprofen has a prolonged half life as compared with Phenylbutazone. Extensive toxicology studies have been carried out, where Carprofen was administered orally to dogs at 35 times the proposed dose rate daily for one year with no clinical or pathological side effects. Pharmacological trials in various species have shown it to be an analgesic and an anti-inflammatory. It is available at present for dogs as a tablet formulation.

Rycovet are developing Carprofen as a product for use in animals [horses, dogs, and cattle]. As part of this development programme we are asking selected veterinary surgeons to assess the efficacy of the drug in reducing pain and discomfort associated with osteoarthritis or degenerative joint disease. Approximately 300 dogs of various ages and breeds will be used in the trial overall.

Your assessments will be recorded on the standard forms noting patient information, treatment and the effect of treatment on lameness, weight bearing and joint mobility using the condition scoring sheet provided. The information from all the reports will be analysed and used in the application to register Carprofen for the treatment of dogs.

Case Selection:

1.Existing Cases:

These dogs will already be receiving treatment with non-steroidal anti-inflammatory drugs or other drugs. The protocol will be as follows:

1. Take the dog off the present drug, noting the regime and efficacy of treatment on the "Patient Information" form.

2. If appropriate and possible, monitor the time taken for the signs of the painful condition to recurr.

3. Note joints affected and score condition for lameness, weight bearing and joint mobility.

4. Start Carprofen treatment if the pain recurrs.

5. Monitor the effects of Carprofen therapy.

2. New Cases:

These will be dogs newly diagnosed as suffering from osteoarthritis or dogs for which the previous history or treatment is not known.

1. Confirm clinically osteoarthritis/ degenerative joint disease and
(a) note joints affected
(b) score condition for lameness, weight bearing and joint mobility.

2. Institute treatment with Carprofen or Phenylbutazone on an alternate dog basis.

3. Monitor the effects of treatment.

Dose Recommendation:

Carprofen:

The recommended dose rate for Carprofen is an initial regime of **0.7mg/kg once a day for 7 days** administered orally. Depending on clinical response, treatment may be discontinued, repeated for another week, or the dose rate increased up to 2mg/kg in 2 daily treatments. As with other NSAIDs, give at approximately 1 hour before or after a meal to reduce the possibility of gastro-intestinal irritation but preferably not with food as this can reduce the effective dose and alters the pharmacokinetics.

Each tablet contains 17.5mg carprofen. At the proposed dose rate of 0.7mg/kg, the dose band will be as follows:

Body Weight [kg]	No. of Tablets
Up to 12.5	0.5
13 to 25	1
26 to 37.5	1.5
38 to 50	2
etc.	

Contra-indications/Precautions: DO NOT USE CONCURRENT ANTI-INFLAMMATORY MEDICATION

Phenylbutazone: (Flexazone [bk])

The suggested dose rate will be ca. **8mg/kg administered in two daily doses for 7 days.** As with other NSAIDs, give at approximately 1 hour before or after a meal to reduce the possibility of gastro-intestinal irritation but preferably not with food as this can reduce the effective dose and alters the pharmacokinetics.

The tablets supplied contain 100mg and the dose band will be:

Body Weight [kg]	No. of Tablets
Up to 12.5	1 [2 x 0.5]
13 to 25	2 [2 x 1]
26 to 37.5	3 [2 x 1.5]
38 to 50	4 [2 x 2]
etc.	

If you have any queries or problems, please contact:

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Glasgow. G61 1QH

Telephone: 041-339-8855, Extn. 5790.
[Evenings: 041-339-8242]

CONDITION SCORING:

Lameness: [L]

0 = Clinically NORMAL

1 = STANDS normally;
WALKS normally;
LAME after vigorous exercise or slight stiffness after rest.

2 = Stands normally;
SLIGHT LAMENESS when walking and stiffness after rest.

3 = Careful when standing;
OBVIOUS LAMENESS when walking.

4 = NOT standing normally.
SEVERE LAMENESS when walking and unwilling to run.

Weightbearing: [W.B.] [where appropriate ie. limb joints affected]

0 = NORMAL weightbearing on all limbs.

1 = Weight only applied temporarily on affected limb.

2 = NO WEIGHT applied on affected limb.

Mobility of Affected Joint(s): [J.M.]

0 = NO LIMITATION of joint movement.
No evidence of pain shown by dog during manipulation.

1 = SOME REDUCTION in joint movement.
Dog shows reluctance during manipulation.

2 = OBVIOUS REDUCTION in joint movement.
Dog shows evidence of pain during manipulation plus crepitus.

PATIENT INFORMATION

Owner: Name:_____ Date:_____

Address:_____

_____

Postcode:_____ Telephone No.:_____

_____

Dog Identification: Name:_____ Age:_____ Sex:M/F/Neu/Preg.

Breed:_____Approx. weight (kg):_____ Ideal weight (kg):_____

_____

Joint(s) Affected:_____

Brief History:_____

_____

Previous Treatment(s) [in the last 3 months] for the condition:

	Product [name + co.]	Dose[mg+no. tabs]	Regime and Duration
1.	_____	* _____	* _____
2.	_____	* _____	* _____
3.	_____	* _____	* _____

Effect of Treatment on the condition: [tick as applicable]

	1.	2.	3.
i) No Effect :	__	__	__
ii) Some Effect :	__	__	__
iii) Marked Improvement :	__	__	__
iv) Sound :	__	__	__

Time taken for return of painful condition after treatment withdrawal:

_____

TREATMENT: Date treatment started:_____

	Product:	Dose[tabs]:	Regime:	Duration:
Carprofen / Phenylbutazone: [Delete as applicable]	_____	* _____	* _____	

Other Advice Given [eg. re exercise or weight]_____

_____

Any concurrent disease or medication: _____

_____

_____

Dose Changes: Date:_____ Dose and Regime:_____

Reason for Dose Change:_____

Premature Treatment Withdrawal? Why?_____

EFFICACY ASSESSMENT: (see Condition Scoring)

1.Veterinary Surgeon: Name: _____

Before Treatment:

Date:_____ Lameness (0 to 4): _____

Weight Bearing (0 to 2): _____

Joint Mobility (0 to 2): _____

After Treatment:

Date:_____	Date:_____	Date:_____
Dose:_____	Dose:_____	Dose:_____
Lameness:____	Lameness:____	Lameness:____
W / B: ____	W / B: ____	W / B: ____
J / M: ____	J / M: ____	J / M: ____
Improved:____	Improved:____	Improved:____

Comments: _____

_____

_____

_____

_____PTO if extra comment

2.Owner (as questioned by the Veterinary Surgeon)

Date:_____

After treatment the dog: improved / deteriorated / did not change

[Time taken for improvement, if any:_____]

Date:_____

Since the last visit, the dog has: improved / deteriorated / not changed

Date:_____

Since the last visit, the dog has: improved / deteriorated / not changed

Owner's comments: _____

_____

_____

CLINICAL ASSESSMENT:

1. Did the treatment work satisfactorily? [Please give details, if possible]

_____

_____

_____

2. How did the test drug compare with the previous treatment? [If applicable]

_____

_____

_____

3. Did the dog show any side effects at any time? Yes ___ No ___

If "Yes", did any of the following occur?	Yes >>>	Date
Vomiting	____	_____
Diarrhoea	____	_____
Constipation	____	_____
Thirst	____	_____
Inappetance	____	_____
Dullness	____	_____
Faecal blood	____	_____
Other	____	_____

Please give details: [eg. signs, course, duration, any treatments etc]

_____

_____

_____

4. Palatability: Good: ___ Average: ___ Poor: ___

Other Comments:

_____

_____

Veterinary Surgeon:

Signed: _____ Date: _____

Veterinarians and Practices Participating in Carprofen Clinical Trial

Miss M. Flanagan
Abbeycraig Park
Causewayhead
Stirling

Mr. N. McIntosh
Andrew, Alladyce, Love & Lealy
71, Canal Street
Paisley

Ashworth and Rodger
Craigforth
Union Terrace
Crieff
Perthshire

Mr. C. Barker
Glasgow University
Lanark Practice
Lanark

Mr G. Barr
16, Kilmarnock Road
Mauchline
Ayrshire

Mr. D. Watson
Batchelor, Davidson and Watson
19, Hillhouse Road
Blackhall
Edinburgh

Mr. P. Frost
Rushton and Browne
Broughton-in-Furness
Cumbria

Miss L. Carmichael
1A Lee Crescent
Portabello
Edinburgh

Mr. J. Gartside
48, Saville Road
Dewsbury
West Yorkshire

Mrs. R. Gilbert
18, Leonard Street
Keswick
Cumbria

Mr. D. Longley
7, Preston Street
Carnforth
Lancashire

L. Gray
183, Main Street
Uddingston
Glasgow

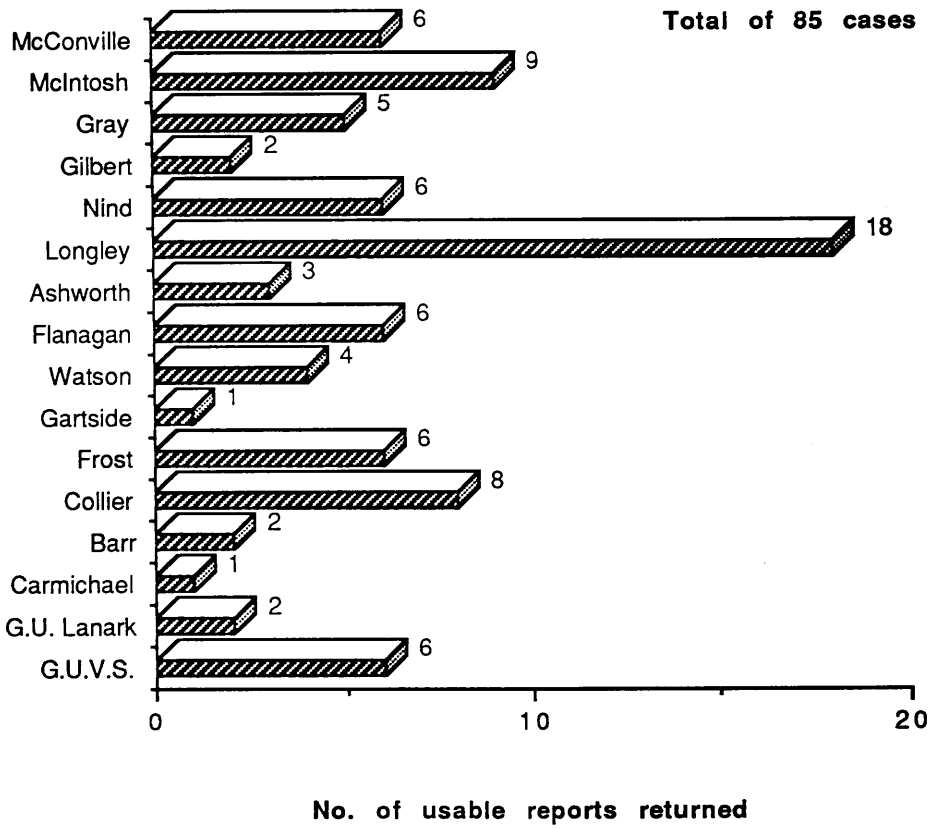
Murphy and Collier
42, Barassie Street
Troon
Ayrshire

Mr. F. Nind
5, Riccarton Mains Road
Currie
Midlothian

Mr. R. McConville
Archway Veterinary Group
Grange-over-Sands
Cumbria

University of Glasgow Veterinary Hospital
Bearsden Road
Bearsden
Glasgow

Number of Case Reports Returned by Veterinary Practitioners in Carprofen Trial



Animal Details of Osteoathritis Cases

Case No.	Owner	Age (yrs)	Sex	Breed	Weight [kg]	Previous Treatment	Trial Treatment
1	John	0.8	M	G.Ret.	30	PBZ, Pirox.	Carprofen
2	John	0.8	M	G.Ret.	30	PBZ, Pirox.	Carprofen
3	Sneddon	0.7	F	Rott.	29	-	Carprofen
4	Harpwood	0.6	F	WHound	50	A.S.A.	Carprofen
5	Dick	9	M/N	Lab.	45+	A.S.A., Ibupro	Carprofen&PBZ
6	Cornelius	4	F/N	B.Collie	23	-	Carprofen
8	Murchison	3.5	M	Lab.	36	-	Carprofen
9	Weir	0.9	M	RetX	20	Paracetamol	Carprofen
10	Keirs	2.5	F	Lab.	30	PBZ	Carprofen
11	Freid	4	M	B.Collie	18	-	Carprofen
12	McRobert	7	F/N	Dobe.	31.4	PBZ	Carprofen
13	MacIntyre	3	F/N	Lab.	28.4	-	Carprofen&PBZ
14	Eggo	3	F/N	Lab.	25	-	Carprofen
15	Glass	12	M	Chihuahua	6.5	PBZ, Pred.	Carprofen
18	Young	11	F/N	Lab.	34.4	PLT	Carprofen
19	Sloan	11	M	PoodleX	9	-	Carprofen&PBZ
20	Stewart	13	M	WHW	9	-	Carprofen
21	Wilson	14	F	R.Collie	24	PBZ	Carprofen
22	Frost	8	F/N	Sp.Spaniel	19	-	PBZ & Carprofen
23	Knowles	0.9	M	J.R.T.	6	-	PBZ & Carprofen
24	Miller	14	F/N	Lab.	27	PBZ	Carprofen
25	Toone	6	M	Lab.	28	Piroxicam	Carprofen
26	Todd	9	M	G.S.D.	35	-	Carprofen&PBZ
27	Gadsby	6	F/N	Be. Collie	30	-	Carprofen
28	Perschke	6	M	Pointer	32	PBZ	PBZ
29	McKay	0.8	M	Lab.	23	PBZ	Carprofen
31	Nicol	12	F/N	Lab.	30.4	PBZ	Carprofen
32	Nisbet	11	M	B.Collie	30	-	Carprofen
33	White	6	F	Lab.	30	PLT	PBZ
34	Scott	9	F/N	Lab.	40	PBZ, PLT, Pirox.	Carprofen
35	Brown	4	F	GHound	30	PBZ	Carprofen
36	Flanagan	12	M	G.Ret.	34	PBZ, PLT	Carprofen
37	Hogg	10	F/N	B.Collie	25	Piroxicam	Carprofen
38	Lyle	12	F	Lab.	34	-	Carprofen
39	MacDonald	12	M	Shet. Shd.	15	PBZ, PLT	Carprofen
40	Garret	12	M	WHW	11	PBZ	Carprofen
41	Fraser	8	F	C.Spaniel	14	-	Carprofen
42	Dawes	3.6	F	Toy Poodle	1.5	Optic, Pardale	Carprofen
43	Dawes	0.6	F	Toy Poodle	1.5	-	Carprofen
44	Potts	5	M	Shet. Shpd.	20	-	PBZ
45	Gilchrist	12	F	R.Collie	26	PLT	PBZ
46	Neild	13	F	O.E.S.	30	A.S.A.	Carprofen
47	Howell	8	F	G.Ret.	35	-	PBZ
48	Molloy	7	F	G.S.D.	35	-	Carprofen
49	Sykes	9	F	Lab.	30	PLT	PBZ
51	Taylor	12	M	Lab.	32.4	-	Carprofen
52	Finlay	14	M	Lab.	39	-	Carprofen&PBZ
54	Lambie	11	M	Lab.	29.4	Pred.	Carprofen&PBZ
55	Stewart	7	M	G.Pointer	35.8	-	PBZ
58	Rowcroft	8	F	Lab.	40	-	PBZ
59	Wally	10	M	G.S.D.	45	PBZ	Carprofen
60	Taylor	8	M	G.S.D.	30	-	Carprofen
61	Hall	14	M	X	22	Pardale	Carprofen
63	Graham	8	M	X	27	PLT, PBZ	Carprofen
64	Jagielko	1.1	M	Mastiff	75	Ceporex, Flagyl	Carprofen

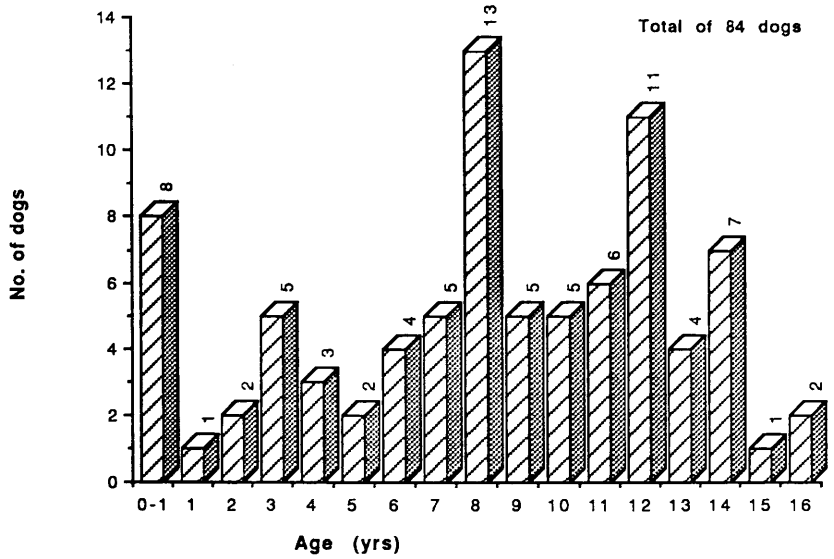
Key overleaf

Animal Details of Osteoathritis Cases

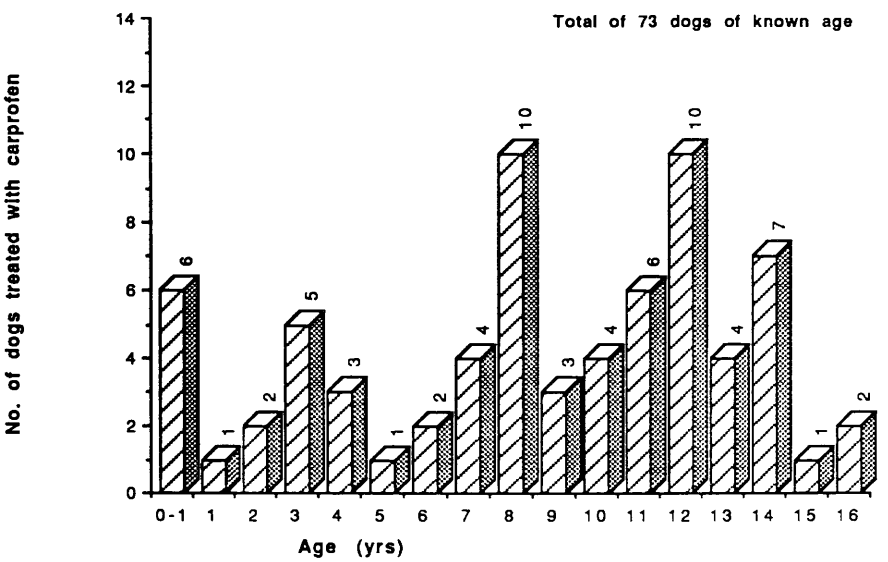
Case No.	Owner	Age (yrs)	Sex	Breed	Weight [kg]	Previous Treatment	Trial Treatment
65	Jack	8	M	G.Ret.	35	PBZ	Carprofen
66	Irwin	8	M	B.Collie	22	PBZ	Carprofen
67	Osbourne	2	F	Lab.	23	-	Carprofen
68	Clark	?	F/N	X	31	PBZ	Carprofen&PBZ
69	Storrie	3	M	G.S.D.	45	-	Carprofen
70	McCallum	11	F/N	Lab.	35	PBZ	Carprofen
71	Talbot	11	M	Cairn T.	9.2	-	Carprofen
72	Johnson	8	F/N	Lab.	27.4	PLT	Carprofen
73	Arnot	7	F/N	G.Ret.	37.5	PLT	Carprofen
101	Bradley	13	M	Lab.	31	PLT	Carprofen
102	Long	8	M	Lab.	33	PBZ	Carprofen
103	Crawford	10	M	Lab.	35	-	PBZ
104	Upton	8	F	Dalm.	26	-	Carprofen
106	Baines	16	M	X	16	-	Carprofen
107	McCaffrey	8	F	C.K.C.S.	10	-	PBZ
108	Peel	13	F	O.E.S.	30	PBZ	Carprofen
109	Pearse	14	M	G.Ret.	31	PBZ	Carprofen
110	Barker	14	M	X	17	PLT, PBZ	Carprofen
201	Smith	12	M	Lab.	45	-	Carprofen
202	Sharples	7	M	Scot. T.	19	PBZ, PLT	Carprofen
203	Edwards	12	M	Peke	5	PLT	Carprofen
204	Sharples	9	M	X	12	Dexafort	PBZ
205	Plenderleith	10	M	Cairn	13	PBZ	Carprofen&PBZ
206	Taylor	15	M	Poodle	7.5	-	Carprofen
208	Jackson	5	F/N	C.K.C.S.	11	PLT, Pardale	Carprofen
209	Buntin	10	M	C.K.C.S.	17	-	Carprofen
210	Sarginson	14	F	Weim.	25	PBZ, PLT	Carprofen
211	Stalker	8	M	Shet. Shpd.	10	Opticorten	Carprofen
212	Scott	16	M	St. Poodle	23	-	Carprofen
213	Clark	12	F/N	Lab.	30	PBZ	Carprofen

Key: Sex: M = Male; F = Female; N = Neutered.
Breed: G.Ret. = Golden Retriever; Rott. = Rottweiler; WHound = Wolfhound; Lab. = Labrador; B. Collie = Border Collie; RetX = Retriever Crossbred; Dobe. = Dobermann; PoodleX = Poodle Croosbred; WHW = West Highland White Terrier; R. Collie = Rough Collie; Sp. Spaniel = Springer Spaniel; J.R.T. = Jack Russell Terrier; G.S.D. = German Shepherd Dog; Be. Collie = Bearded Collie; GHound = Greyhound; Shet. Shpd. = Shetland Sheepdog; C.Spaniel = Cocker Spaniel; O.E.S. = Old English Sheepdog; G.Pointer = German Pointer; X = Cro ssbred; Cairn T. = Cairn Terrier; Dalm. = Dalmatian; C.K.C.S. = Cavalier King Charles Spaniel, Weim. = Weimaraner; St. Poodle = Standard Poodle.
Previous Treatments:
PBZ = Phenylbutazone;
Pirox. = Piroxicam (Feldene ®; 10 mg Tablets or Capsules);
A.S.A. = Acetyl salicylic acid or Aspirin;
Ibupro = Ibuprofen;
Pred. = Prednisolone;
PLT = Predno-Leucotropin Tablets ® [BK Veterinary Products Ltd] containing Cinchophen 200 mg, Prednisolone 1 mg, Hexamine 100 mg.
Optic. = Opticorten ® Tablets 0.25mg [Ciba-Geigy Agrochemicals] containing Dexamethazone 0.25 mg
Pardale = Pardale-V Tablets ® [Arnolds Veterinary Products] containing Paracetamol 400 mg, Codeine phosphate 9 mg, Caffeine hydrate 10 mg.
Dexafort = Dexafort ® injection [Intervet UK Ltd] containing Dexamethazone 3 mg/ml.
Ceporex = Ceporex ® Tablets [Glaxovet Ltd] containing Cephalexin 250 mg
Flagyl = Flagyl ® Tablets [RMB Animal Health Ltd] containing Metronidazole 200 mg.
Trial Treatments:
Carprofen = Carprofen 17.5 mg Tablets [Ro 20-5720/659; Lot No. G MZ 626 B 01; Expiry date: 07.91]
PBZ = Flexazone ® Tablets 100 mg [BK Veterinary Products Ltd], Batch no. 80302A/1

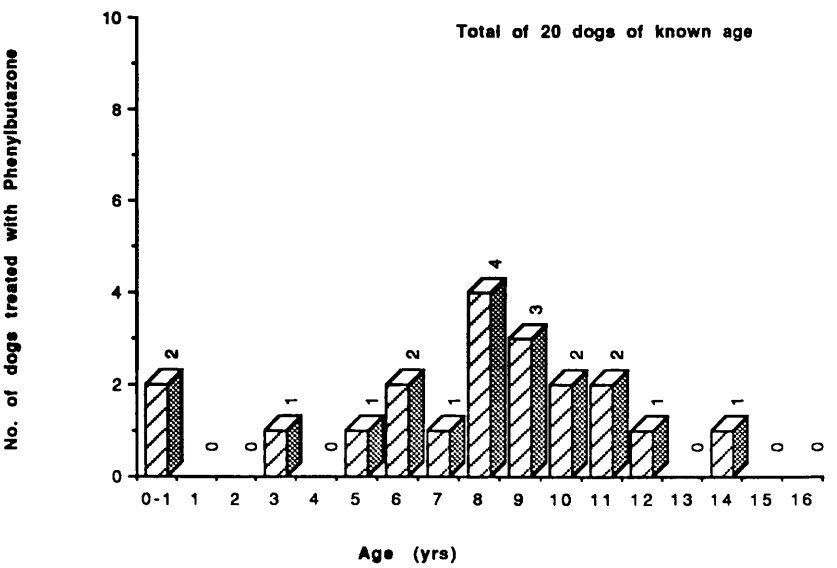
Age Distribution of All Osteoarthritis Cases in Carprofen Clinical Trial



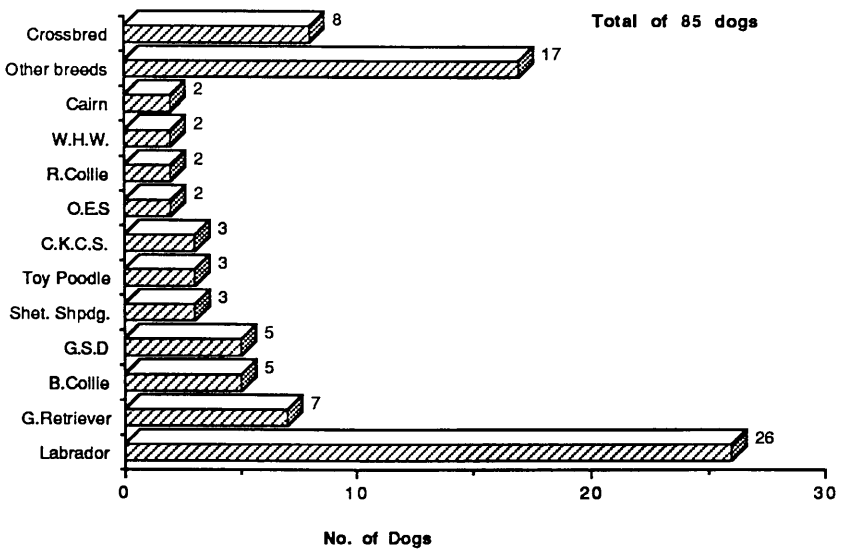
Age Distribution of Carprofen Treated Dogs



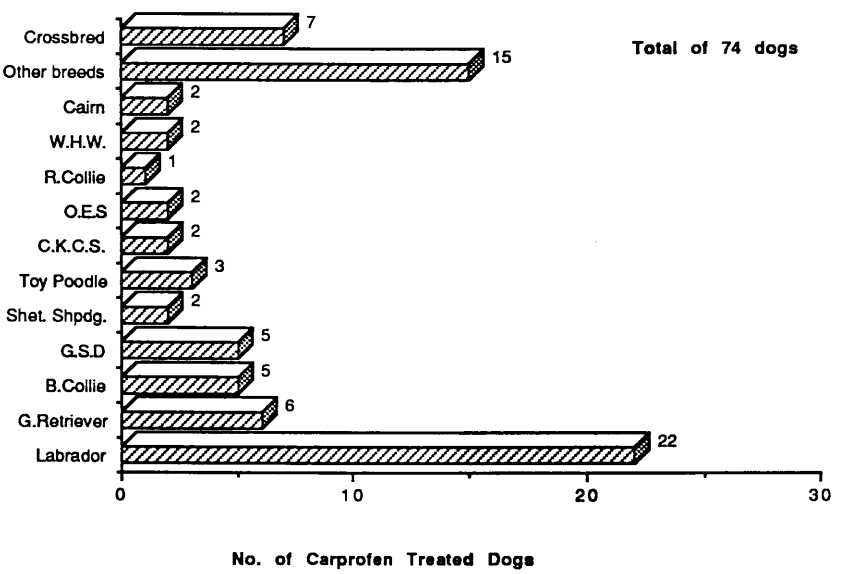
Age Distribution of Phenylbutazone Treated Dogs



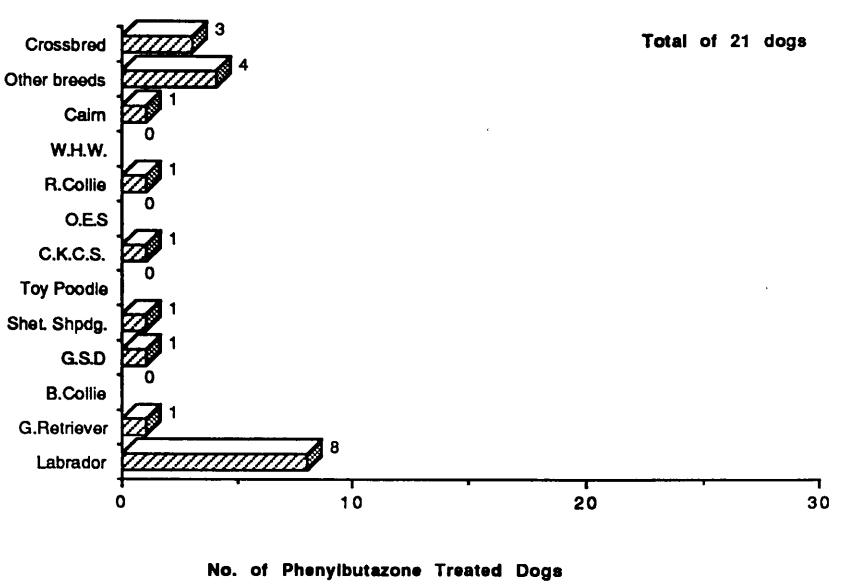
Breed Distribution of All Treated Dogs



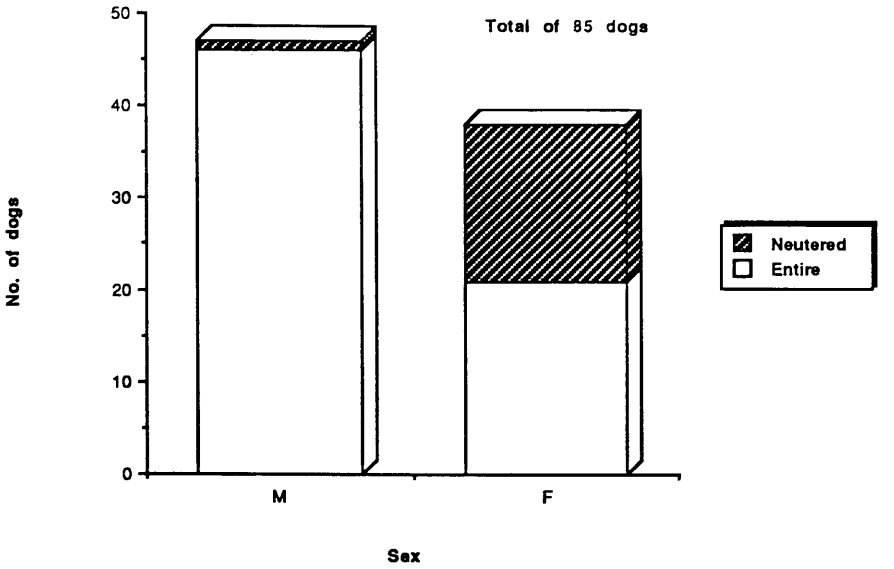
Breed Distribution of Carprofen Treated Dogs



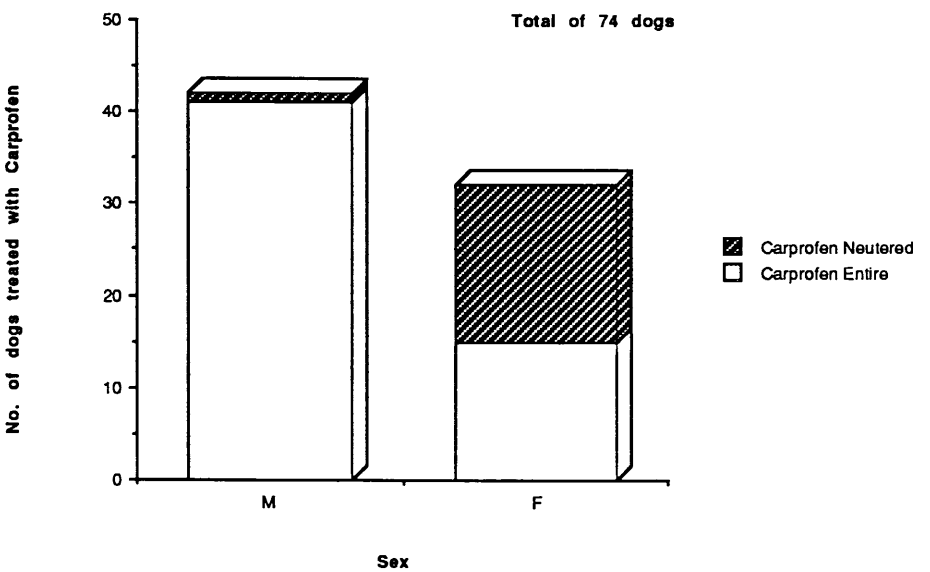
Breed Distribution of Phenylbutazone Treated Dogs



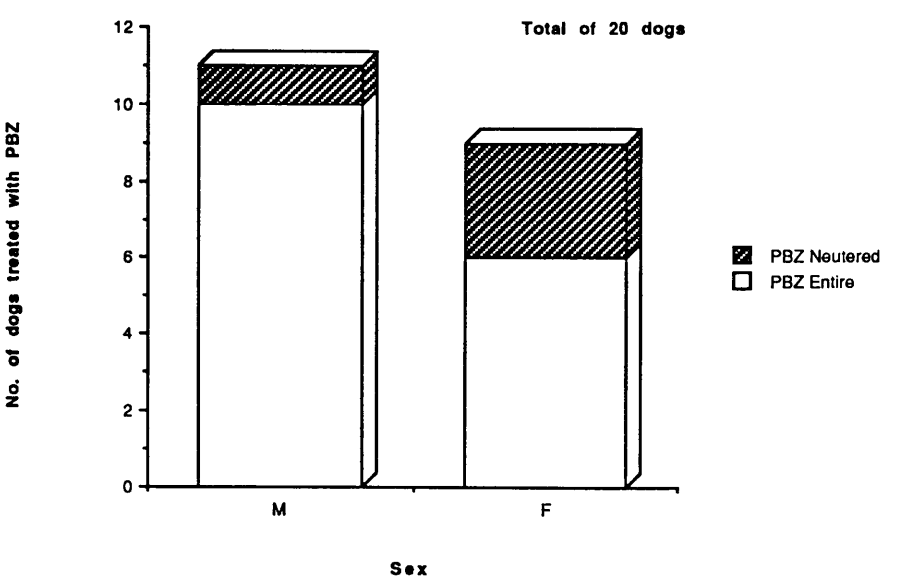
Sex Distribution of All Osteoarthritis Dogs



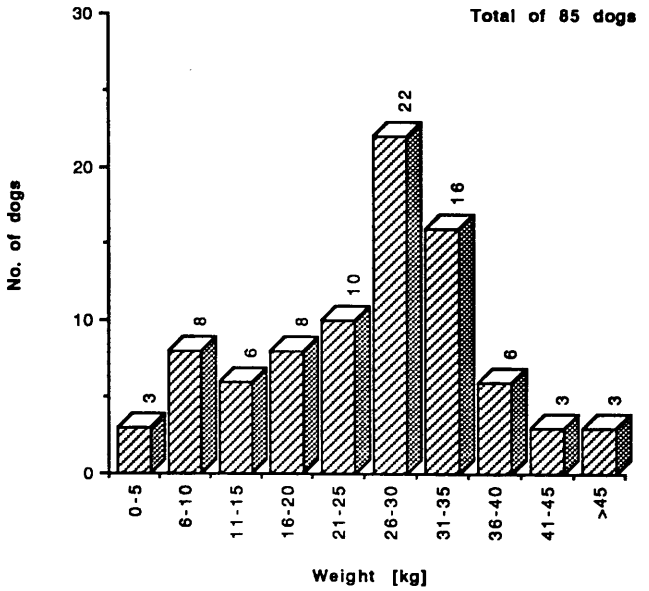
Sex Distribution of Carprofen Treated Dogs



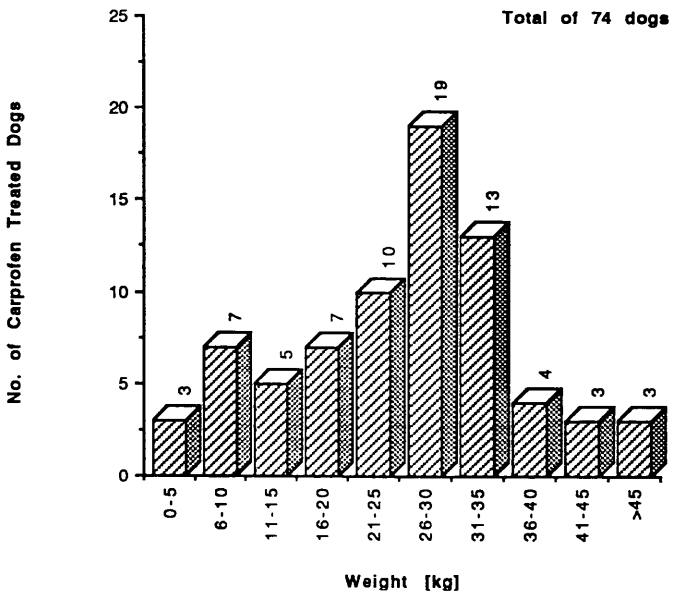
Sex Distribution of Phenylbutazone Treated Dogs



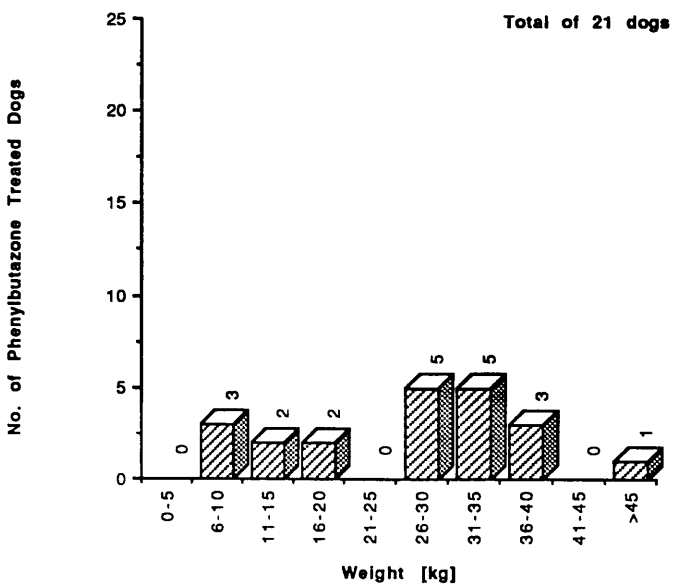
Weight Distribution of All Treated Dogs



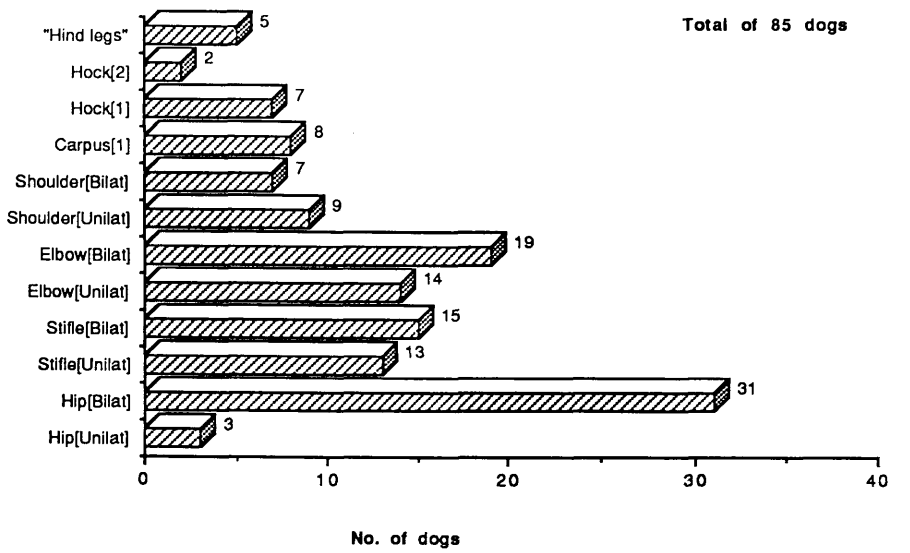
Weight Distibution of Carprofen Treated Dogs



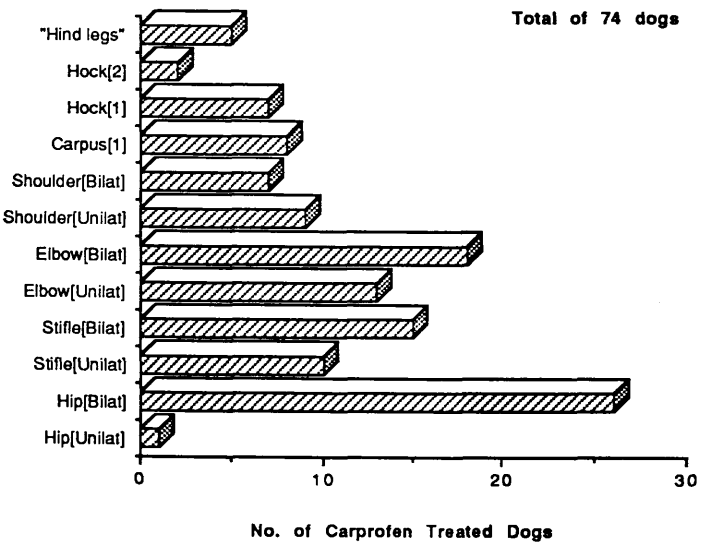
Weight Distribution of Phenylbutazone Treated Dogs



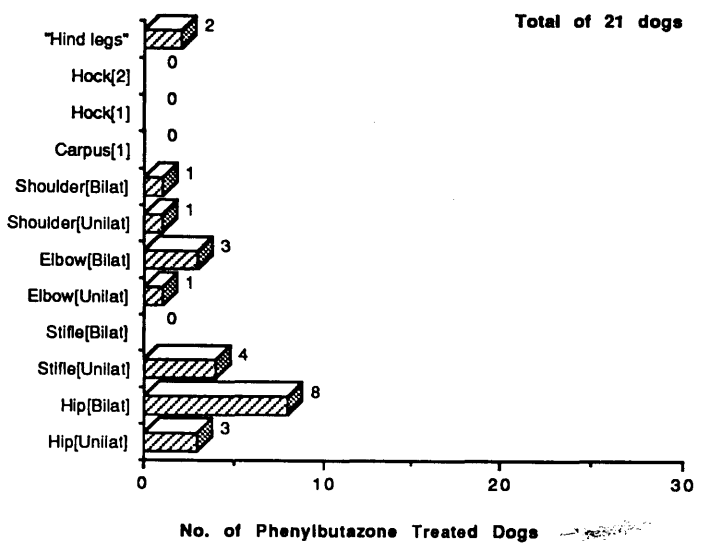
Joints Affected in All Osteoarthritis Cases



Joints Affected in Carprofen Treated Dogs



Joints Affected in Phenylbutazone Treated Dogs



Joints Affected and Known History

Case	Joint(s) Affected	Reported Brief History (if given)
1	EE	Severe O.A. both elbows. Radiographic confirmation. O.C.D. lesions in both elbows found at surgery performed on both elbows 2 months before start of treatment for severe 2° O.A.
2	EEHH	Severe O.A. in both elbows and hips. Radiographic confirmation. Surgery for O.C.D. elbows. Treatment started 2 months post-op. for severe 2° O.A.
3	E	Elbow instabilty and O.A. 2° to radius/ulna shortening.
4	ShSh	Bilateral O.C.D. Right shoulder operated on 5 weeks before trial. Left shoulder: radiographic lesions but no pain until 7 days before start of treatment.
5	Hind limbs	Creaks/Stiff for about 2 years. Inability to rise & NSAIDs for 12 months.
6	EE	None
8	Hock	Intermittent lameness for 2 years after acute onset joint pain and swelling at about 9 months old (Probably O.C.D.).
9	EEHH	Three bouts of lameness in right fore and both hind legs. Slight when presented.
10	S	Injury 1 year previously. Hairline fracture of distal femur and exostosis distal medial femur.
11	S	Lame for about 2 years.
12	Sh	Lame for about 2 weeks. Radiography:"Slight roughening of shoulder joint surface".
13	Sh	Lame for 4 months. Radiograph: N.A.D.
14	Sh	Chronic lameness. Radiography: N.A.D.
15	EE	Chronic obesity. 2° osteoarthritis and breathing difficulties.
18	E	O.A. for 14 months.
19	Hind legs	Old age arthritis.
20	Sh	Fall one year before trial. Stiff on rising for 2 months.
21	HH	Right hip more severely affected.
22	SS	None
23	H	Avascular necrosis of left hip and excision arthroplasty one month before trial.
24	Sh	Lame left fore when examined. However, stiff on all legs. PBZ for 18 months.
25	HH	Right hip more severe. NSAIDs for over 18 months.
26	HH	Left hip most affected.
27	ShE[C?]	Discomfort after exercise.
28	S	None
29	E [Sh?]	May be Osteochondrosis.
31	EHH	None
32	C	Intermittent lameness and pain in carpal joint for 3-4 years.
33	EE	6 months before trial: intermittent forelimb lameness. Bilateral elbow problem diagnosed. Radiography confirmed O.A. ++. ? Old O.C.D. lesions.
34	HH	Mild hip dysplasia and O.A. Difficulty in rising. Very lame after exercise.
35	C	Old racing injury. Possibly fractured accessory carpal bone. Radiographic confirmation.
36	SS	A.C.L. ruptures when younger. Joints thickened and stable but severe 2° O.A.
37	EHH	Hindlimb stiffness/mild lameness. Right elbow: severe intermittent lameness and joint swelling, crepitus ++ and poor range of movement.
38	E	Had had very occasional slight stiffness previously. Presented quite lame.
39	E	First lame 4 months before trial. No history of any injury.
40	S	PBZ for 3 months.
41	SS	None
42	SS	Both stifles operated on for subluxating patellas 19 months before trial.
43	Hind limbs	Standing in crouched position.
44	S	None
45	All	None
46	All joints	None
47	HH	Radiography: Arthritic changes.
48	E	None
49	E [All]	None
51	EHH	Gradually increasing stiffness over the last year.

Key overleaf

Joints Affected and Known History

Case	Joint(s) Affected	Reported Brief History (if given)
52	EEHH	Increasing difficulty rising over the last 2 years.
54	EE	Three year history
55	H	Lame after rest. Stiffness right hind for 2 weeks.
58	HH	None
59	HH	Right hip more severely affected.
60	HH	Injury to right hip as a pup. Lame on and off since. Worse now. Hip dyspasia/O.A.
61	HH	Stiffness and difficulty jumping. Recently, exercise pain as well.
63	HHSS	O.A. for 4 months
64	EE	Bilateral ununited coronoid process. Surgery 5 months before trial.
65	S	Lame. Worse after post-exercise rest.
66	S	Muscle wasting, stifle pain, much worse after exercise. 2 year history.
67	E	Lame for more than a year.
68	S	A.C.L. rupture. Surgery performed. Still very lame & disuse muscle atrophy.
69	E	Lame intermittently for 6 months.
70	HHSSEEHoHo	Old age, chronic arthritis.
71	S	Acute bout of lameness.
72	E	Gun dog. Lame for 2 months.
73	S	None
101	Sh	None
102	EE	None
103	ShHH	
104	HH	None
106	SS	None
107	HH	None
108	All	None
109	All	None
110	All	Especially hind legs.
201	HHSSHoHo	Previous problems, worsened by age.
202	EESS	None
203	S [All]	None
204	HS	None
205	HH	18 month history. Deteriorating despite chronic PBZ treatment.
206	Hind legs	"Cold" lameness.
208	S	Severe 2° O.A. due to patellar luxation. Trochleoplasty 2 months before trial.
209	HHSh	One year right fore stiffness. Also cardiac disease.
210	All	Especially right stifle.
211	Right hind	None
212	HH	Gradually stiffening after rest for 18 months. Eases off with exercise.
213	EEHH	Right fore stiffness for over 3 years. Hip problems for 4 months.

Key:

Joints Affected:

E = Elbow; EE = Both elbows; H = Hip; HH = Both hips; Sh = Shoulder; ShSh = Both shoulders; S = Stifle; SS = Both stifles; C = Carpus; Ho = Hock; HoHo = Both hocks; All = All joints stated as affected.

History Abbreviations:

O.A. = Osteoarthritis; O.C.D. = Osteochondrosis dissecans;
NSAID = Non-Steroidal Anti-Inflammatory Drug; N.A.D. = No Abnormality Detected;
PBZ = Phenylbutazone; A.C.L. = Anterior Cruciate Ligament.

Carprofen Treatments:

Case No.	Dosage [mg/kg/day]	Regime	Duration [days]	Other Advice	Other disease/treatment
1	2.33	bid	2*	Lead exercise	-
2	2.33	bid	2*	Lead exercise	-
3	2.41	bid	14	Lead exercise	-
4	1.75	bid	7	Restrict exercise	-
5	2.33	bid	10	-	-
6	0.76	sid	14	Strict rest and diet	-
8	1.94	sid	28	Lead exercise	-
9	2.19	sid	28	Lead exercise	-
10	0.88	sid	7	-	-
11	0.97	sid	7	Lead exercise	-
	1.94	sid	8	Lead exercise	-
12	1.11	sid	10	Walking only	-
13	1.23	bid	10	Restrict exercise Reduce weight	
14	1.40	bid	10	-	-
15	1.35	sid	7	-	-
	2.02	sid	13	-	-
18	0.76	sid	7	Walking only	-
19	0.97	sid	21	-	-
20	0.97	sid	7	Walking only	-
21	0.73	sid	7	-	Incontinence
22	0.92	sid	14	-	-
23	2.92	bid	1†	Physiotherapy	Femoral Head Excision 7 d pre-T.
24	0.97	sid	7	-	-
25	0.94	sid	7	-	-
26	2.00	bid	7	-	Pre-T skin disease, conjunctivitis and rhinitis.
27	0.88	sid	14	Strict rest 1 week	-
	2.33	bid	28	Walking exercise	-
	1.75	bid	28	Walking exercise	-
29	0.76	sid	12	Restrict exercise	-
31	0.86	sid	7	Hills r/d: Weight loss	-
	0.86	eod	21	" " "	-
32	0.88	sid	7	-	-
34	1.75	sid	14	Strict diet	Abscess: Abc treatment
35	2.04	sid	14	Rest. Support bandage for 2-3 days	-
36	1.54	sid	7	Restrict exercise	Occasional bout of colitis, usually treated by dietary changes.
37	1.40	sid	4Δ	Decrease exercise	-
38	2.06	sid	7	-	-
39	1.17	sid	10	-	-
40	0.80	sid	14	-	-
	1.59	bid	7	-	-
41	1.25	bid	7	-	-
	2.50	bid	16	-	-
42	0.97	sid	19	-	-
43	0.73	sid	8	-	-
46	2.33	bid	21	-	-
48	0.75	sid	7	-	-

Key:

sid = one treatment daily; bid = two treatments daily; tid = three treatments daily;
eod = treatment every other day.
pre-T. = Pre treatment; Abc = Antibiotic;
* = overuse due to analgesia. Treatment withdrawn.
† = Vomited. Treatment withdrawn.
Δ = Treatment withdrawn because condition deteriorating.

Carprofen Treatments:

Case No.	Dosage [mg/kg/day]	Regime	Duration [days]	Other Advice	Other disease/treatment
51	2.16	bid	14	Regular light exercise	-
52	2.69	tid	9	-	Amp.19mg/kg/day post-op. after removal of superficial growth on left fore.
54	0.89	sid	7	-	Polydipsia; Hills k/d prescribed.
59	0.78	bid	24	-	-
	0.39#	bid	3	-	-
	0.58	tid	18	-	-
60	0.73	sid	7	-	Piperazine (Verocid®x6) on day1
	1.46	sid	7	-	-
61	0.80	sid	6	Regular light exercise	-
	1.59	bid	60	" " "	-
63	1.30	sid	7	Weight loss	-
	1.94	sid	4	" "	-
64	1.17	sid	26	Restricted exercise	-
	1.87	sid	7	" "	-
65	0.75	sid	7	Lead exercise	-
	1.50	sid	14	Lead exercise	-
66	1.19	sid	10	Reduce weight slightly	
				Frequent short walks	-
67	2.28	bid	9	Continue as normal	-
68	1.13	bid	19	Gentle exercise	
				Encourage use of leg	-
69	1.17	sid	7	Restrict exercise	-
70	2.00	sid	10	Reduce weight	
	1.50	sid	7	" "	-
71	2.85	tid	7	Limited exercise	-
72	2.55	bid	7	Reduce exercise	-
73	0.93	sid	7	Reduce weight	-
	1.87	bid	7	Reduce weight	-
101	0.71	sid	14	-	-
	2.11	sid	14	-	-
102	0.79	sid	7	-	-
	1.59	sid	7	-	-
104	1.35	sid	14	Split exercise	-
106	2.19	sid	14	Restrict exercise	-
108	2.33	bid	40	-	-
109	2.25	bid	14	-	-
110	2.05	bid	7	-	Chronic nephritis
	3.09	bid	7	-	" "
201	1.16	sid	7	Moderate exercise	Conjuctivitis, Lymphadenopathy: Ampicillin given
	1.16	sid	20	Short, frequent walks	?Lymphosarcoma; Aural haematoma
202	1.84	bid	7	-	Chronic nephritis: Ceporex tablets
	2.76	tid	7	-	" "
	1.84	bid	7	-	" "
203	1.75	bid	14	-	CVS disease: Digitalis 0.5/day.
	3.50	bid	14	-	" " " "

Key:

sid = one treatment daily; bid = two treatments daily; tid = three treatments daily;
Abc = Antibiotic; Amp. = Ampicillin; Post-op. = Post-operatively;
CVS = Cardiovascular.
# = Dose reduced when diarrhoea present and increased when diarrhoea stopped.
Digitalis = Digitalis Tablets [Veterinary Drug Co. PLC]; contain Digitalis BP 30 or 60 mg.

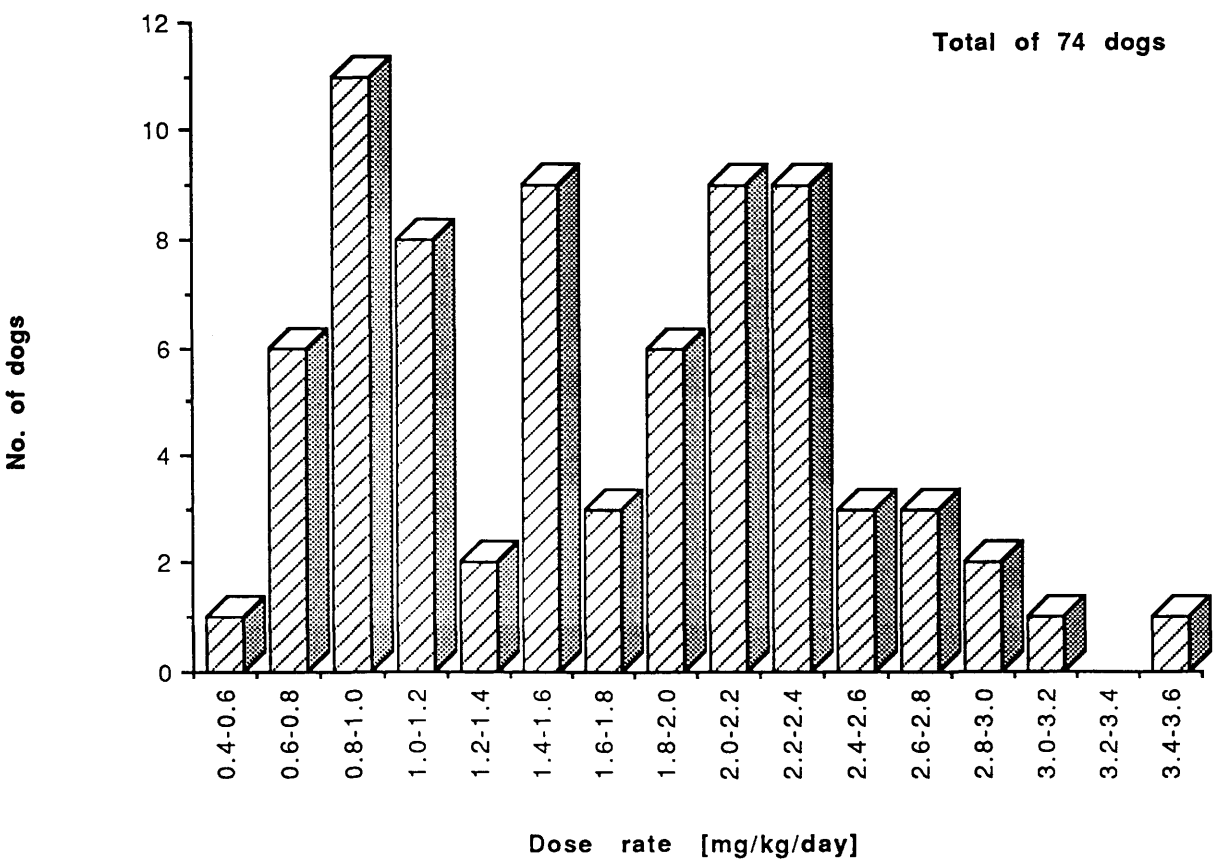
Carprofen Treatments:

Case No.	Dosage [mg/kg/day]	Regime	Duration [days]	Other Advice	Other disease/treatment
205	1.35	sid	7	-	CVS disease: Frusemide
	2.69	sid	4	-	" " "
206	1.16	sid	8	-	"Wheeze": Millophyline
208	2.39	sid	21	Regular light exercise	Bronchitis,CCF: Fruse, Millophyline
209	1.03	sid	21	Reduced exercise	CCF & Bronchitis: Millophyline 2 bid; Fruse. 1.5 sid
210	2.10	bid	21	-	HTS tablets, Vit. B12 inj.
211	0.88	sid	31	-	HTS tablets, Frusemide
212	2.28	sid	21	-	CVS disease: Millophyline.
213	0.88	sid	7	-	CVS disease: Millophyline,
	2.63	sid	7	-	Frusemide.

Key:

sid = one treatment daily; bid = two treatments daily; tid = three treatments daily;
CVS = Cardiovascular
CCF = Congestive Cardiac Failure
Vit. B12 inj. = Vitamin B12 Injection
Fruse. = Frusemide or Lasix® Tablets [Hoechst Animal Health].
Millophyline = Millophyline-V ® Tablets [Arnolds Veterinary Products];
contain Etamiphylline camsylate 100 mg.
HTS Tablets = Heart Tonic and Stimulant Tablets [Duphar Veterinary Ltd];
contain Digitalis BP 30 mg, Belladonna Dry Extract BP 0.25 mg & Glyceryl trinitrate 0.32 mg.

Carprofen Treated Dogs: Dose Rates

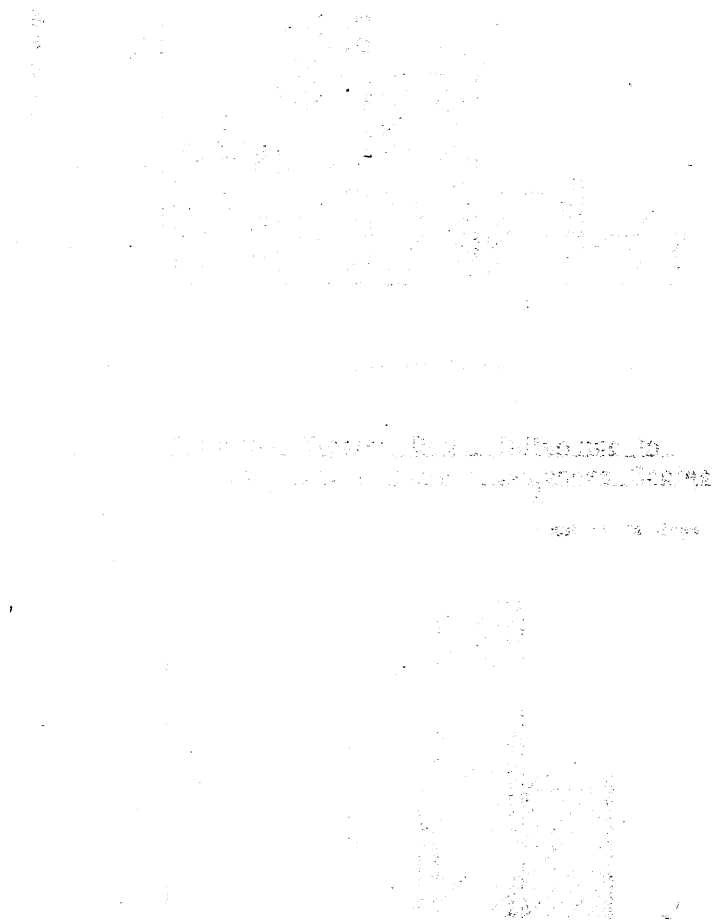


Carprofen Treatment: Pre and Post Treatment Condition Scores

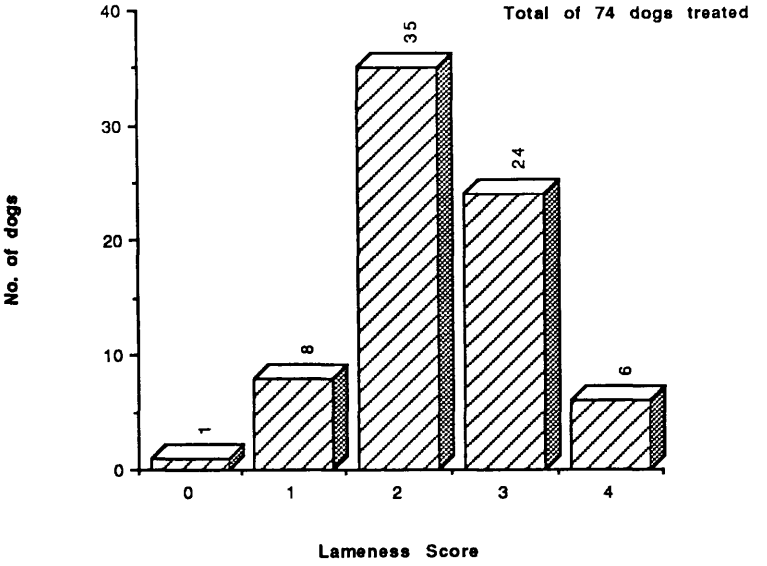
Case No.	Lameness		Weightbearing		Joint Mobility		Total Condition Score	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	3	1	1	0	2	2	6	3
2	3	1	1	0	2	2	6	3
3	2	1	1	0	2	2	5	3
4	2.5	1.5	1	1	1	0.5	4.5	3
5	3	2	1	1	1	1	5	4
6	2	1	0	0	1	1	3	2
8	0	0.5	1	0	1	1	2	1.5
9	1.5	0	0	0	1	1	2.5	0.5
10	3	1	1	0	1	0	5	2
11	3	1	1	0	0	0	4	1
12	2	2	0	0	0	0	2	2
13	2	2	0	0	1	1	3	3
14	1	0	0	0	0	0	1	0
15	4	2	1	1	1	1	6	4
18	4	2	1	1	2	1	7	4
19	1	0	0	0	0	0	1	0
20	2	1	0	0	0	0	2	1
21	1	1	0	0	1	1	2	2
22	1	1	0	0	1	1	2	2
23	4	3	1.5	1.5	1.5	1	7	5.5
24	3	2.5	1	1	1	1	5	4.5
25	2.5	1.5	1	0.5	1	0.5	4.5	2.5
26	2	1	0	0	1	1	3	2
27	2	0.5	2	2	2	2	6	4.5
29	2	0	0	0	1	0	3	0
31	2	0	0	0	1	0	3	0
32	2	2	0	0	1	1	3	3
34	2	1	0	0	1	1	3	2
35	4	1	1	0	2	0	7	1
36	2	2	0	0	1	1	3	3
37	2	4	0	1	2	2	4	7
38	3	2.5	1	0.5	2	1	6	4
39	2	1	0.5	0	1	1	3.5	2
40	3	1	1	1	1	0	5	2
41	3	2	1	1	1	1	5	4
42	3	3	1	1	1	1	5	5
43	2	1	1	1	0	0	3	2
46	2	1	1	0	1	0	4	1
48	2	2	1	1	1	1	4	4
51	3	3	0	0	1	1	4	4
52	3	4	0	1	1	2	4	7
54	3	3	1	1	1	2	5	6
59	3	2	1	1	1	1	5	4
60	2	1	0	0	1	1	3	2
61	2	1	0	0	2	0	4	1
63	2	2	0	0	1	1	3	3
64	3	3	1	1	2	2	6	6
65	2	1	0	0	0	0.5	2	1.5
66	2	1	0	0	1	1	3	2
67	2	1	0	0	0	0	2	1
68	4	4	2	1	0	0	6	5
69	2	0	0	0	1	0	3	0
70	3	2	1	1	2	2	6	5
71	3	0	1	0	1	1	5	1
72	3	3	0	0	1	1	4	4
73	2	2	1	1	1	0.5	4	3.5

Carprofen Treatment: Pre and Post Treatment Condition Scores

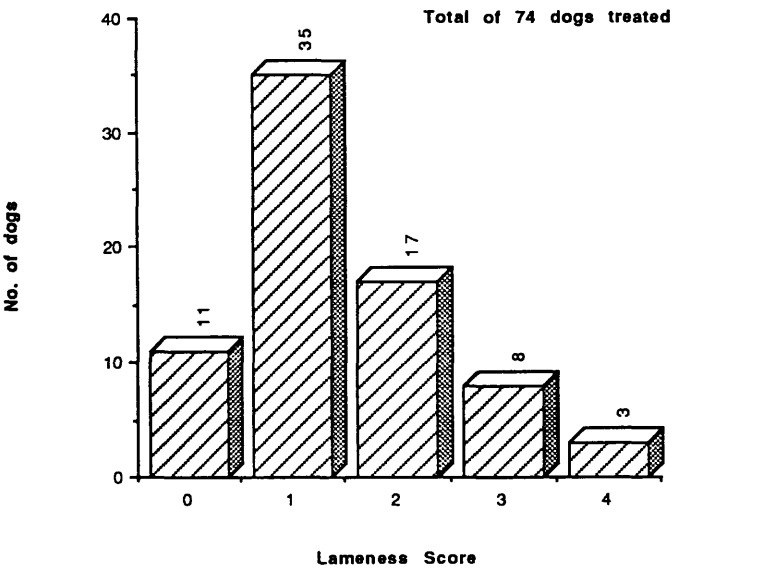
Case No.	Lameness		Weightbearing		Joint Mobility		Total Condition Score	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
101	1.5	1	2	2	1	1	4.5	4
102	2	2	1	1	1	1	4	4
104	1	1	2	2	2	2	5	4
106	1	0	2	2	2	2	5	4
108	3	1	1	0	1	1	5	2
109	2	1	1	0	0	0	3	1
110	2	1	1	0	1	1	4	2
201	3	1	1	1	1	1	5	3
202	2	1	1	0	1	1	4	2
203	2	1	1	0	1	1	4	2
205	3	3	1	1	1	1	5	5
206	2	0	0	0	0	0	2	0
208	3	3	1	1	1	1	5	5
209	3	1	1	0	1	0	5	1
210	4	2	2	1	2	1	8	4
211	3	1	1	0	0	0	4	1
212	2	1	0	0	2	1	4	2
213	2	1	0	0	2	2	4	3



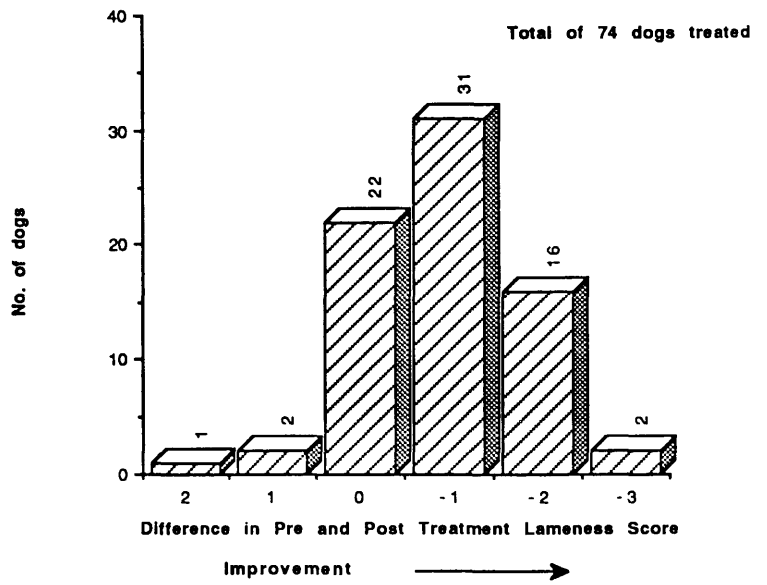
Carprofen Treated Dogs:
Pre Treatment Lameness Score



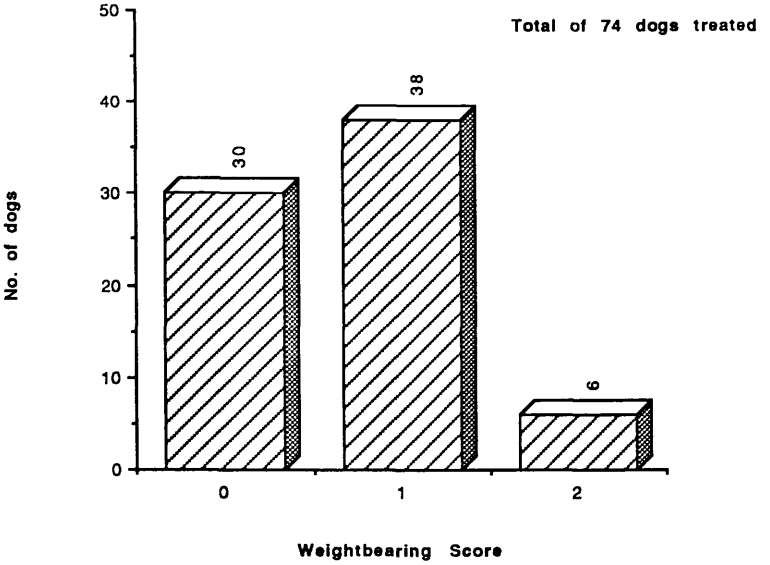
Carprofen Treated Dogs:
Post Treatment Lameness Score



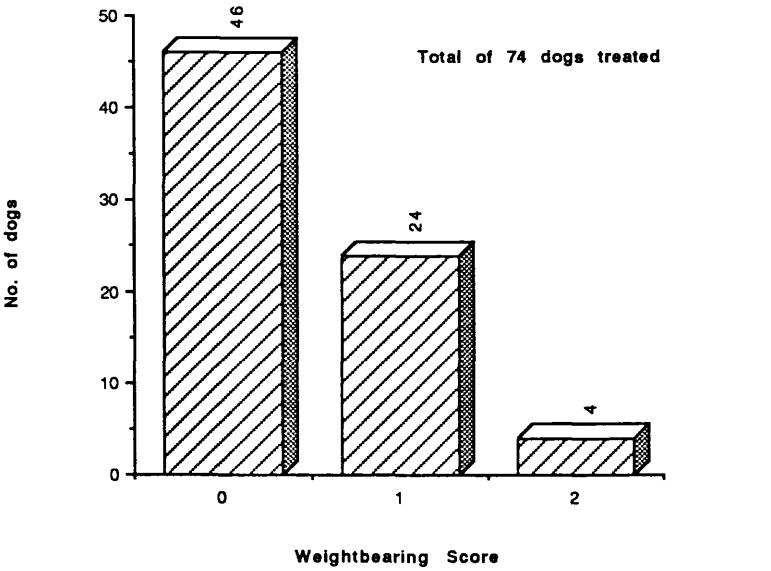
Carprofen Treated Dogs: Difference in
Pre and Post Treatment Lameness Scores



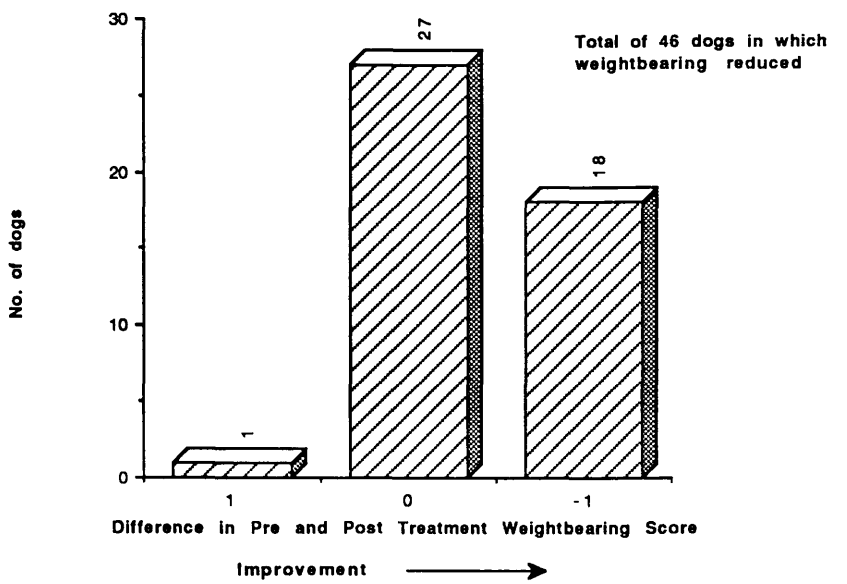
Carprofen Treated Dogs:
Pre Treatment Weightbearing Scores



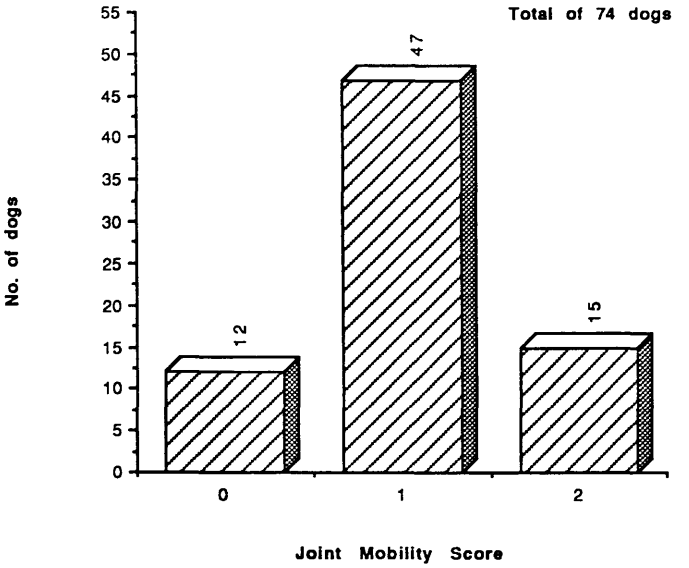
Carprofen Treated Dogs:
Post Treatment Weightbearing Score



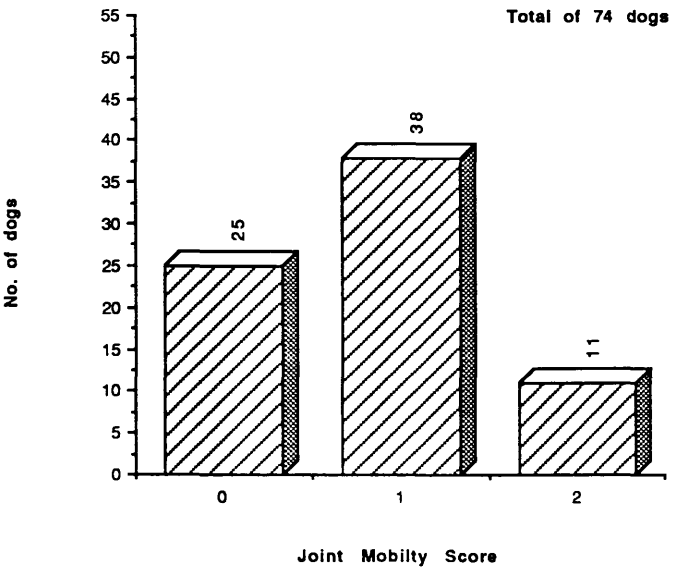
Carprofen Treated Dogs: Difference in
Pre and Post Treatment Weightbearing Scores



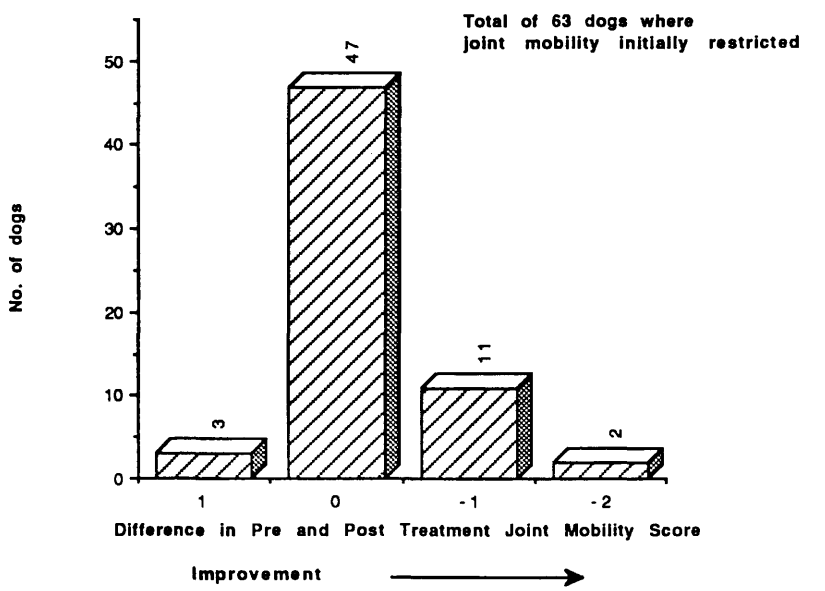
Carprofen Treated Dogs:
Pre Treatment Joint Mobility Scores



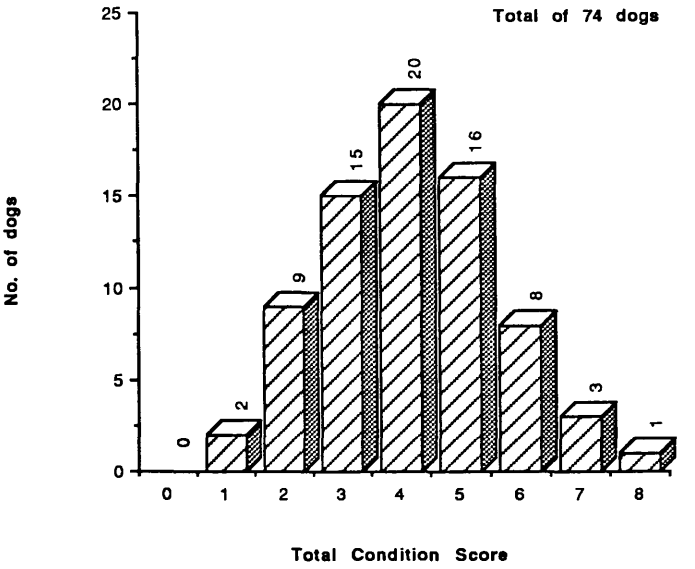
Carprofen Treated Dogs:
Post Treatment Joint Mobility Scores



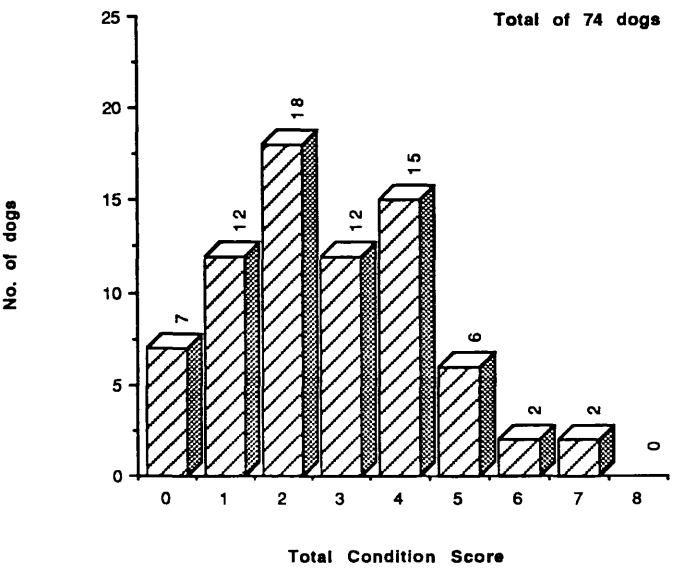
Carprofen Treated Dogs: Difference in
Pre and Post Treatment Joint Mobilty Scores



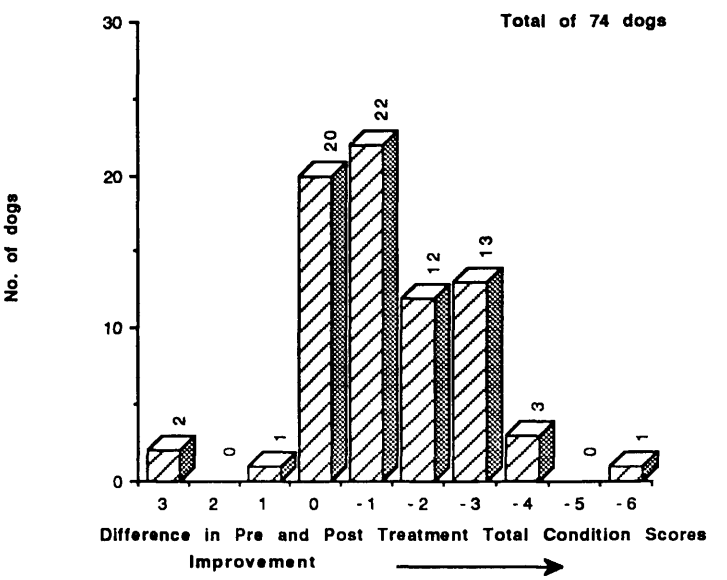
Carprofen Treated Dogs:
Pre Treatment Total Condition Score



Carprofen Treated Dogs:
Post Treatment Total Condition Score



Carprofen Treated Dogs: Difference in
Pre and Post Treatment Total Condition Scores



Phenylbutazone Treatments:

Case No.	Dosage [mg/kg/day]	Regime	Duration [days]	Other Advice	Other disease/treatment
5	13.3	tid	7	-	-
13	8.26	bid	NS	Restrict exercise; reduce weight	-
19	11.1	NS	10	-	-
22	10.5	bid	7	-	-
23	33.3	bid	7	-	-
26	11.4	bid	21	-	-
28	18.8	tid	8	Restrict exercise	-
33	10.0	tid	10	Restrict exercise; reduce weight	-
44	10.0	bid	28	-	-
45	11.5	tid	21	-	-
47	8.57	bid	21	-	-
49	13.3	NS	7	-	-
	10.0	NS	7	-	-
	6.67	NS	7	-	-
52	7.69	bid	14	Minimise exercise	-
54	10.2	bid	7	Diet	-
55	11.1	bid	17	15 mins. exercise/day-	
58	10.0	bid	26	-	-
68	12.9	bid	14	Light exercise	-
103	5.71	sid	4	-	-
107	10.0	sid	50	-	-
204	16.7	bid	21	-	HTS Tablets
205	15.4	bid	7	-	Lasix

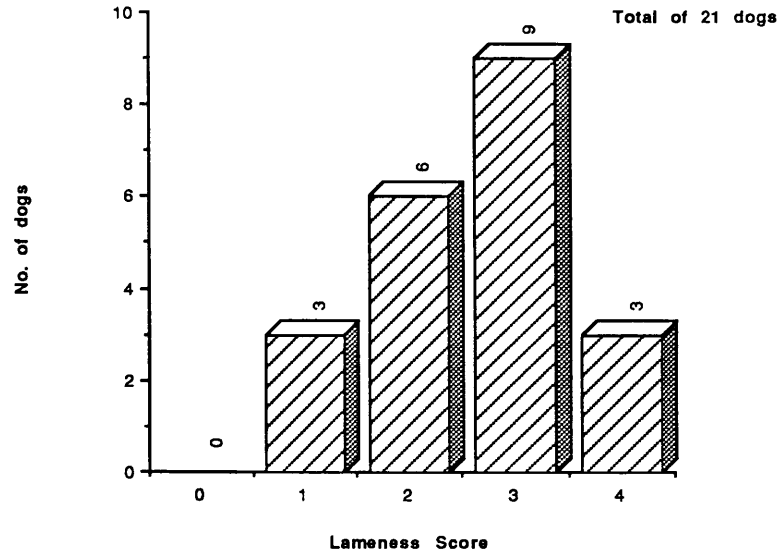
Key:

sid = one treatment daily; bid = two treatments daily; tid = three treatments daily;
HTS Tablets = Heart Tonic and Stimulant Tablets [Duphar Veterinary Ltd];
contain Digitalis BP 30 mg, Belladonna Dry Extract BP 0.25 mg & Glyceryl trinitrate 0.32 mg.
Lasix = Lasix® Tablets [Hoechst Animal Health].
NS = Not Stated

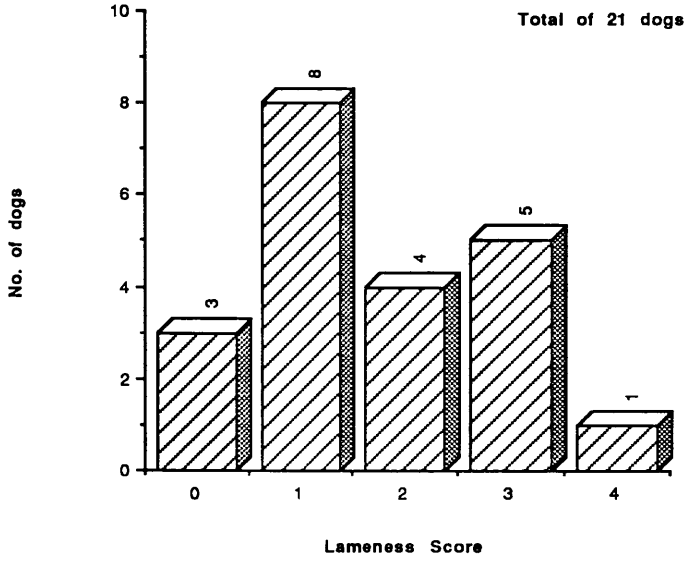
Phenylbutazone Treatment: Pre and Post Treatment Condition Scores

Case No.	Lameness		Weightbearing		Joint Mobility		Total Condition Score	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
5	3	2.5	1	1	1	1	5	4.5
13	2	0	0	0	1	1	3	1
19	1	0.5	0	0	0	0	1	0.5
22	1	1	0	0	1	1	2	2
23	4	3.5	1.5	1.5	1.5	1.5	7	6.5
26	2	1.5	0	0	1	1	3	2.5
28	3	3	2	1	2	2	7	6
33	2	1	0	0	2	1	4	2
44	3	1	1	1	1	1	5	3
45	3	1	1	1	1	1	5	3
47	4	1	1	1	1	1	6	3
49	3	1	1	0	1	1	5	2
52	3	3	0	1	1	2	4	6
54	3	3	1	1	1	2	5	6
55	2	2	0	1	1	1	3	4
58	2	1	0	0	1	1	3	2
68	4	4	2	2	0	0	6	6
103	2	2	1	1	1	1	4	4
107	1	0.75	2	2	1	1	4	3.75
204	3	2	1	1	0	0	4	3
205	3	3	1	1	1	1	5	5

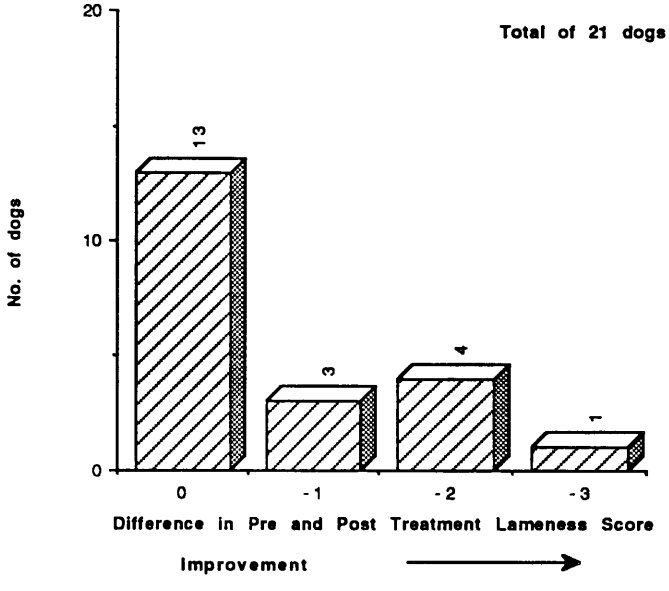
Phenylbutazone Treated Dogs:
Pre Treatment Lameness Scores



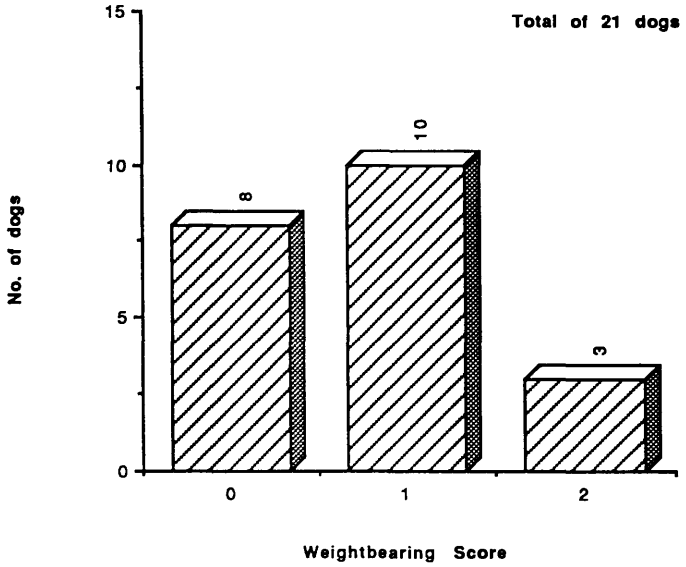
Phenylbutazone Treated Dogs:
Post Treatment Lameness Scores



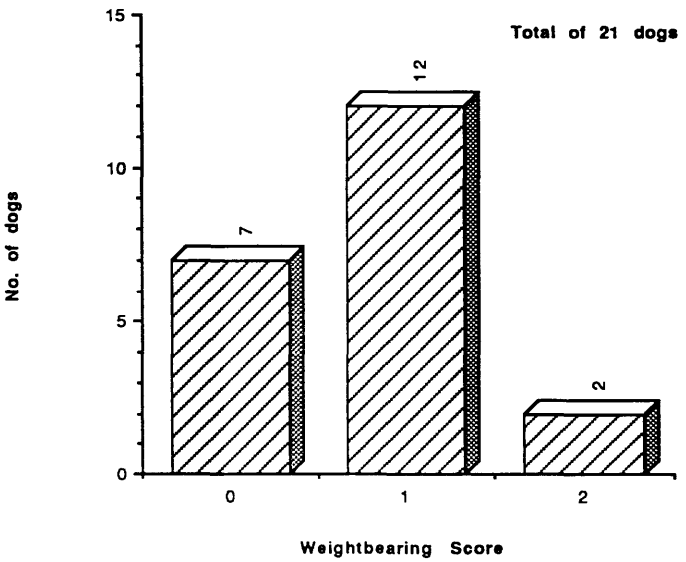
Phenylbutazone Treated Dogs: Difference in
Pre and Post Treatment Lameness Scores



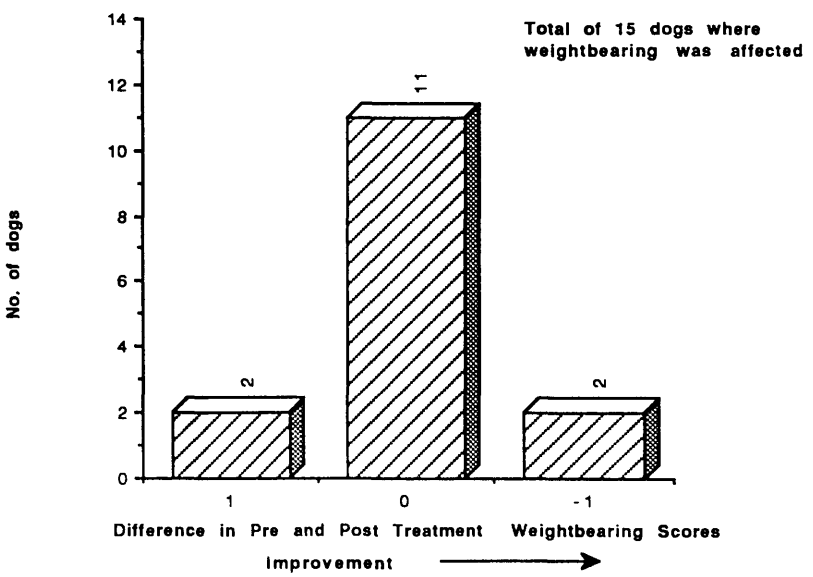
Phenylbutazone Treated Dogs: Pre Treatment Weightbearing Score



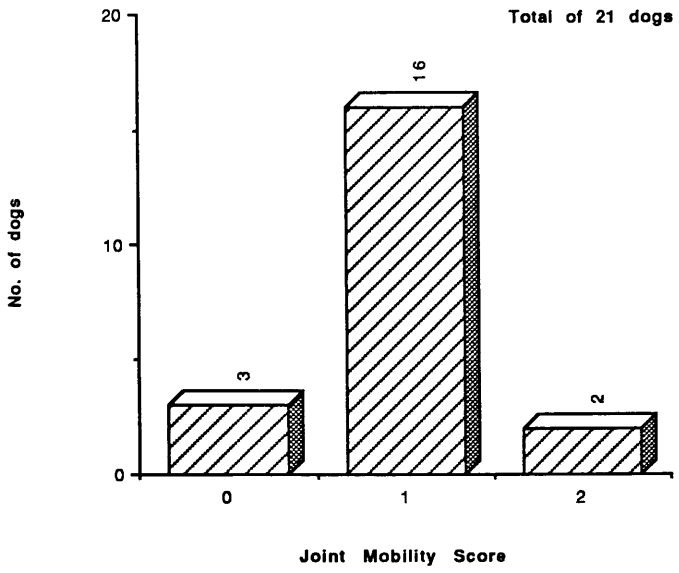
Phenylbutazone Treated Dogs: Post Treatment Weightbearing Scores



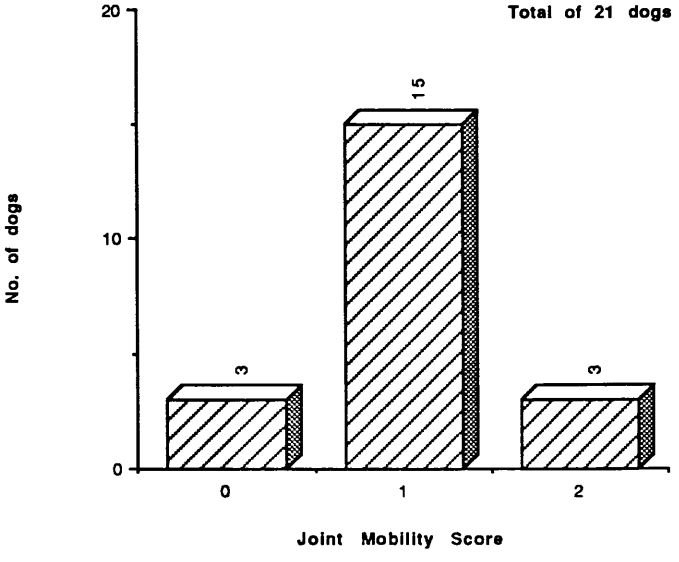
Phenylbutazone Treated Dogs: Difference in Pre and Post Treatment Weightbearing Scores



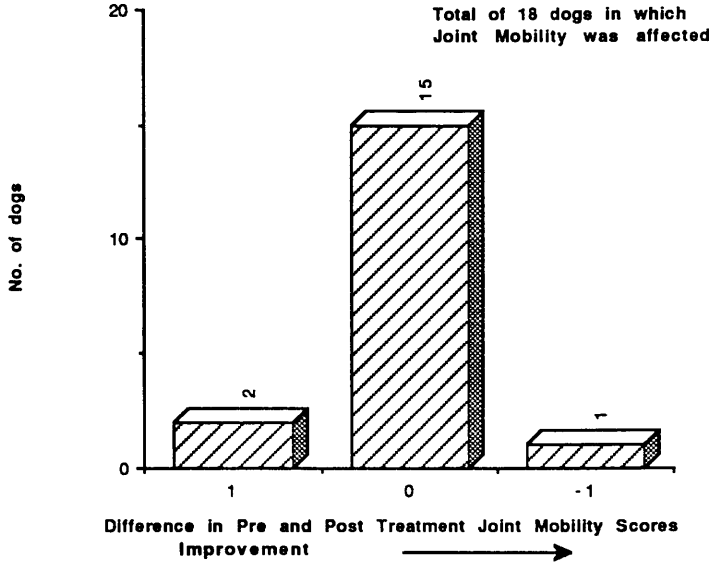
Phenylbutazone Treated Dogs:
Pre Treatment Joint Mobility Scores



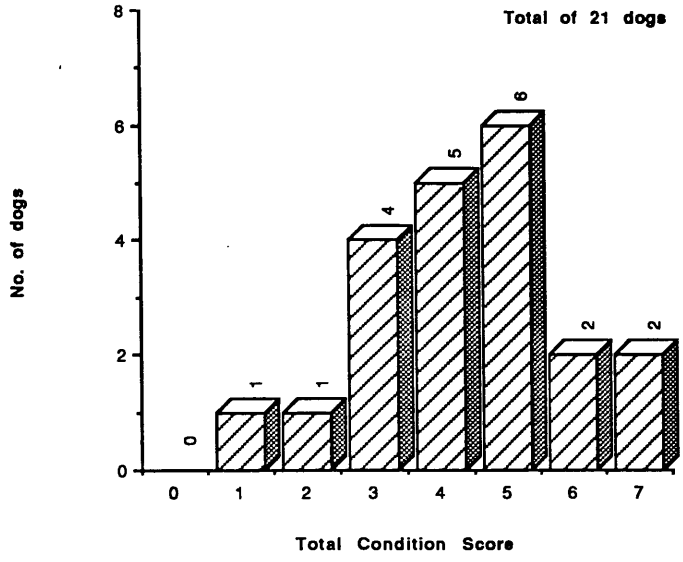
Phenylbutazone Treated Dogs:
Post Treatment Joint Mobility Scores



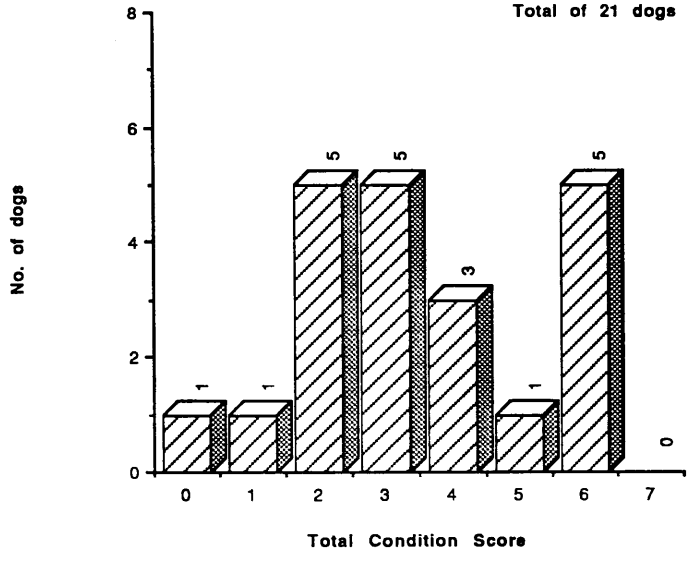
Phenylbutazone Treated Dogs: Difference in
Pre and Post Treatment Joint Mobility Scores



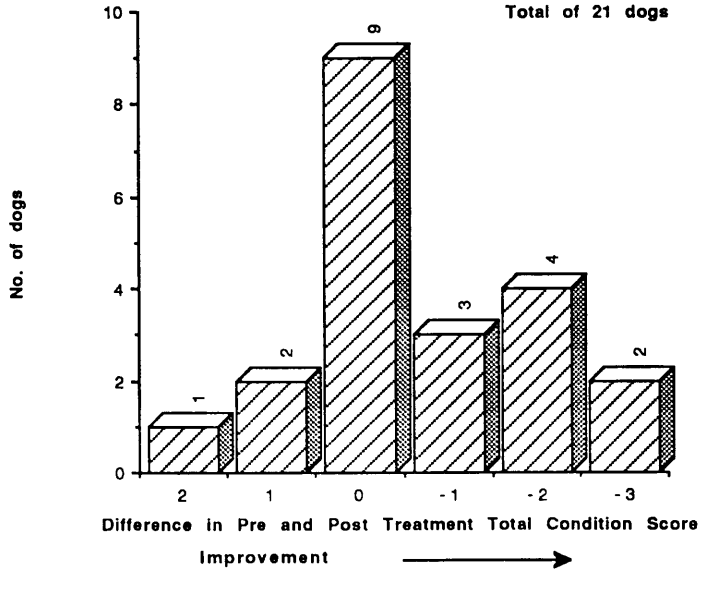
Phenylbutazone Treated Dogs:
Pre Treatment Total Condition Score



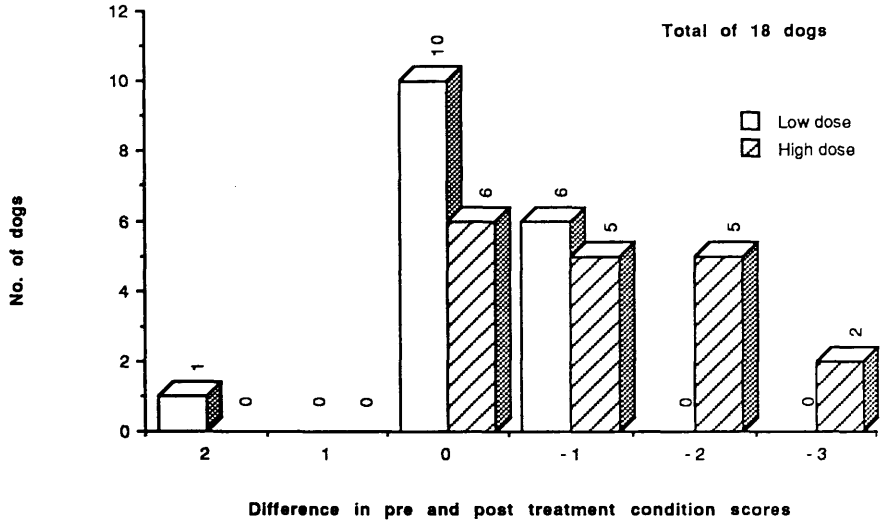
Phenylbutazone Treated Dogs:
Post Treatment Total Condition Score



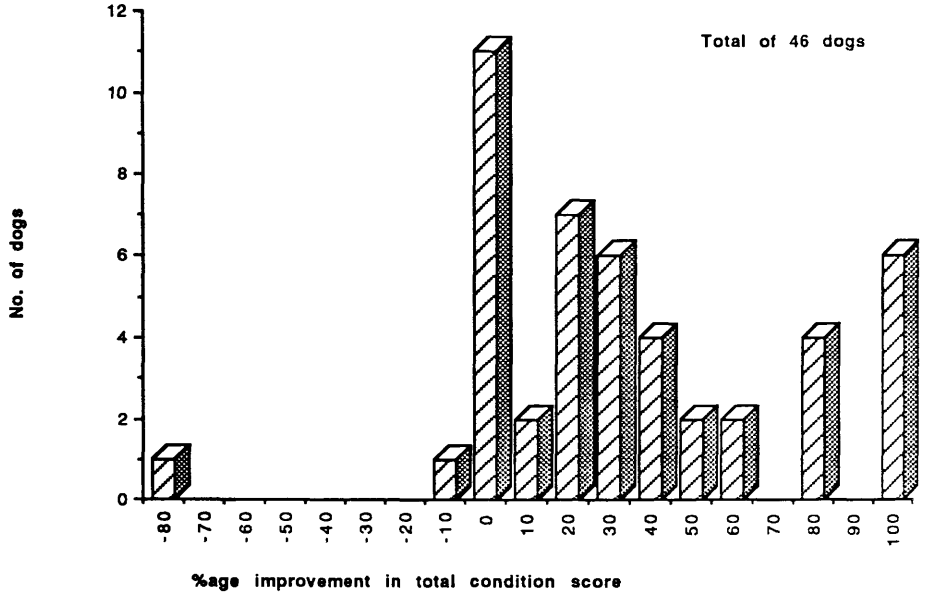
Phenylbutazone Treated Dogs: Difference in
Pre and Post Treatment Total Condition Score



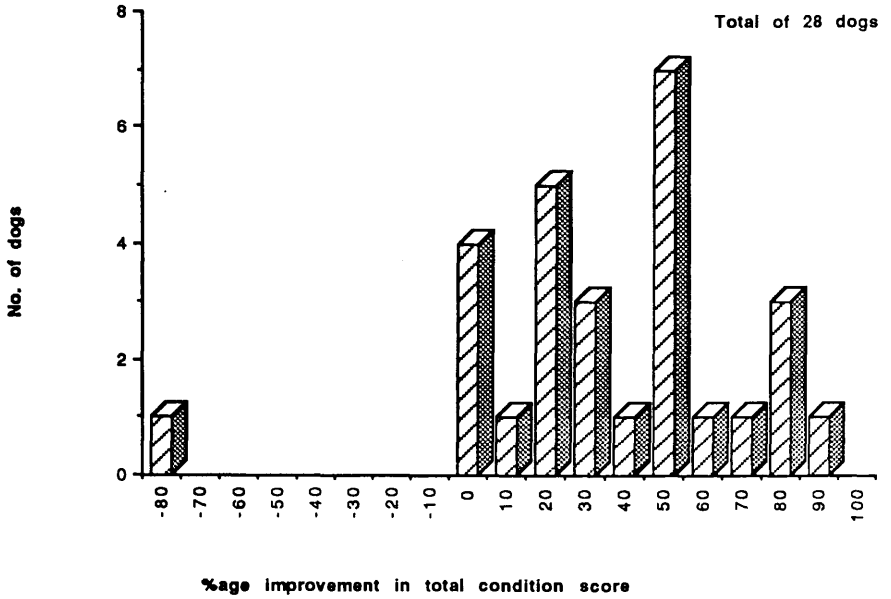
Cases Treated with Two Doses of Carprofen: Effect on Total Condition Score



Carprofen Treated Dogs: Percentage improvement in total condition score in dogs treated at < 2 mg/kg/day



Carprofen Treated Dogs:Percentage improvement in total condition score in dogs treated at ≥ 2 mg/kg/day



Previous Treatments and Effects

Case No.	Drug Preparation	Dosage [mg/kg/day]	Duration	Effect [0 to 3]	Time for painful signs to recurr
1	Piroxicam	0.33 e.o.d.	7 days	1	NS
2	Piroxicam	0.33 e.o.d.	7 days	1	NS
4	Aspirin 300 mg	12	5 weeks	1	Swift
5	Ent. Coat. A.S.A. 600 mg Ibuprofen 400 mg	27 18	-- 6 months	1 1*	 Few days
9	Paracetamol	NS	NS	NS	NS
10	Phenylbutazone	13	NS	1†	Exercise dependent
12	Phenylbutazone	12.7	7 days	2	2 weeks
15	Phenylbutazone Prednisolone	15 0.15	NS NS	1 0	NS N/A
18	Predno-Leucotropin Tabs. Cinchophen 200 mg Prednisolone 1 mg	 17.4 0.09	 "Constant"	 1	 NS
21	Phenylbutazone	8.3	2.5 years	1-2	Not withdrawn
24	Phenylbutazone	11 as req.	18 months	1	2 days
25	Piroxicam	0.36 e.o.d.	6 months	1	7 days
28	Phenylbutazone	19	8 days	1	NS
29	Phenylbutazone	26	10 days	2	3 days
31	Phenylbutazone	20	10 days	1	2 days
33	Predno-Leucotropin Tabs. Cinchophen 200 mg Prednisolone 1 mg	 13 0.07	 As req.	 1	 NS
34	Phenybutazone Predno-Leucotropin Tabs. Cinchophen 200 mg Prednisolone 1 mg Piroxicam	15 30 0.15 0.33 e.o.d.	3-4 weeks 14 7 days	1 2 2Δ	- - NS
35	Phenylbutazone	20	10 days	2	3 weeks/ Exercise
36	Phenylbutazone Predno-Leucotropin Tabs. Cinchophen 200 mg Prednisolone 1 mg	18 17.6 0.09	As req. NS	1 2	NS NS
37	Piroxicam	0.40 e.o.d.	14 days	2	No T. 2-3 months
39	Phenylbutazone Predno-Leucotropin Tabs. Cinchophen 200 mg Prednisolone 1 mg	27 27 0.13	4 weeks 10 days	2 2	- 7 days

Previous Treatments and Effects

Case No.	Drug Preparation	Dosage [mg/kg/day]	Duration	Effect [0 to 3]	Time for painful signs to recurr
40	Phenylbutazone	9	4 months	1	3 days
42	Opticorten [Dexameth.]	0.08	14 days	0	-
	Pardale-V [Paracetamol +]	267	28 days	0	N/A
45	Predno-Leucotropin Tabs.	NS	7 days	2	2 days
46	Aspirin 500 mg	16.7	NS	1	NS
49	Predno-Leucotropin Tabs.				
	Cinchophen 200 mg	13	NS	1	2 days
	Prednisolone 1 mg	0.07			
54	Prednisolone	0.51 e.o.d.	NS	1	NS
59	Phenylbutazone	9	5 months	2	7 days
61	Pardale-V [Paracetamol +]	72	10 days	1	2 days
63	Predno-Leucotropin Tabs.				
	Cinchophen 200 mg	30	7 days	0	N/A
	Prednisolone 1 mg	0.15			
	Phenylbutazone	15	6 weeks	1	NS
64	Ceporex [Cephalexin]	27	10 days	2	_
	& Flagyl [Metronidazole]	21			
65	Phenylbutazone	17	7 days	2	
	"	11	10 days	2	5 days
66	Phenylbutazone	18	14 days	2	3 days
68	Phenylbutazone	13	28 days	0	N/A
70	Phenylbutazone	17	NS	0	N/A
72	Predno-Leucotropin Tabs.				
	Cinchophen 200 mg	22	NS	2	NS
	Prednisolone 1 mg	0.11			
73	Predno-Leucotropin Tabs.				
	Cinchophen 200 mg	5	NS	1	2-3 days
	Prednisolone 1 mg	0.03			
101	Predno-Leucotropin Tabs.				
	Cinchophen 200 mg	13	18 days	3	7 days
	Prednisolone 1 mg	0.06			
102	Phenylbutazone	6	NS	2	4 days
108	Phenylbutazone	10	NS	0	N/A
109	Phenylbutazone	10	NS	1	2 days
110	Phenylbutazone	12	4-5 months	1	-
	Predno-Leucotropin Tabs.				
	Cinchophen 200 mg	23	34 days	2	2 days
	Prednisolone 1 mg	0.12			

Previous Treatments and Effects

Case No.	Drug Preparation	Dosage [mg/kg/day]	Duration	Effect [0 to 3]	Time for painful signs to recurr
202	Phenylbutazone	11	NS	2	NS
	Predno-Leucotropin Tabs.				
	Cinchophen 200 mg	21	NS	1	NS
	Prednisolone 1 mg	0.11			
203	Predno-Leucotropin Tabs.				
	Cinchophen 200 mg	40	7 days	1	2 days
	Prednisolone 1 mg	0.20			
204	Dexafort Inj.[Dexameth.]	0.125	1 dose	0	N/A
205	Phenylbutazone	15	"Constant"	1	2-3 days
208	Predno-Leucotropin Tabs.				
	Cinchophen 200 mg	27	10 days	0	N/A
	Prednisolone 1 mg	0.14			
	Pardale-V [Paracetamol +]	55	4 days	1	-
210	Phenylbutazone	12	7 days	1	-
	Predno-Leucotropin Tabs.				
	Cinchophen 200 mg	24	21 days	1	2-3 days
	Prednisolone 1 mg	0.12			
211	Opticorten [Dexameth.]	0.025 occasionally		1	4 days
213	Phenylbutazone	7	NS	2	NS

Key:

Drug Preparations:

Ent. Coat. A.S.A. = Enteric Coated Aspirin;

Opticorten [Dexameth.] = Opticorten ® Tablets 0.25 mg [Ciba-Geigy Agrochemicals]; contain Dexamethazone BP 0.25 mg.

Pardale-V [Paracetamol +] = Pardale-V ® Tablets [Arnolds Veterinary Products]; contain Paracetamol BP 400 mg, Codeine phosphate BP 9 mg & Caffeine hydrate BP 10 mg per tablet.

Ceporex = Ceporex ® Tablets [Glaxovet Ltd]; contain 50 or 250 mg Cephalexin.

Flagyl = Flagyl ® Tablets [RMB Animal Health Ltd]; contain Metronidazole BP 200 mg.

Dexafort Inj. = Dexafort ® [Intervet UK Ltd]; contains Dexamethazone 3 mg.

Other Abbreviations:

e.o.d. = every other day; as req. = as required; NS = Not stated; N/A = Not applicable;

* = Caused diarrhoea and constipation; † = caused vomiting; Δ = Gastroenteritis.

Effect of Treatment:

0 = No Effect

1 = Some Effect

2 = Marked Improvement

3 = Sound

Recommended Daily Dosages for Previous Treatments:

Aspirin/ Enteric Coated Aspirin = 25 mg/kg every 8 hours [50-75 mg/kg/day]

Phenylbutazone = 2-20 mg/kg/day divided [8-16 mg/kg/day usually used]

Predno-Leucotropin Tablets = 20-40 mg Cinchophen; 0.1-0.2 mg Prednisolone/kg/day.

Piroxicam = 0.3 mg/kg every 48 hours

Pardale-V = 0.5-3 tablets every 8 hours [equivalent to about 40-80 mg Paracetamol/kg/day]

Ibuprofen = Not recommended

Opticorten Tabs. = 1-8 tablets daily [equivalent to about 0.05 mg Dexamethazone/kg/day]

Dexafort = 0.5-1 ml [3mg/ml]

Ceporex = 20-30 mg/kg/day.

Flagyl = 20 mg/kg/day for 10-20 days.

Carprofen Compared to Previous Treatments

[Where the veterinary surgeon stated the comparative effect of the previous treatment and Carprofen treatment]

	Carprofen		
	Better	Same	Worse
cf. All Previous Treatments	26	6	14
cf. Phenylbutazone	12	3	6
cf. Predno-Leucotropin	5	0	6
cf. Piroxicam	2	1	2
cf. Aspirin	3	0	0
cf. Pardale-V	1	1	0
cf. Ibuprofen	1	0	0
cf. Opticorten	1	1	0
cf. Prednisolone	1	0	0

Carprofen and Phenylbutazone Treatments in the Same Dog: Comparative Efficacy

Case No.	PBZ Dose [mg/kg/day]	T.C.S. Diff.	Carprofen dose [mg/kg/day]	T.C.S. Diff.	Most effective Treatment
5	13.3	0.5	2.33	1	Carprofen
13	8.26	2	1.23	0	Phenylbutazone
19	11.1	0.5	0.97	1	Carprofen
22	10.5	0	0.92	0	Neither
23	33.3	0.5	2.92	1.25	Neither
26	11.4	0.5	2.00	1	Carprofen
52	7.69	-2	2.69	-3	Neither
54	10.2	-1	0.89	-1	Neither
68	12.9	0	1.13	1	Carprofen
205	15.4	0	1.35	0	Phenylbutazone

Carprofen Dose Rate Changes in the Same Dog: Comparative Efficacy

Case No.	Dose 1 [mg/kg/day]	T.C.S. Diff.	Dose 2 [mg/kg/day]	T.C.S. Diff.	Most Effective Dose Rate
11	0.97	1	1.94	3	1.94
15	1.35	1	2.02	2	2.02
27	0.88	1	2.33	2	2.33
40	0.80	1	1.59	2	1.59
41	1.25	0	2.50	1	2.50
60	0.73	0	1.46	1	1.46
61	0.80	0	1.59	3	1.59
63	1.30	0	1.94	0	Neither
64	1.17	0	1.87	0	Neither
65	0.75	1	1.50	1	Not stated
70	1.50	1	2.00	1	Same
73	0.93	-2	1.87	0.5	Neither
101	0.71	0	2.11	0.5	Neither
102	0.79	0.5	1.59	0.5	Neither
202	1.84	0	2.76	2	2.76
203	1.75	1	3.50	2	3.50
205	1.35	0	2.69	0	Neither
213	0.88	0	2.63	1	2.63/Neither

T.C.S. Diff. = Total Condition Score Difference between Pre and Post Treatment Examinations

Carprofen Treatments Compared to Previous Treatments

Case No.	Previous Treatment	Effect	Carprofen Dosage [mg/kg/day]	Carprofen cf. Previous Treatment		
				Worse	Same	Better
	Phenylbutazone					
68	"	0	1.13			Ô
70	"	0	2.00			Ô
108	"	0	2.33			Ô
10	"	1†	0.88			Ô
24	"	1	0.97			Ô
34	"	1	1.75		Ô	
63	"	1	1.94	Ô		
15	"	1	2.02			Ô
205	"	1	2.69	Ô		
110	"	1	3.09			Ô
21	"	1-2	0.73			Ô
29	"	2	0.76		Ô	
59	"	2	0.78		Ô	
12	"	2	1.11	Ô		
39	"	2	1.17			Ô
66	"	2	1.19			Ô
65	"	2	1.50			Ô
102	"	2	1.59	Ô		
35	"	2	2.04	Ô		
213	"	2	2.63	Ô		
202	"	2	2.76			Ô
	Predno-Leucotropin Tablets					
63	"	0	1.94			Ô
18	"	1	0.76	Ô		
73	"	1	1.87	Ô		
202	"	1	2.76			Ô
203	"	1	3.50			Ô
39	"	2	1.17			Ô
36	"	2	1.54	Ô		
34	"	2	1.75	Ô		
72	"	2	2.55	Ô		
110	"	2	3.09			Ô
101	"	3	2.11	Ô		
25	**Piroxicam**	1	0.94	------Ô?-------		
1	**Piroxicam**	1	2.33			Ô
2	**Piroxicam**	1	2.33			Ô
37	**Piroxicam**	2	1.40	Ô		
73	**Piroxicam**	2	1.87	Ô		
4	**Aspirin**	1	1.79			Ô
5	**Aspirin**	1	2.33			Ô
46	**Aspirin**	1	2.33			Ô
42	**Pardale-V**	0	0.97		Ô	
61	**Pardale-V**	1	1.59			Ô
42	**Opticorten**	0	0.97		Ô	
211	**Opticorten**	1	0.88			Ô
5	**Ibuprofen**	1*	2.33			Ô
15	**Prednisolone**	0	2.02			Ô

† = caused vomiting; * = caused diarrhoea and constipation

APPENDIX
D

PLT tablets are a development of Prednoleucotropin tablets which have been widely used in veterinary practice for 20 years.

Prednoleucotropin tablets contain 3 active constituents:

Cinchophen	200 mg/ tablet
Hexamine	100 mg/ tablet
Prednisolone	1 mg/ tablet

Experimental studies in laboratory animals have shown that the anti-inflammatory activity of cinchophen and prednisolone is not enhanced by the addition of hexamine. The purpose of this study is to determine the clinical efficacy of the cincophen/ prednisolone combination alone (ie. PLT tablets) in the therapy of osteoarthritis in the dog.

PLT tablets contain:

Cinchophen	200 mg/ tablet
Prednisolone	1 mg/ tablet

and will be administered in a divided dose on a theroretical 25 mg cinchophen and 0.125 mg prednisolone per kg body weight.

You, the veterinary surgeon, are asked to treat suitable cases of clinical osteoarthritis. Treatment of existing cases will allow comparison of efficacy between two treatments in the same animal. New cases will be treated with PLT tablets or Flexazone (phenylbutazone) tablets on an alternate case basis. New cases may alternatively be treated with a 14 day course of one drug then, after a short interval of 3 to 4 days to allow the return of clinical signs, switched to the other drug.

Case Selection

1. EXISTING CASES

These are animals already receiving treatment for osteoarthritis using Non-Steroidal Anti-Inflammatory Drugs.

i) Take the animal off the drug
ii) Monitor the time taken for the return of the painful condition
iii) Score the clinical condition
iv) Institute PLT treatment
iv) Monitor effects of treatment eg. at 2 weeks, re-examine the dog and re-score

2. NEW CASES

i) Confirm osteoathritis (as distinct from traumatic, septic or immune based arthritis)
Identify the joint(s) affected
Score the clinical condition
ii) Institute PLT or Phenylbutazone treatment on an "alternate dog" basis
iii) Monitor effects of treatment eg. at 2 weeks, re-examine the dog and re-score

Your assessment should be recorded on the standard form using the condition scoring table provided. Where possible, the owner should be questioned as to the efficacy of the treatment. At the end of the treatment period, fill in the EFFICACY ASSESSMENT sheet provided.

The information from all the reports will be analysed and used in the application to register PLT for use in the treatment of osteoarthritis in the dog.

Dose Recommendation

PLT

PLT tablets contain:

Cinchophen	200 mg/ tablet
Prednisolone	1 mg/ tablet

and will be administered in a divided dose on a theroretical 25 mg cinchophen and 0.125 mg prednisolone per kg body weight.

In practical terms, due to the fixed combination and set quantity per tablet, the dose rates will be:

Bodyweight [kg]	Tablets	Cinchophen [mg/kg]	Prednisolone [mg/kg]
8	**1/2 tablet twice daily**	25	0.125
9 - 16	**1 tablet twice daily**	25 - 44	0.125 - 0.22
17 - 24	**1.5 tablets twice daily**	25 - 35	0.125 - 0.176
25 - 32	**2 tablets twice daily**	25 - 32	0.125 - 0.160

Due to the prednisolone content, treatment should be reduced gradually.

The initial treatment period will be 14 days, subject to clinical response.

Phenylbutazone: [Flexazone (BK)]

Suggested dose rate is 8 to 16 mg/kg body weight in two divided daily doses. With the 100 mg tablets provided, the table below gives guideline dose rates:

Bodyweight [kg]	Tablets	Phenylbutazone[mg/kg]
Up to 12.5	**1 [2 x 0.5]**	8 to 16+
13 to 25	**2 [2 x 1]**	8 to 16
26 to 37.5	**3 [2 x 1.5]**	8 to 11.5
38 to 50	**4 [2 x 2]**	8 to 10.5

etc.

Contra-indications/ Warnings:

Cardiac, renal or hepatic insufficiency and in animals showing signs of or having a history of anaemia.

If you have any queries or problems, please contact me at the telephone numbers below:

Tim Pearson: Work: 041-339-8855 extn. 5790
Home: 041-339-8242

CONDITION SCORING:

Where possible, score the dog's clinical condition as below. If the clinical signs do not fit the scores given please describe them in the " Comments" section.

Lameness: [L]

0 = Clinically NORMAL

1 = STANDS normally;
WALKS normally;
LAME after vigorous exercise

2 = Stands normally;
SLIGHT LAMENESS when walking

3 = Careful when standing;
OBVIOUS LAMENESS when walking.

4 = NOT standing normally.
SEVERE LAMENESS when walking and unwilling to run.

Weightbearing: [W.B.] [where appropriate ie. limb joints affected]

0 = NORMAL weightbearing on all limbs.

1 = Weight only applied temporarily on affected limb.

2 = NO WEIGHT applied on affected limb.

Mobility of Affected Joint(s): [J.M.]

0 = NO LIMITATION of joint movement.
No evidence of pain shown by dog during manipulation.

1 = SOME REDUCTION in joint movement.
Dog shows reluctance during manipulation.

2 = OBVIOUS REDUCTION in joint movement.
Dog shows evidence of pain during manipulation plus crepitus.

Stiffness: [S]

0 = NO STIFFNESS at any time

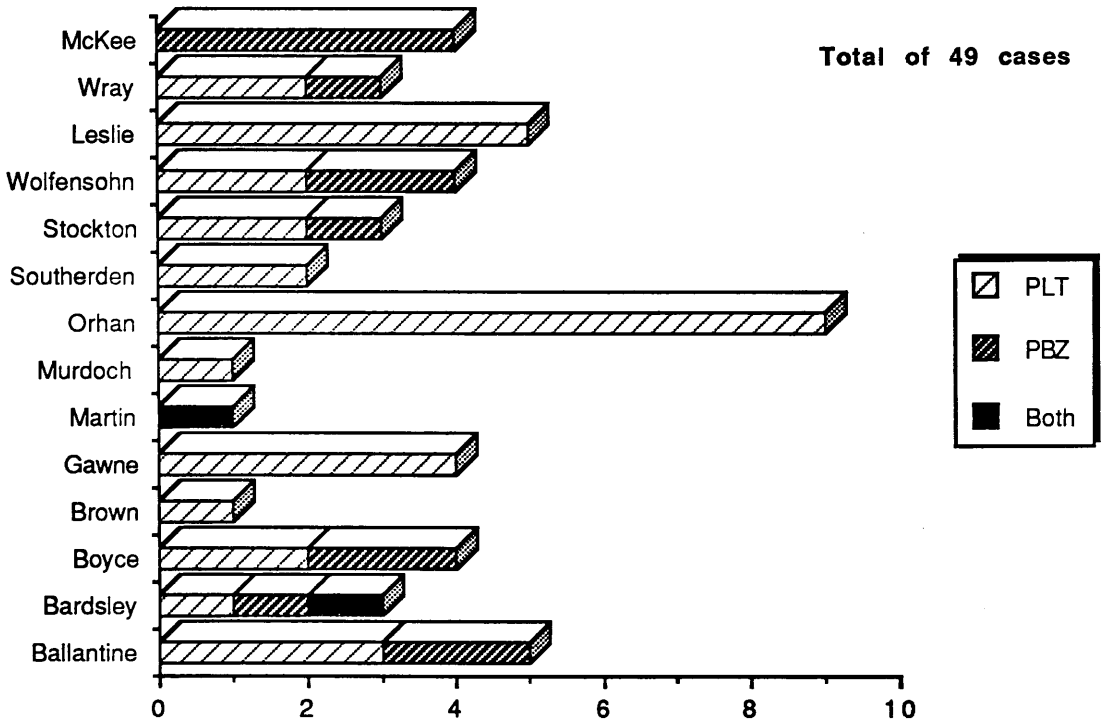
1 = SLIGHT STIFFNESS after post-exercise rest or first thing in the morning

2 = MODERATE STIFFNESS " " " " " " " " " "

3 = MARKED STIFFNESS after rest plus SLIGHTLY STIFF GAIT when walking

4 = SEVERE STIFFNESS after rest and MARKEDLY STIFF when walking

Number of Usable Case Results Returned by Veterinarians



Animal Details of Clinical Osteoathritis Cases

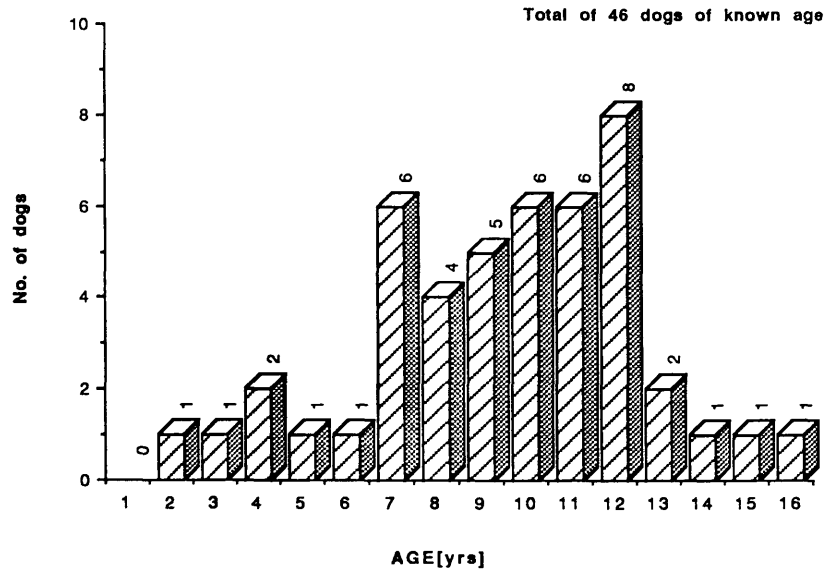
CASE NO.	OWNER NAME	AGE[yrs]	SEX	BREED	WEIGHT[kg]	PREV. T.	TRIAL TREATMENT
1	Hannington	10	M	Dalm.	30	—	PLT
2	Matthews	11	M	Lab.	35	Predn.	PLT
3	Baxter	11	F/N	G.S.D	45	—	PBZ
4	Martin	?	M	G.S.D	45	—	PBZ
5	Sharman	9	F/N	Lab.	35	Piroxicam	PLT
6	Kerr	7	F/N	Lab.	40	—	PLT
7	Gould	8	F/N	Lab.	35	—	PLT & PBZ
10	Hook	6	M	G.Ret.	35	Voren Susp	PLT & PBZ
11	Murton	7	M	G.S.D.	46	—	PBZ
12	Gooch	3	M/N	G.Ret.	52	—	PLT
14	Avenell	4	F/N	Lab.	30	—	PBZ
16	Edmunds	8	M	G.S.D.	40	PrLT	PBZ
18	Ricketts	10	F/N	Lab.	35	—	PLT
19	Fowler	9	M/N	LabX	35	—	PLT
20	Dowdall	10	F/N	CollieX	20	PrLT	PLT
21	Holt	13	M	Eng Sett	35	PrLT	PLT
22	Timberlake	12	F	Lab.	35	PrLT	PLT
23	Dykins	?	M	B.Collie	25	PBZ/Optic.	PLT
24	Lomas	11	M	Lab.	30	PBZ	PLT
25	Greenhough	2	F	Rott.	35	—	PLT
26	Giles	14	M	B.Collie	18	—	PLT
27	Laybourne	9	F	B.Collie	20	PBZ/Predn.	PLT
29	Joynsohn	4	M	Dobe.	45	—	PLT
30	Bowman	8	M	Lab.	40	Fluvet	PLT
31	Johnston	15	F/N	G.S.D.X	15	PBZ	PLT
32	Thorpe	12	F/N	St.Poodle	35	—	PLT
33	Boothroyd	12	F	J.R.T.	13	—	PLT
34	Love	8	F	Lab.	27	—	PLT
36	Reynolds	7	F	G.Ret.	30	PrLT, A.S.A.	PBZ
37	Holwerda	12	F/N	Dobe.	30	A.S.A.	PLT
38	Duncan	10	F/N	Corgi	13	—	PLT
41	Dunton	12	F/N	O.E.S.	40	PrLT, PBZ/Predn.	PLT
42	Andrews	16	M	G.Ret.	28	—	PLT
43	Marshall	5	M	Lab.	35	—	PLT
44	Young	12	M	Be. Collie	33	PBZ	PLT
45	Shar	?	F/N	Boxer	35	—	PLT
46	Love	9	M	Lab. X	20	PrLT	PLT
47	Hobbs	9	F/N	G.S.D.	37	—	PLT
48	Jeremiah	10	F/N	Lab.	36	PrLT	PBZ
49	Ramsden	11	M/N	X	25	A.S.A.	PLT
50	Campbell	11	M	Collie	35	—	PLT
51	McNiven	12	F/N	Lab.	40	—	PBZ
52	Shivaes	7	F/N	Lab.	40	—	PBZ
53	Robertson	7	F	X	20	—	PBZ
54	Kerr	12	M	K.B. Terr.	20	PrLT	PBZ
55	McNeish	11	F/N	G.Ret.	25	—	PBZ
56	Donaldson	13	F	CollieX	16	PBZ	PLT
57	Burchell	10	M	Lab.	25	PrLT	PLT
58	Gaston	7	F/N	Lab.	32	PBZ	PBZ

(Key overleaf)

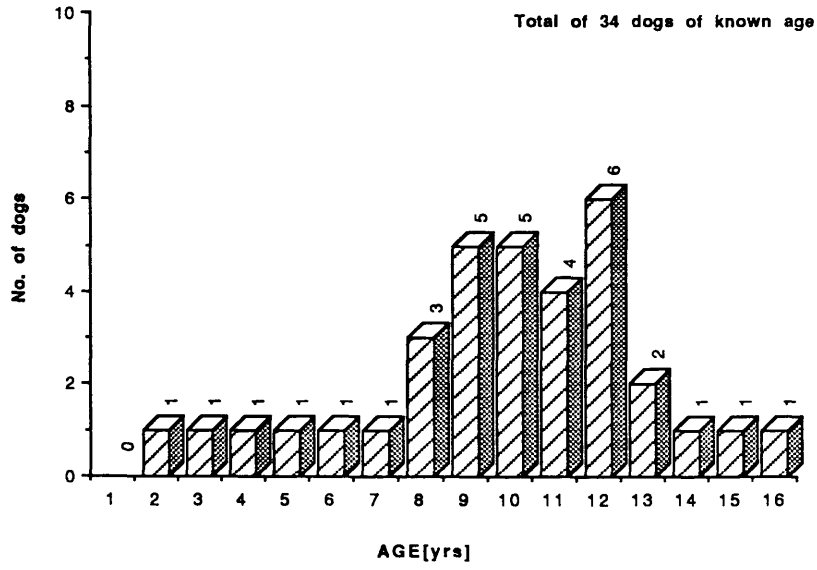
Key:

Sex: M = Male, F = Female, M/N = Castrated Male, F/N = Spayed Female
Breed: Dalm. = Dalmatian, Lab. = Labrador Retriever, G.S.D. = German Shepherd Dog [Alsatian], G.Ret. = Golden Retriever, LabX = Labrador Retriever Crossbred, CollieX = Collie Type Crossbred, Eng Sett = English Setter, B.Collie = Border Collie, Rott. = Rottweiler, Dobe. = Dobermann, G.S.D.X = German Shepherd Dog Crossbred, St.Poodle = Standard Poodle, J.R.T. =Jack Russell Terrier, O.E.S. = Old English Sheepdog, K.B.Terr. = Kerry Blue Terrier.
Previous Treatment:
Predn. = Prednisolone.
Voren Susp. = Voren Suspension [Boehringer Ingelheim Ltd] Dexamethasone.
PrLT = Predno-Leucotropin Tablets[BK Veterinary Products] Cinchophen, hexamine, Prednisolone.
PBZ = Phenylbutazone
Optic. = Opticorten Tablets 0.25 mg [Ciba-Geigy Agrochemicals] Dexamethasone.
Fluvet = Fluvet Tablets [Syntex Animal Health] Flumethasone.
A.S.A. = Acetylsalicylic acid [Aspirin]
Trial Treatment:
PLT = PLT Tablets [BK Veterinary Products] Cinchophen, Prednisolone.
PBZ = Flexazone Tablets 100mg [BK Veterinary Products] Phenylbutazone

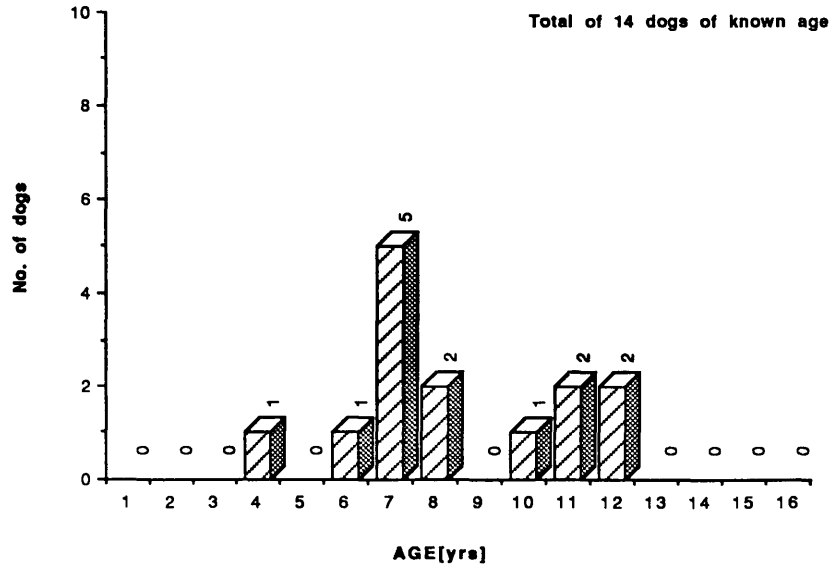
Age Distribution of PLT Trial Osteoarthritis Cases



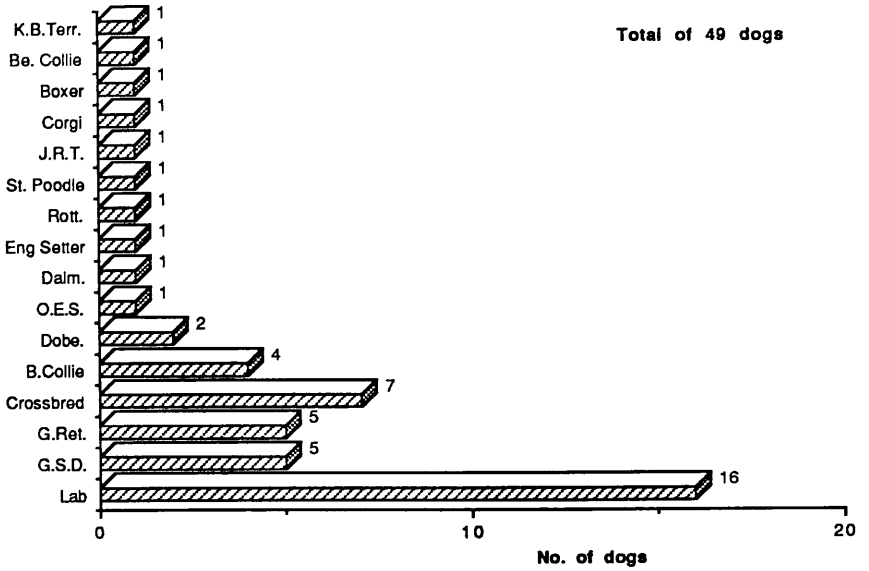
Age Distribution: PLT Treated Dogs



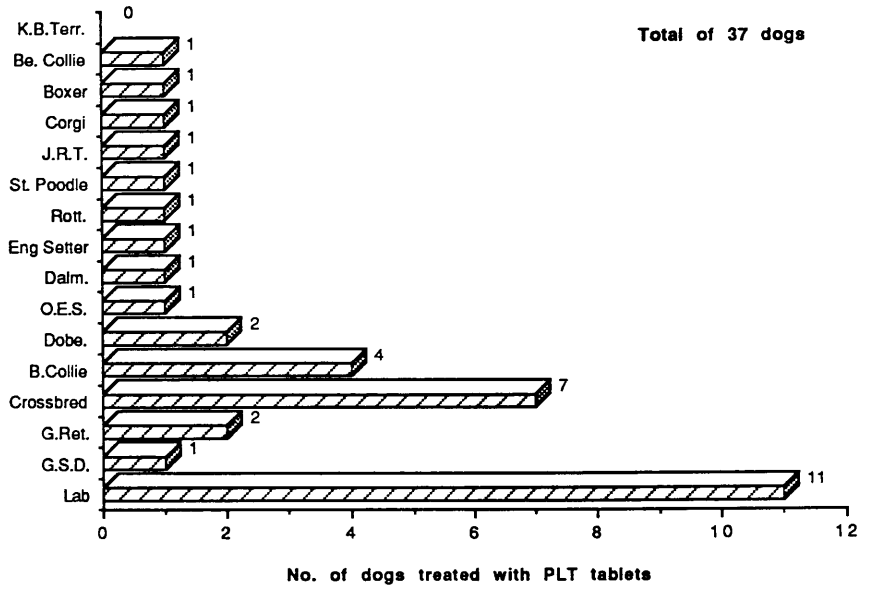
Age Distribution: PBZ Treated Dogs



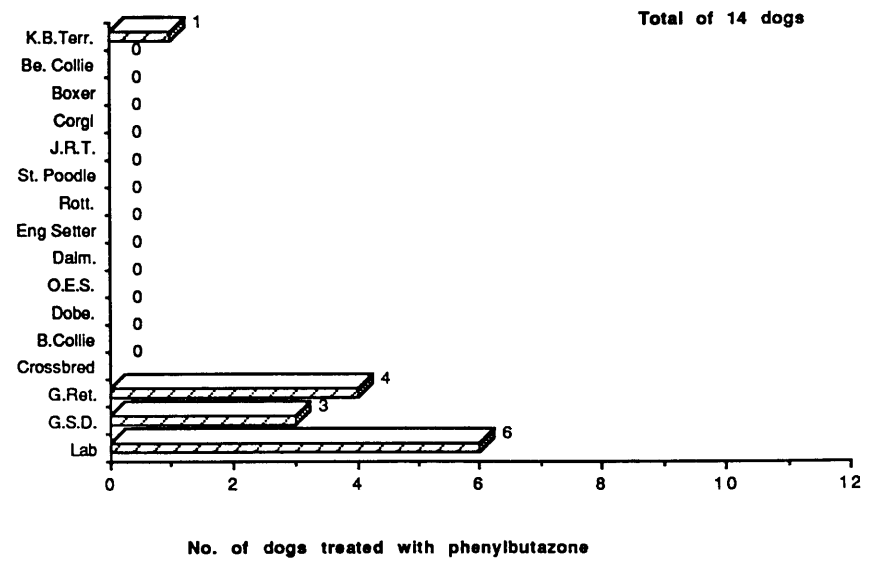
Breed Distribution: Osteoarthritis Cases



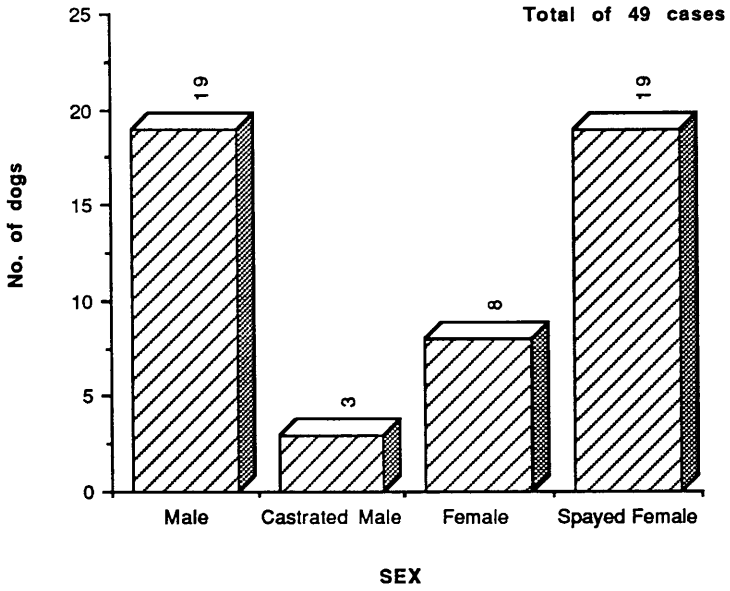
Breed Distribution: PLT Treated Dogs



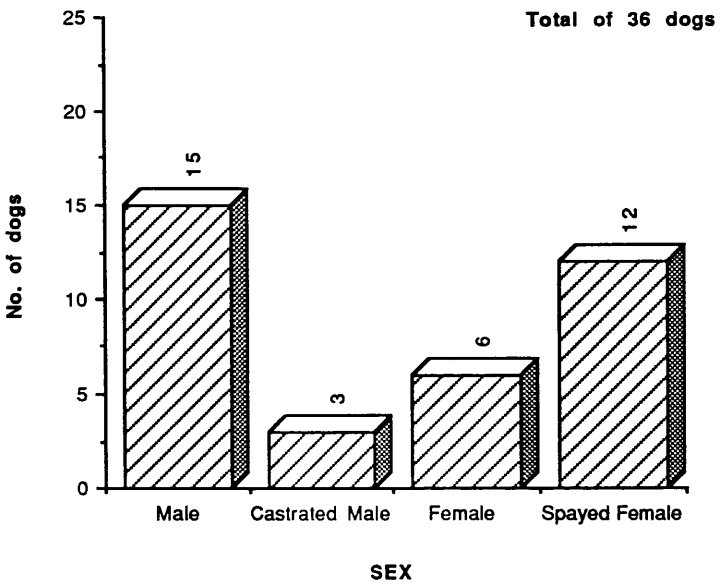
Breed Distribution: Phenylbutazone Treated Dogs



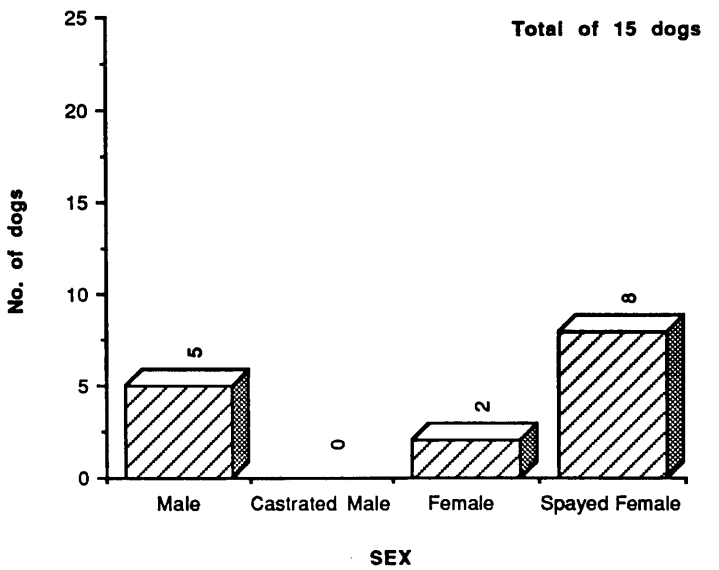
Sex Distribution: Osteoarthritis Cases



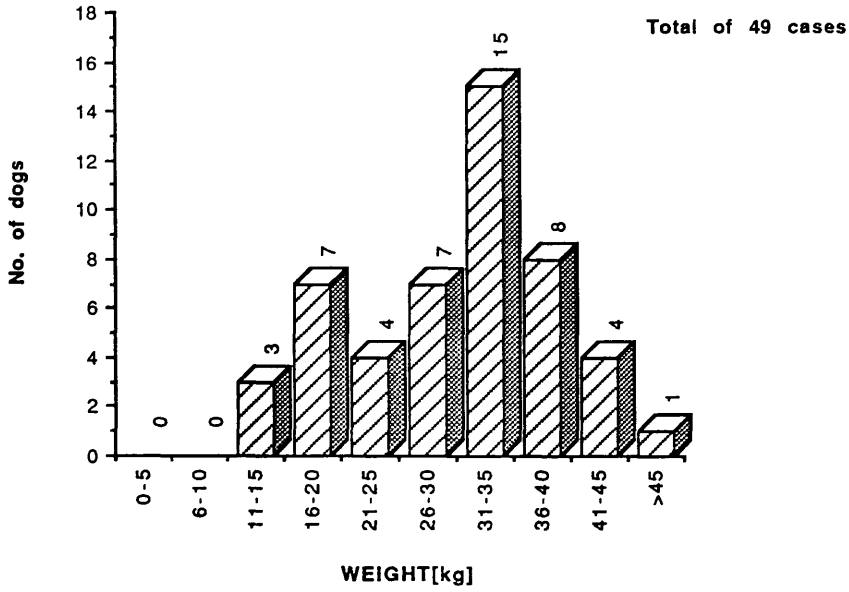
Sex Distribution: PLT Treated Dogs



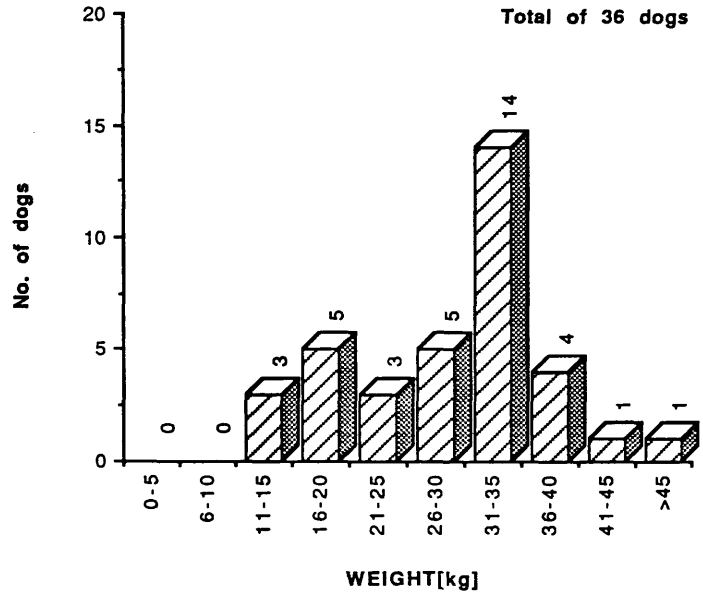
Sex Distribution: Phenylbutazone Treated Dogs



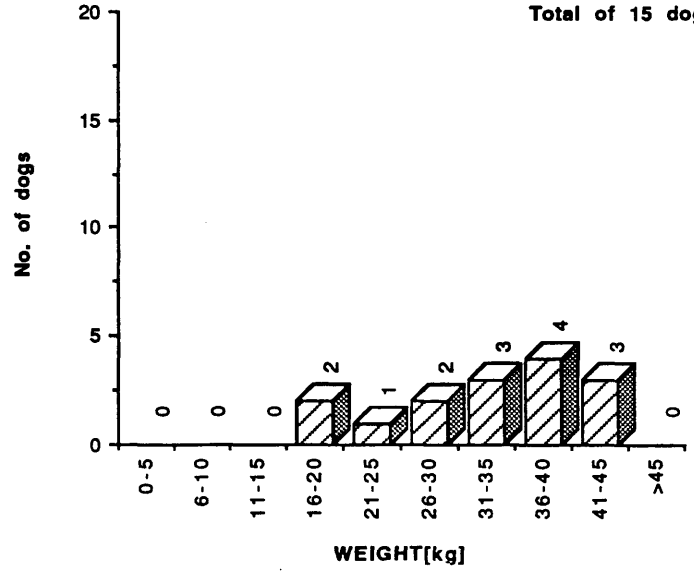
Weight Distribution: Osteoarthritis Cases



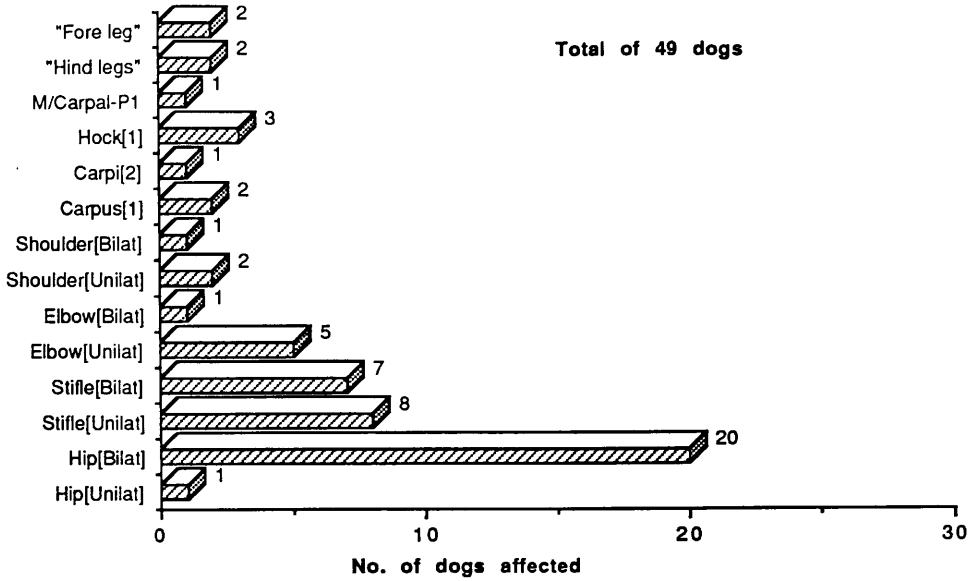
Weight Distribution: PLT Treated Dogs



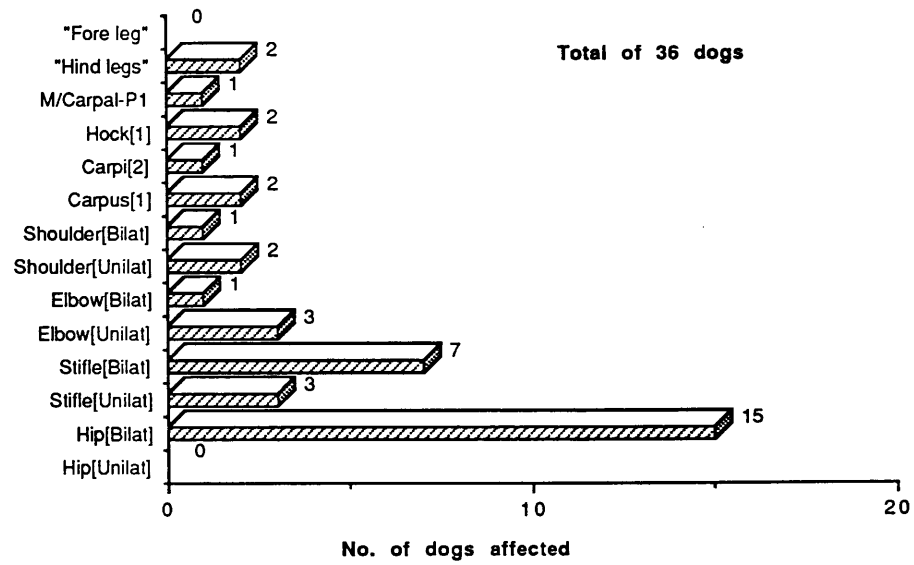
Weight Distribution: Phenylbutazone Treated Dogs



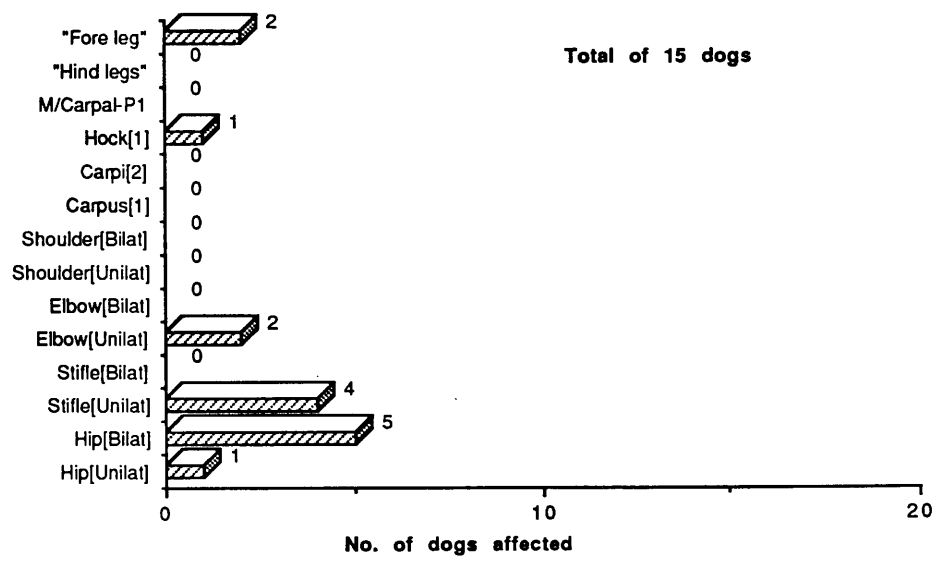
Joints Affected in All Osteoarthritis Cases



Joints Affected: PLT Treated Dogs



Joints Affected: Phenylbutazone Treated Dogs



Clinical Osteoarthritis Cases: Joints Affected and Known History

CASE NO.	JOINT[S] AFFECTED	BRIEF HISTORY IF GIVEN
1	HH S	Arthritis for several months. No previous treatment.
2	HH	No history given. 14 months of prednisolone treatment.
3	HH	Chronic arthritis. Gradual onset over 3 years. Also C.D.R.M.
4	HH	Gradual onset stiffness especially after resting. Worsened with recent febrile illness.
5	SS	Right stifle A.C.L. rupture and sugical replacement 12/86. Left stifle arthritis and cranial instability developing over 7 months.
6	SS	Surgery for A.C.L. rupture on both stifles 1983 and 1985.
7	S	A.C.L. rupture repair and medial meniscectomy. Also Hip Dysplasia.
8	sh	R.T.A. Lame left fore plus proprioceptive deficit. ?Brachial plexus injury.
9	Spine	"Spondylitis"
10	E	Acute exas erbation of chronic O.A. Radiographic confirmation.
11	HH	Gradually increasing stiffness in hind quarters.
12	Hock	Swollen left hock. Lameness, stiffness after exercise, history of injury as a puppy.
14	HH	Especially right hip. Very bad Hip Dysplasia. Gradual onset lameness in right hind. Sudden onset collapse.
15	Digit V	Acute onset lameness 3 days ago. Localised to Digit V, Phalanx 1.
16	H	Hind leg lameness/weakness for 1 year. Radiographic confirmation of Hip Dysplasia 4/88. Predno-Leucotropin treatment since 4/88.
18	HH	Right hip worse than left. Increasing stiffness over last 6 months,
19	HH	Especially left.
20	HH	Severe hip dysplasia since a few weeks old.
21	HHSS	Arthritic hips and stifles. Radiographic confirmation.
22	SS	An overweight dog with arthritic stifles.
23	Hind legs	No history. Long term medical therapy.
24	HH	Also severe pruritis.
25	SS	Bad conformation. One stifle A.C.L. rupture and surgical replacement.
26	Hind legs	Pain in back legs and spine.
27	HH	7 year history of Hip Dysplasia. Long term therapy with PBZ & Prednisolone.
29	Carpus	Carpal valgus and crepitation.
30	E	Long standing O.A. of left elbow.
31	HH	Increasing stiffness since 9/86. Pain/stiffness on rising.
32	HH	Worsening over 6 months.
33	HH	Always been overweight. Recently unwilling to walk as much.
34	HH	Stiffness and slight discomfort.
36	E	6/88 Slight stiffness. N.A.D. on examination. 9/88 detected stiffness in elbow. Slowly deteriorating.
37	S [HH?]	Stiff on rising. Unable to jump into car.
38	sh	Lame for 2 months. Worse on exercise.
41	shshEECCHH	Longstanding Hip Dysplasia. Responded well to PBZ in 1985. 9/88 presented with severe forelimb stiffness.
42	HH [S?]	Stiff and mild ataxia.
43	Hock	Old R.T.A.
44	shC	Right fore intermittent lameness for 7 years.
45	S	OA. Problem for last 4 days.
46	Metacarpal-P1	Cut foot stitched 12/88. Pain increased by 29/12. Arthritic changes in joint confirmed by radiography.
47	SS	Gradual lameness in both hind legs for 1 year. Crepitus in both stifles.
48	Hock	5/87 swollen and painful. Radiography: severe O.A. changes. 18 months PrLT. Lame at presentation.
49	E HH	11/88 Pain in fore leg. Reluctant to walk.? hips also affected.
50	SS	Left stifle A.C.L. rupture and repair 1982.
51	S	Chronic lameness
52	Right fore	"Limping on right fore for 6 months. All joints in leg"
53	Right fore	Lame for 14 days. Chronic problem.
54	HH	R.T.A. some years ago. 6 months hip pain and stiffness.
55	S	Lame after rest for two weeks. Radiography: marked arthritis.
56	S	Gradual onset lameness from 9/88. O.A. confirmed on radiography.
57	E	Slight lameness left fore increasing since 10/87.
58	S	Stiff left hind after rest for 4 months. No stifle instability reported.

Key overleaf

Key:

H = Unilateral hip; HH = Bilateral hip; S = Unilateral stifle; SS = Bilateral stifle; E = Unilateral elbow; EE = Bilateral elbow; sh = Unilateral shoulder; shsh = Bilateral shoulder; C = Carpus; CC = Carpi; P1=Phalanx 1.

C.D.R.M. = Chronic Degenerative Radiculo-Myelopathy
A.C.L. = Anterior (Cranial) Cruciate Ligament
O.A. = Osteoarthritis
PBZ = Phenylbutazone
PrLT=Predn-Leucotropin®
NAD = No Abnormalities Detected
R.T.A. = Road Traffic Accident

PLT Treatments:

CASE NO.	Dosage[mg/kg/day] Cinch.	Pred.	Regime	Duration [days]	Other advice	Other disease/treatment
1	20.0	0.10	tid	28	Restrict exercise	-
2	22.8	0.11	bid	5	Restrict exercise	-
5	22.8	0.11	bid	14	Rest	-
6	10.0	0.05	sid	14	Reduce weight	-
12	22.8	0.11	bid	5	Reduce weight	-
	16.5	0.08	bid	5	Reduce exercise	-
	8.8	0.04	bid	5		-
18	22.9	0.11	bid	14	Reduce weight	-
19	22.9	0.11	bid	3	Reduce weight	-
	11.4	0.06	bid	4*	" "	
20	20.0	0.10	bid	21	Normal exercise	-
21	11.4	0.06	bid	14	Normal exercise	Pruritis
22	17.1	0.09	tid	7	-	-
23	16.0	0.08	bid	12	-	-
24	20.0	0.10	tid	7	-	-
	13.3	0.07	bid	7	-	-
25	11.4	0.06	bid	7	Increase exercise slowly	-
26	22.2	0.11	bid	8	-	-
27	20.0	0.10	bid	7	-	-
29	13.3	0.07	tid	7	Reduce weight	-
30	20.0	0.10	bid	28	-	Pevidine baths-dermatitis
31	26.7	0.13	bid	14	Freq. short walks	-
32	22.9	0.11	bid	14	Reduce weight	Mild "stroke" 4wks ago Bilateral cataracts
33	30.8	0.15	bid	14	Reduce weight	-
34	14.8	0.07	bid	14	Lead exercise	-
37	20.0	0.10	bid	12	Normal exercise	Metronidazole-Gingivitis
38	46.2	0.23	tid	7	Reduce exercise	-
	30.8	0.15	bid	7	" "	-

* Treatment withdrawn because of vomiting

PLT Treatments:

CASE NO.	Dosage[mg/kg/day] Cinch.	Pred.	Regime	Duration [days]	Other advice	Other disease/treatment
41	20.0	0.10	bid	14	-	-
42	21.4	0.11	tid	10	Normal exercise	Theocardin 1 tid
	14.3	0.07	bid	28	" "	"
43	11.4	0.06	bid	14	Limited exercise	-
44	12.1	0.06	bid	45	Regular short walks	Diarrhoea at 6 weeks PLT - Kaobiotic, Buscopan.
45	22.9	0.11	qid	14	Diet advised. Walking exercise only.	-
	11.4	0.06	bid	NS	""	-
46	20.0	0.10	bid	10	Rest	-
	10.0	0.05	sid	50	Increase exercise	-
47	21.6	0.11	bid	21	Lead exercise Reduce weight	-
49	8.0	0.04	sid	90	Reduce excessive exercise	-
50	17.1	0.09	tid	10*	-	-
56	25.0	0.13	bid	42	Restrict exercise	-
57	16.0	0.08	bid	10	Walking exercise	-

* Treatment withdrawn because of vomiting

Phenylbutazone Treatments:

CASE NO.	Dosage [mg/kg/day]	Regime	Duration [days]	Other advice	Other disease/treatment
3	8.9	bid	14	Reduce weight	C.D.R.M.
4	8.9	bid	14	-	Cotrimoxazole - U.T.Inf.
11	8.8	bid	14	Reduce exercise Reduce weight	-
14	10.0	tid	14	Diet control	-
16	10.0	bid	3*	-	-
36	10.0	bid	14	Lead exercise	-
48	8.3	bid	42	Lead exercise	-
51	7.5	tid	14	Reduce weight	-
52	5.0	bid	14	Diet and rest	-
53	10.0	bid	14	Rest	-
54	5.0	sid	18	Reduce exercise	Flea dermatitis: Insecticidal Spray ev. 10d
55	8.0	bid	60	Restrict to walking exercise. Reduce weight.	-
58	6.3	sid	14	Reduce exercise Reduce weight	-

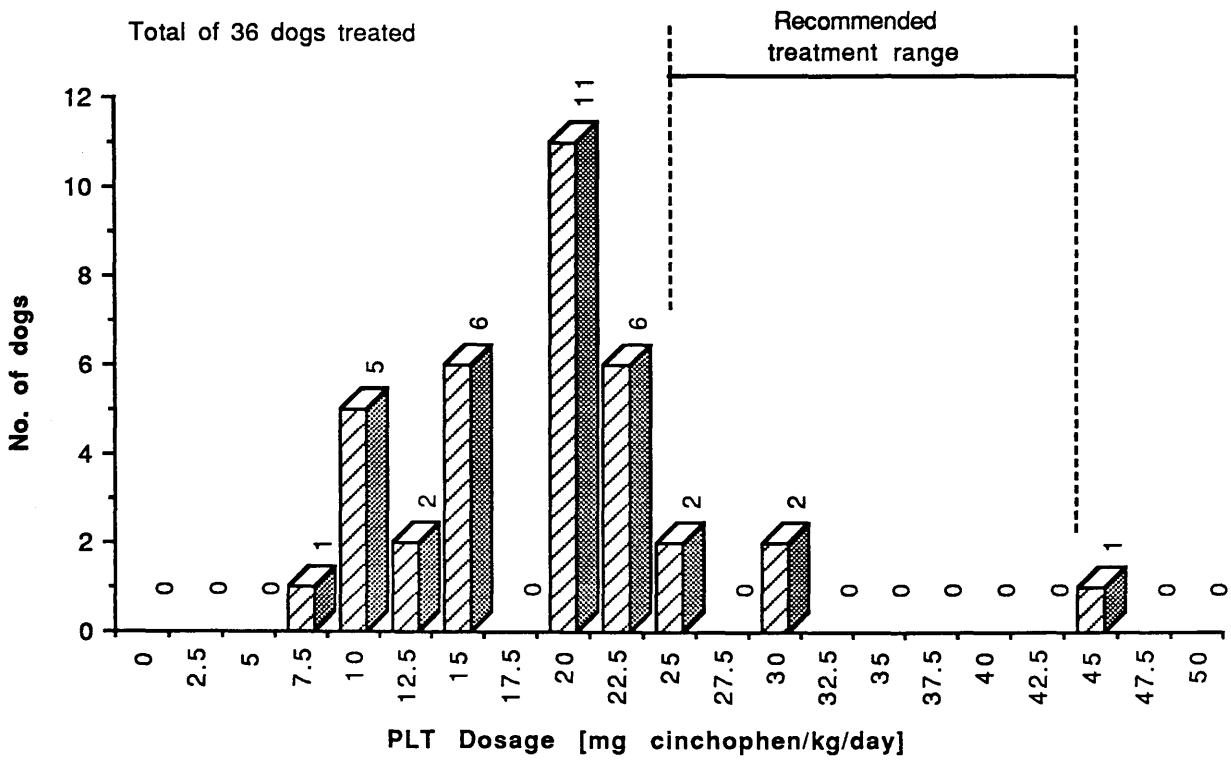
* Treatment withdrawn because of vomiting, inappetance and dullness.
C.D.R.M. = Chronic Degenerative Radiculo-Myelopathy
U.T.Inf. = Urinary tract infection

PLT and Phenylbutazone Treatments:

CASE NO.	Treatment	Dosage [mg/kg/day]	Regime	Duration [days]	Other advice
7	PLT	Cinch. 22.9 Pred. 0.11	bid	14	Reduce weight & light exercise
	PBZ	11.4	bid	14	" " " "
10	PBZ	8.5	tid	14	Lead exercise
	PLT	Cinch. 22.7 Pred. 0.11	bid	5	" "
		Cinch. 11.4 Pred. 0.06	bid	5	" "
		Cinch. 5.7 Pred. 0.03	sid	5	" "

[No other diseases or treatments in these two dogs]

Initial PLT Dose Rates [mg cinchophen/kg/day]



PLT Treatment: Effect on Condition Scores

Case no.	Lameness			Weightbearing			Joint Mobility			Stiffness		
	Pre	Post	Diff	Pre	Post	Diff	Pre	Post	Diff	Pre	Post	Diff
1 [30d]	3	1	2	1	0	1	1	1	0	3	1	2
2 [6d]	4	4	0	1	1	0	0	0	0	4	4	0
5 [17d]	3	2	1	0	0	0	0	0	0	2	0	2
6 [17d]	2	0	2	0	0	0	1	0	1	2	0	2
7 [14d]	2	0	2	1	1	0	1	0	1	3	0	3
10[21d]	4	0	4	0	0	0	2	2	0	3	1	2
12[37d]	3	1	2	1	0	1	2	1	1	3	0	3
18[15d]	1	0	1	0	0	0	1	1	0	3	1	2
19[21d]	1	1	0	0	0	0	1	1	0	3	3	0
20[7d]	1	1	0	0	0	0	0	0	0	1	1	0
21[14d]	0	0	0	0	0	0	0	0	0	0	0	0
22[7d]	1	1	0	0	0	0	0	0	0	0	0	0
23[12d]	2	0	2	0	0	0	0	0	0	2	0	2
24[14d]	4	1	3	1	0	1	2	0	2	4	1	3
25[7d]	4	0	4	0	0	0	0	0	0	1	0	1
26[8d]	1	0	1	0	0	0	0	0	0	3	0	3
27[7d]	0	0	0	1	0	1	0	0	0	3	0	3
29[7d]	4	1	3	0	0	0	0	0	0	4	1	3
30[28d]	3	1	2	1	0	1	1	1	0	3	1	2
31[14d]	0	0	0	0	0	0	2	2	0	4	2	2
32[18d]	3	1	2	1	0	1	1	1	0	3	2	1
33[14d]	1	1	0	0	0	0	1	1	0	2	1	1
34[21d]	1	0	1	0	0	0	1	1	0	1	0	1
37[12d]	0	0	0	1	0	1	1	1	0	1	0	1
38[12d]	3	0	3	1	0	1	1	0	1	0	0	0
41[14d]	3	2	1	0	0	0	1	1	0	4	3	1
42[40d]	2	0	2	1	1	0	1	1	0	2	1	1
43[14d]	2	2	0	0	0	0	0	0	0	1	1	0
44[45d]	2	0	2	1	0	1	1	1	0	3	2	1
45[14d]	3	1	2	1	0	1	1	0	1	3	1	2
46[48d]	3	1	2	1	0	1	2	2	0	2	2	0
47[25d]	2	0	2	0	0	0	1	1	0	2	1	1
49[90d]	2	0	2	1	0	1	1	1	0	2	1	1
50[16d]	Treatment discontinued due to vomiting											
56[42d]	3	2	1	1	0	1	2	1	1	4	2	2
57[10d]	3	2	1	0	0	0	1	1	1	3	2	1

PLT Treatment: Overall Improvement

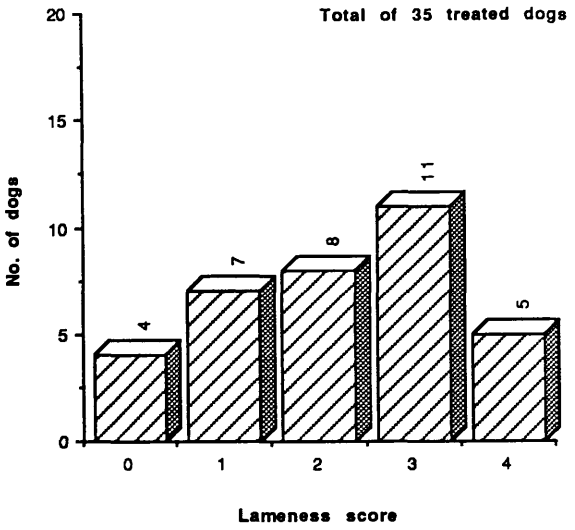
Case No.	Time for Improvement [days]	TOTAL SCORE Pre	Post	Diff	Improvement Rating -1	0	1	2	3
1 [30d]	-	8	3	5				•	
2 [6d]	-	9	9	0	•*				
5 [17d]	2	5	2	3				•	
6 [17d]	2-3	5	0	5					•
7 [14d]	2-3	7	1	6				•	
10[21d]	-	9	3	6				•	
12[37d]	-	9	2	7				•	
18[15d]	5	5	2	3				•	
19[21d]	-	5	5	0		•†			
20[7d]	-	2	2	0				•◊	
21[14d]	-	0	0	0					•◊
22[7d]	-	1	1	0				•◊	
23[12d]	2	4	0	4					•
24[14d]	3	11	2	9				•	
25[7d]	1	5	0	5					•
26[8d]	1	4	0	4				•	
27[7d]	-	4	0	4				•	
29[7d]	7	8	2	6			•		
30[28d]	short	8	3	5				•	
31[14d]	1	6	4	2				•	
32[18d]	7	8	4	4				•	
33[14d]	3	4	3	1			•		
34[21d]	<2	3	1	2			•		
37[12d]	2	3	1	2				•	
38[12d]	1	5	0	5				•	
41[14d]	-	8	6	2			•		
42[10d]	3	6	4	2			•		
43[14d]	-	3	3	0		•			
44[45d]	-	7	3	4				•	
45[14d]	7	8	2	6				•	
46[48d]	-	8	5	3				•	
47[25d]	2	5	2	3			•		
49[90d]	1	7	2	5				•	
50[16d]	Treatment withdrawn because of vomiting								
56[42d]	4	10	5	5				•	
57[10d]	-	7	5	2		•			

* Case 2: PLT treatment had no effect. Euthanased due to deteriorating condition.

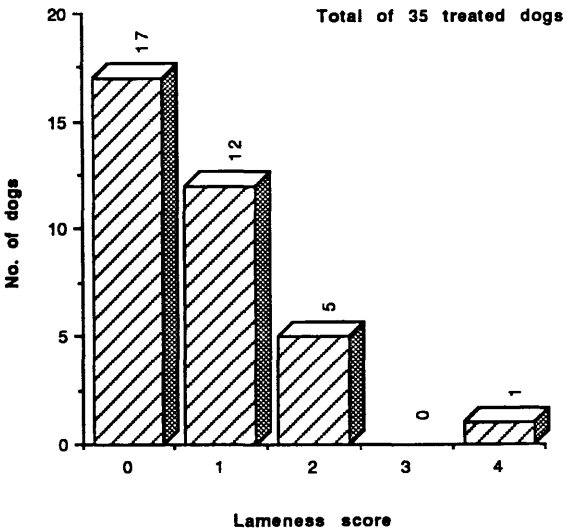
† Case 19: PLT treatment was withdrawn after 8 days because of persistent vomiting.

◊ Cases 20, 21 and 22 were switched from treatment with Predno-Leucotropin to PLT without the withdrawal of treatment. Clinical signs without treatment were therefore not assessed.

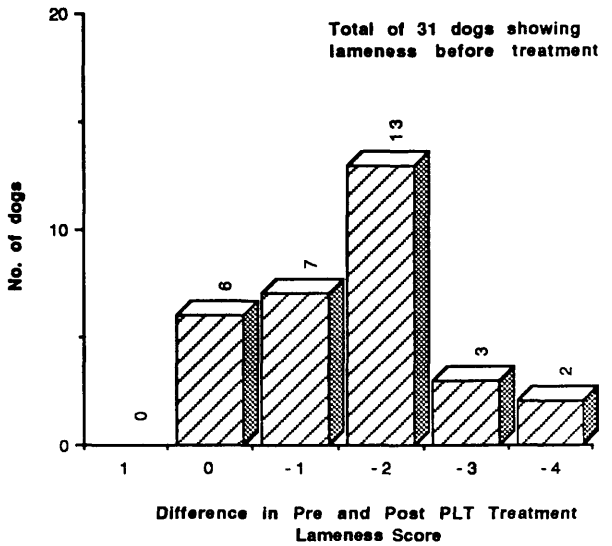
PLT Treated Dogs: Pre Treatment Lameness Scores



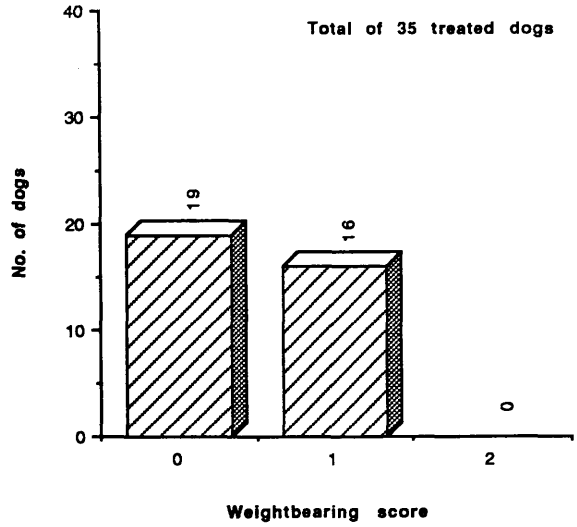
PLT Treated Dogs: Post Treatment Lameness Scores



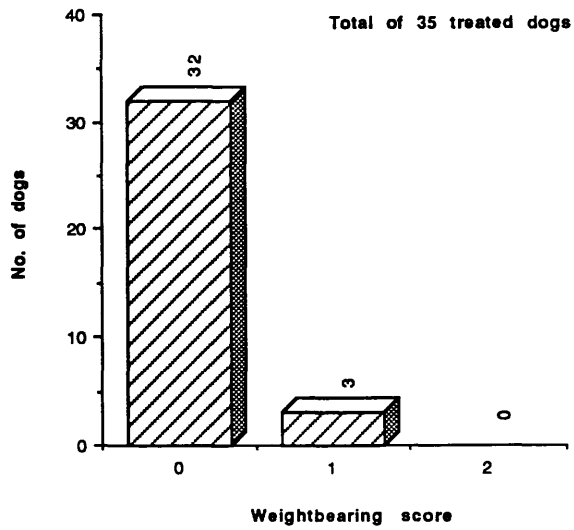
PLT Treated Dogs: Difference in Pre and Post Treatment Lameness Score



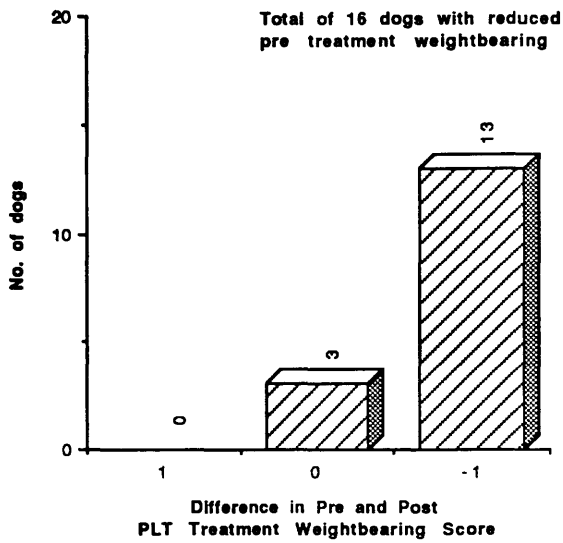
PLT Treated Dogs: Pre Treatment Weightbearing Scores



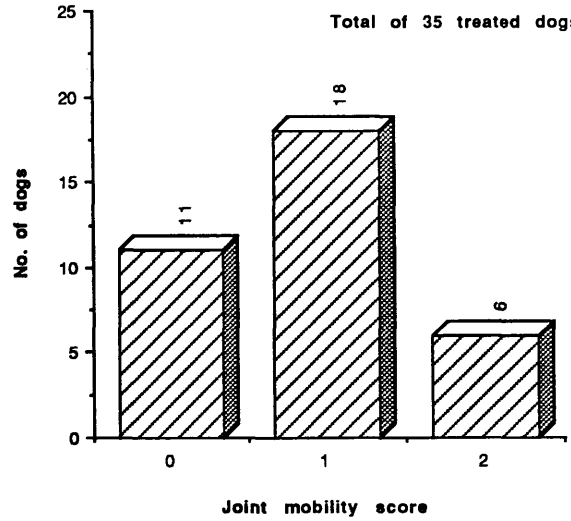
PLT Treated Dogs: Post Treatment Weightbearing Scores



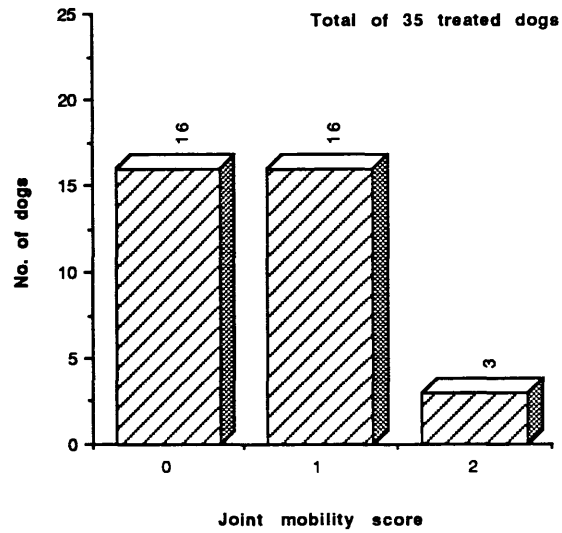
PLT Treated Dogs: Difference in Pre and Post Treatment Weightbearing Scores



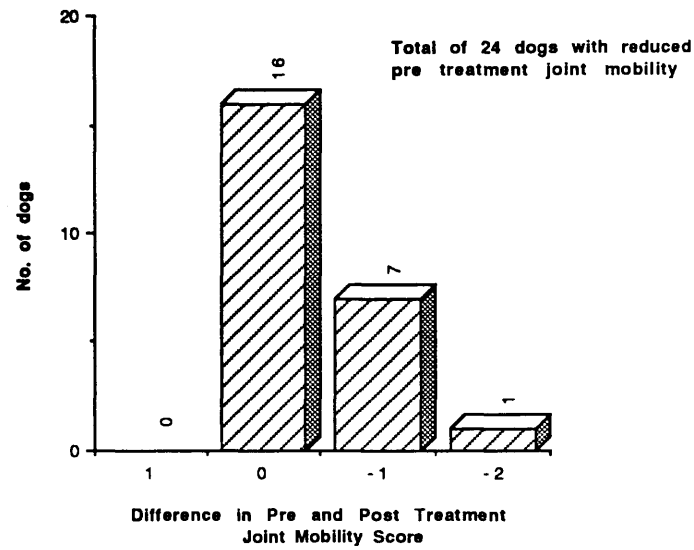
PLT Treated Dogs: Pre Treatment Joint Mobility Scores



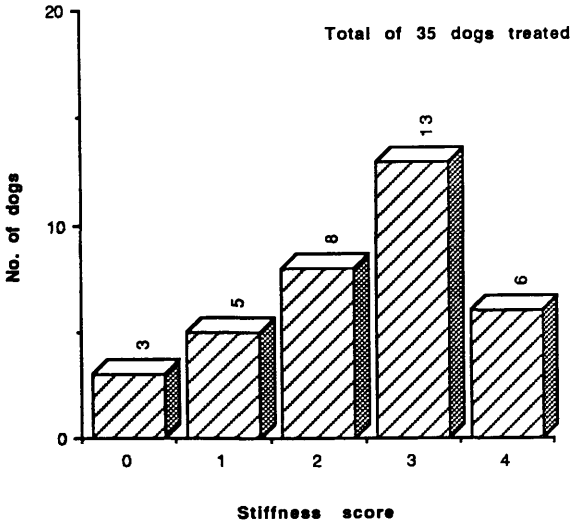
PLT Treated Dogs: Post Treatment Joint Mobility Scores



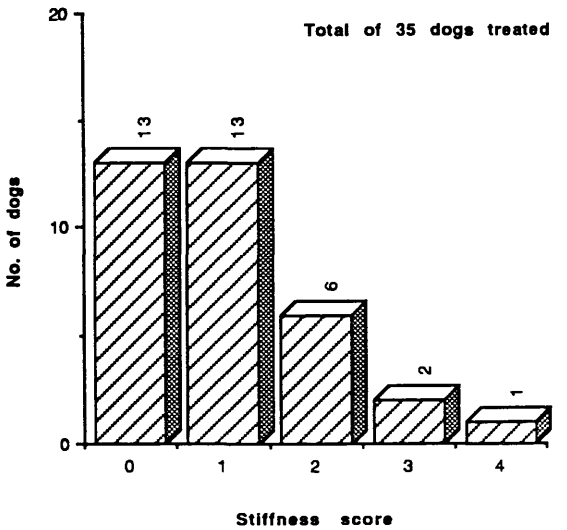
PLT Treated Dogs:
Difference in Pre and Post Treatment Joint Mobility Score



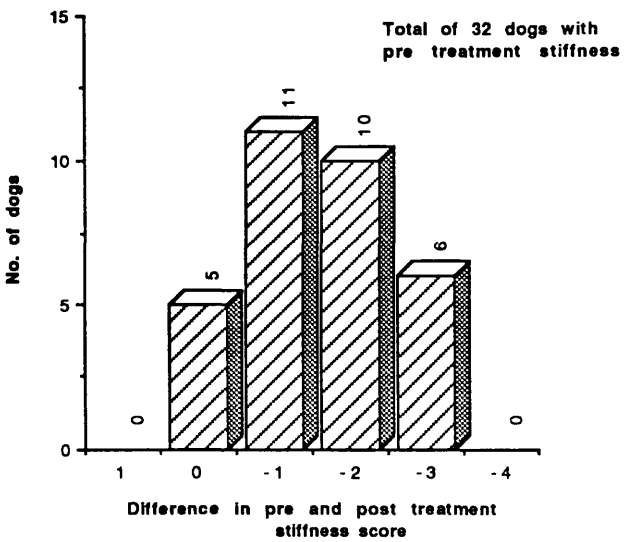
PLT Treated Dogs: Pre Treatment Stiffness Scores



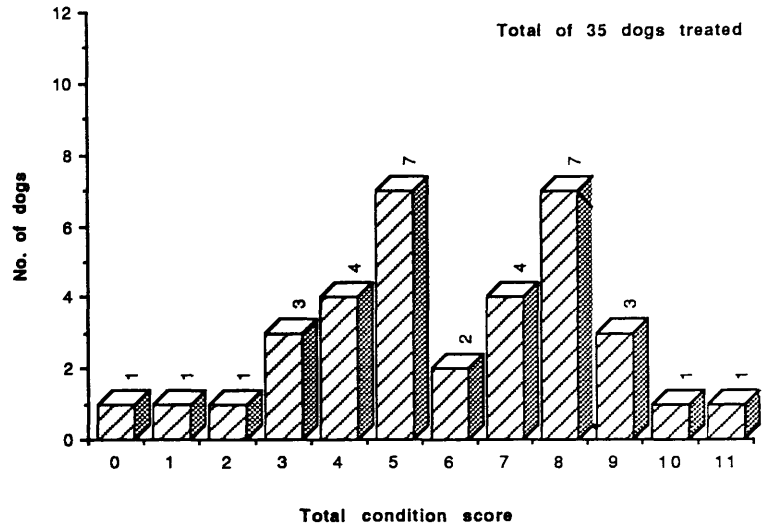
PLT Treated Dogs: Post Treatment Stiffness Scores



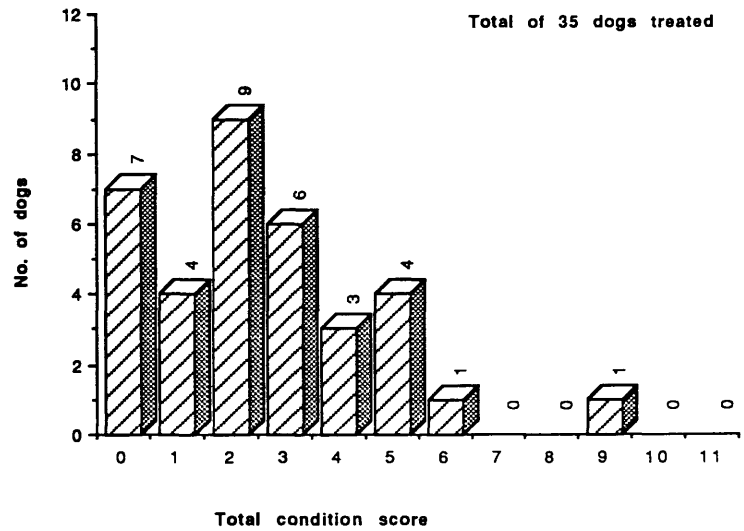
PLT Treated Dogs:
Difference in Pre and Post Treatment Stiffness Score



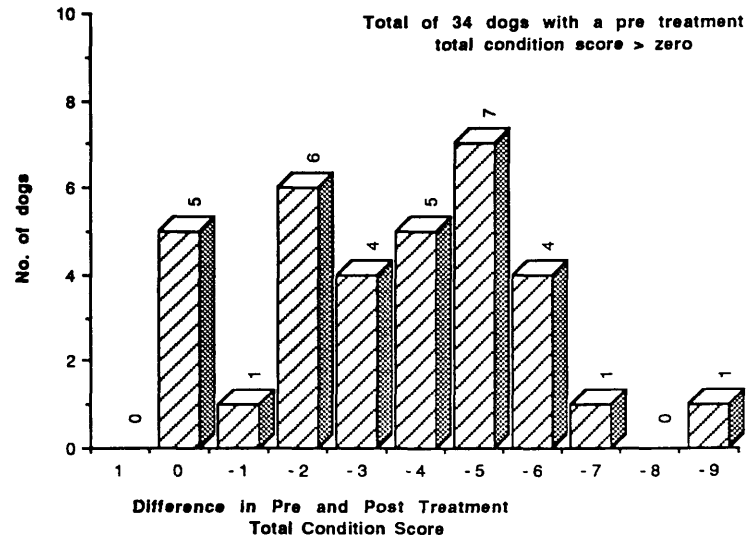
PLT Treated Dogs; Pre Treatment Total Condition Scores



PLT Treated Dogs; Post Treatment Total Condition Scores



PLT Treated Dogs: Difference in Pre and Post Treatment Total Condition Score



Phenylbutazone Treatment: Effect on Condition Scores

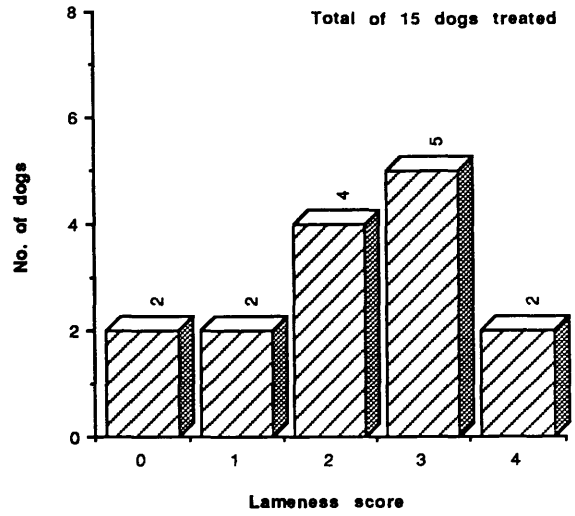
Case no.	Lameness			Weightbearing			Joint Mobility			Stiffness		
	Pre	Post	Diff	Pre	Post	Diff	Pre	Post	Diff	Pre	Post	Diff
3 [15d]	4	4	0	1	1	0	2	2	0	4	4	0
4 [14d]	1	0	1	1	0	1	2	1	1	3	0	3
7 [14d]	2	0	2	1	1	0	1	0	1	3	0	3
10[14d]	3	1	2	0	0	0	2	2	0	3	2	1
11[18d]	0	0	0	1	0	1	1	0	1	2	0	2
14[10d]	3	0	3	1	0	1	2	1	1	3	1	2
16[3d]	1	2	-1	0	0	0	1	1	0	2	2	0
36[14d]	3	3	0	2	1	1	2	2	0	0	0	0
48[42d]	4	2	2	2	1	1	2	2	0	4	2	2
51[14d]	2	1	1	1	0	1	2	1	1	3	1	2
52[14d]	3	1	2	1	0	1	1	0	1	2	1	1
53[14d]	2	1	1	1	0	1	0	0	0	2	1	1
54[18d]	0	0	0	0	0	0	1	1	0	2	1	1
55[28d]	2	1	1	0	0	0	1	1	0	3	1	2
58[14d]	3	1	2	1	0	1	1	0	1	3	1	2

Phenylbutazone Treatment: Overall Improvement

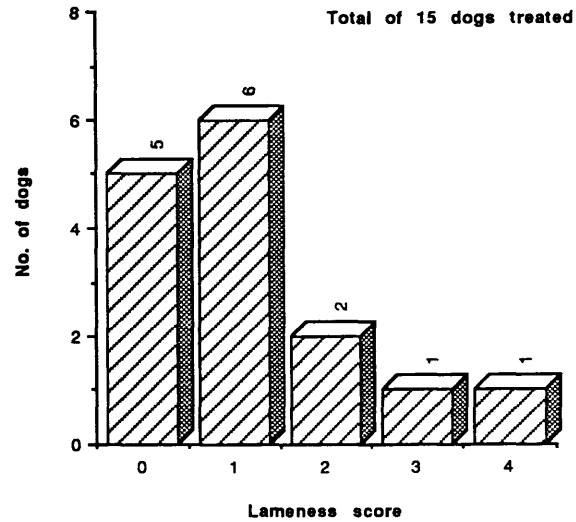
Case No.	Time for Improvement [days]	TOTAL SCORE			Improvement Rating				
		Pre	Post	Diff	-1	0	1	2	3
3 [15d]	-	11	11	0	•*				
4 [14d]	7	7	1	6				•	
7 [14d]	-	7	1	6				•	
10[14d]	-	8	5	3			•		
11[18d]	-	4	0	4					•
14[10d]	5	9	2	7				•	
16[14d]	-	4	5	-1	•†				
36[14d]	2	7	6	1				•	
48[42d]	10	12	7	5			•		
51[14d]	6	8	3	5			•		
52[14d]	4	7	2	5			•		
53[14d]	3	5	2	3				•	
54[18d]	2	3	2	1			•		
55[28d]	10	6	3	3			•		
58[14d]	2	7	3	4				•	

* Case 3: Deteriorated during treatment. Later euthanased.
† Case 16: Treatment withdrawn after 3 days because of vomiting, inappetance and dullness.

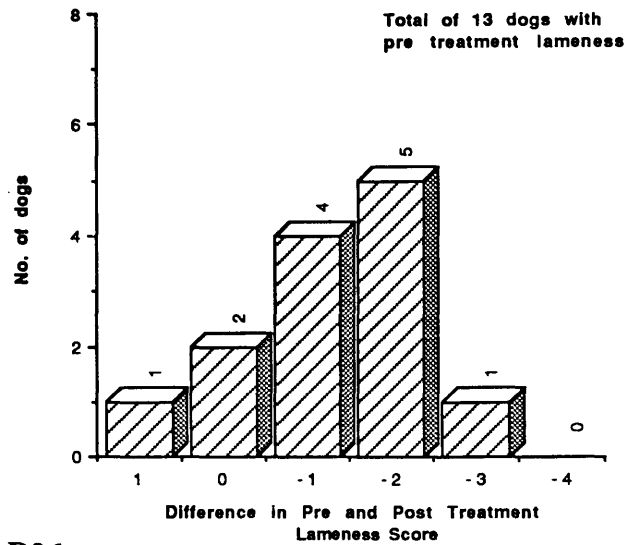
Phenylbutazone Treated Dogs: Pre Treatment Lameness Scores



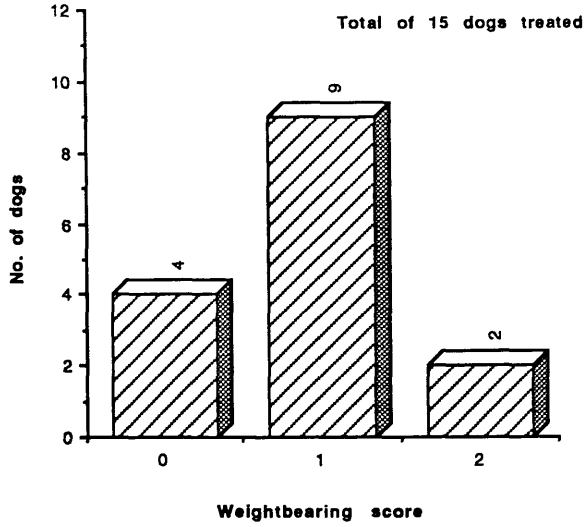
Phenylbutazone Treated Dogs: Post Treatment Lameness Scores



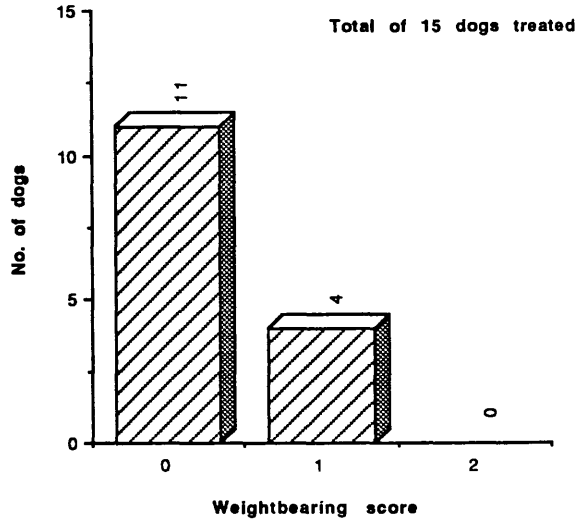
Phenylbutazone Treated Dogs: Difference in Pre and Post Treatment Lameness Score



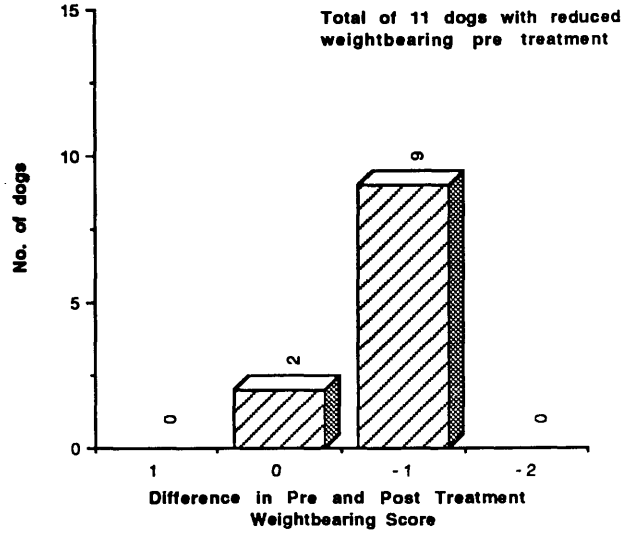
Phenylbutazone Treated Dogs:
Pre Treatment Weightbearing Scores



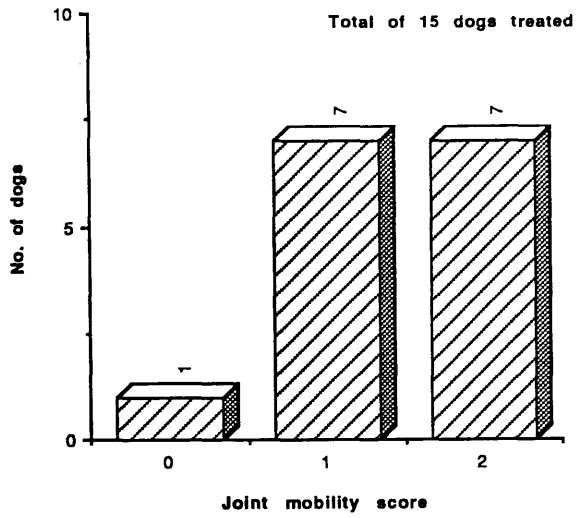
Phenylbutazone Treated Dogs:
Post Treatment Weightbearing Scores



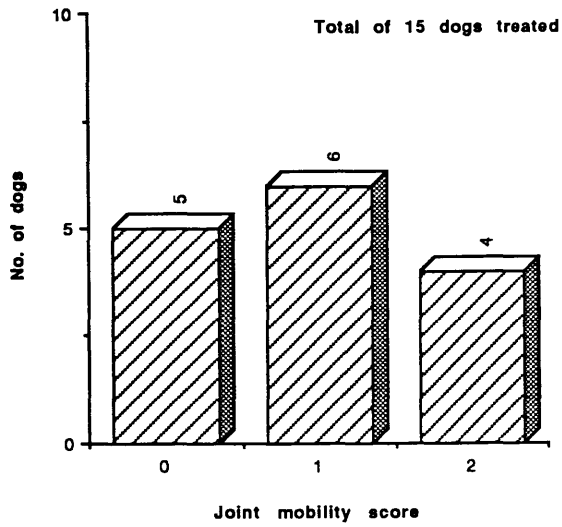
Phenylbutazone Treated Dogs: Difference in
Pre and Post Treatment Weightbearing Score



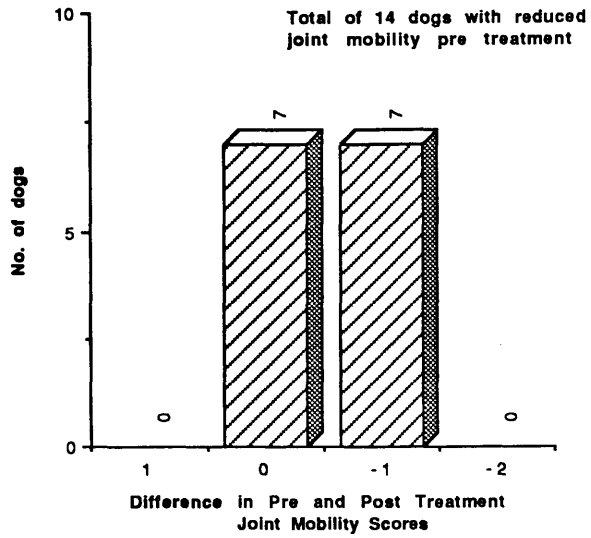
Phenylbutazone Treated Dogs:
Pre Treatment Joint Mobility Scores



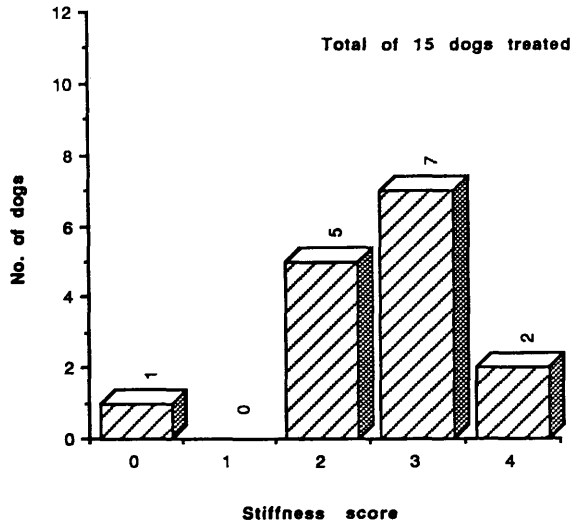
Phenylbutazone Treated Dogs:
Post Treatment Joint Mobility Scores



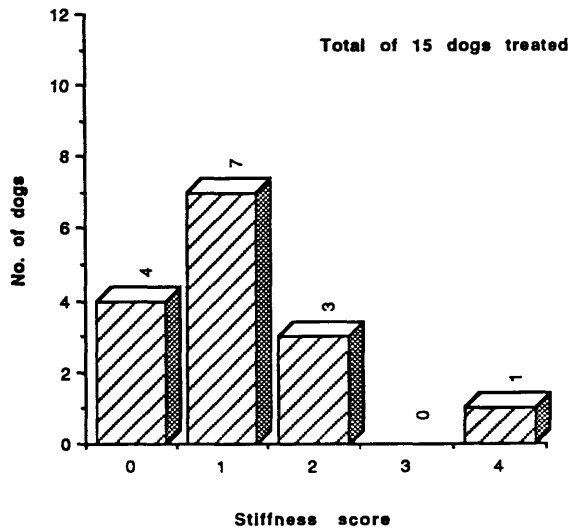
Phenylbutazone Treated Dogs: Difference in Pre and Post Treatment Joint Mobility



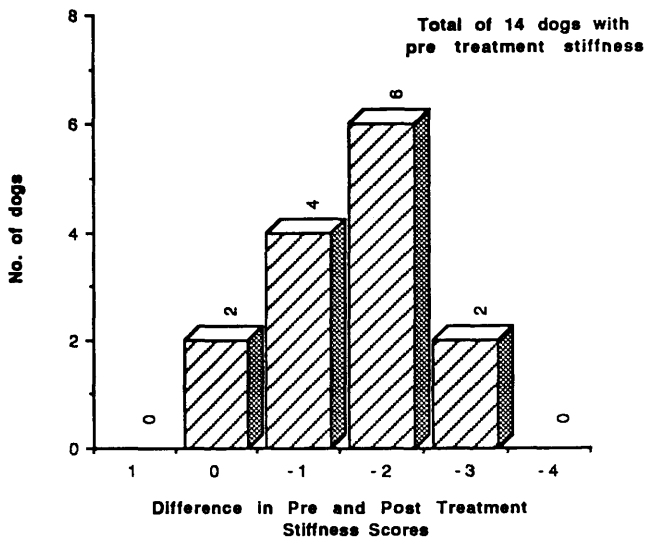
Phenylbutazone Treated Dogs:
Pre Treatment Stiffness Scores



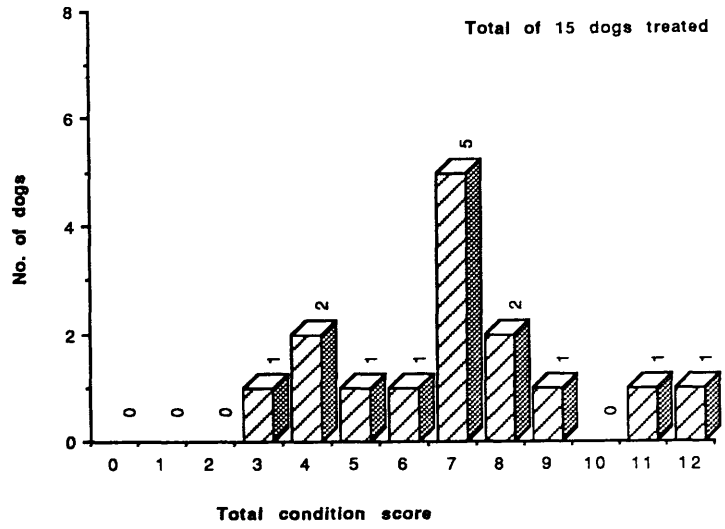
Phenylbutazone Treated Dogs:
Post Treatment Stiffness Scores



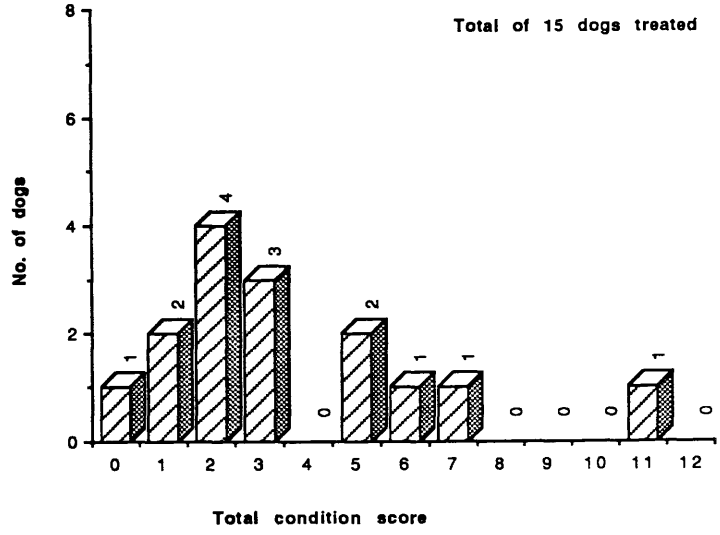
Phenylbutazone Treated Dogs: Difference in
Pre and Post Treatment Stiffness Score



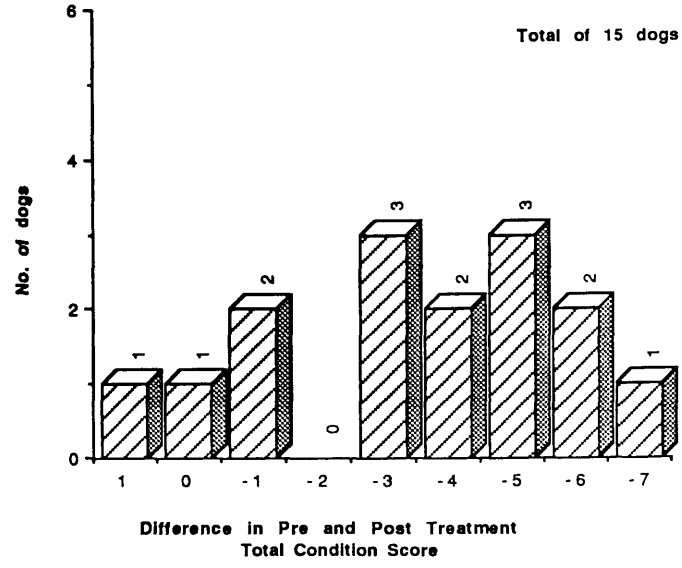
Phenylbutazone Treated Dogs:
Pre Treatment Total Condition Scores



Phenylbutazone Treated Dogs:
Post Treatment Total Condition Scores



Phenylbutazone Treated Dogs: Difference in
Pre and Post Treatment Total Condition Score

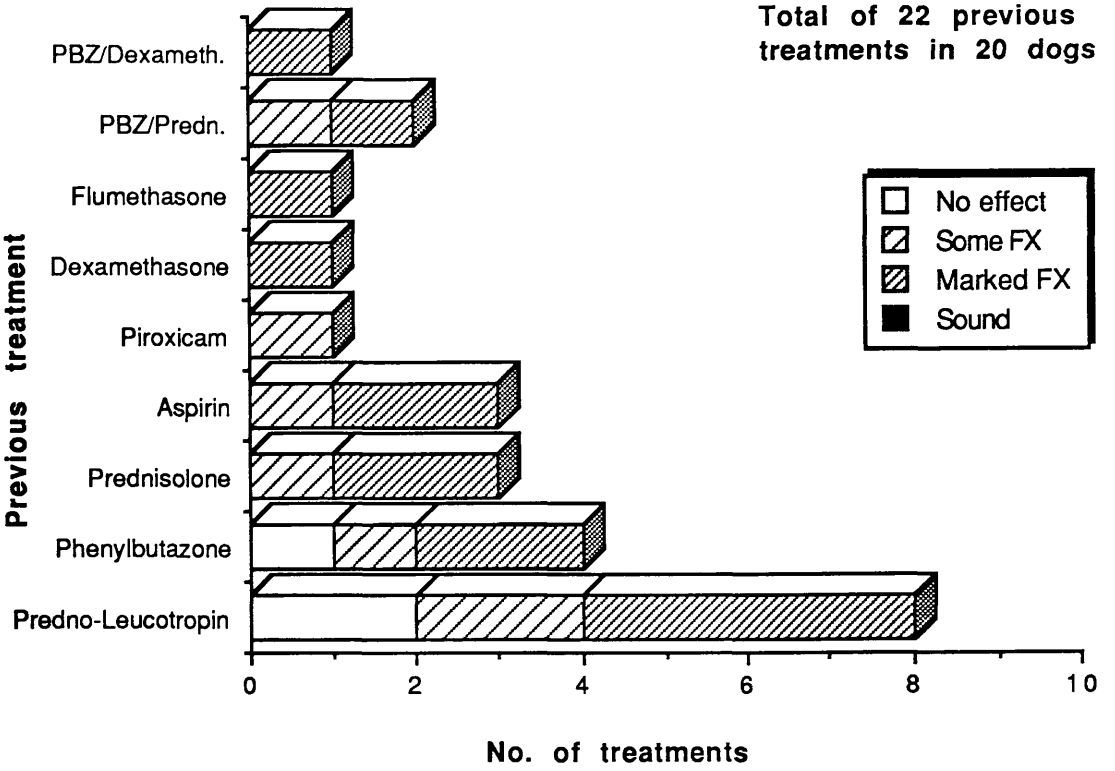


Previous Treatments and Effects:

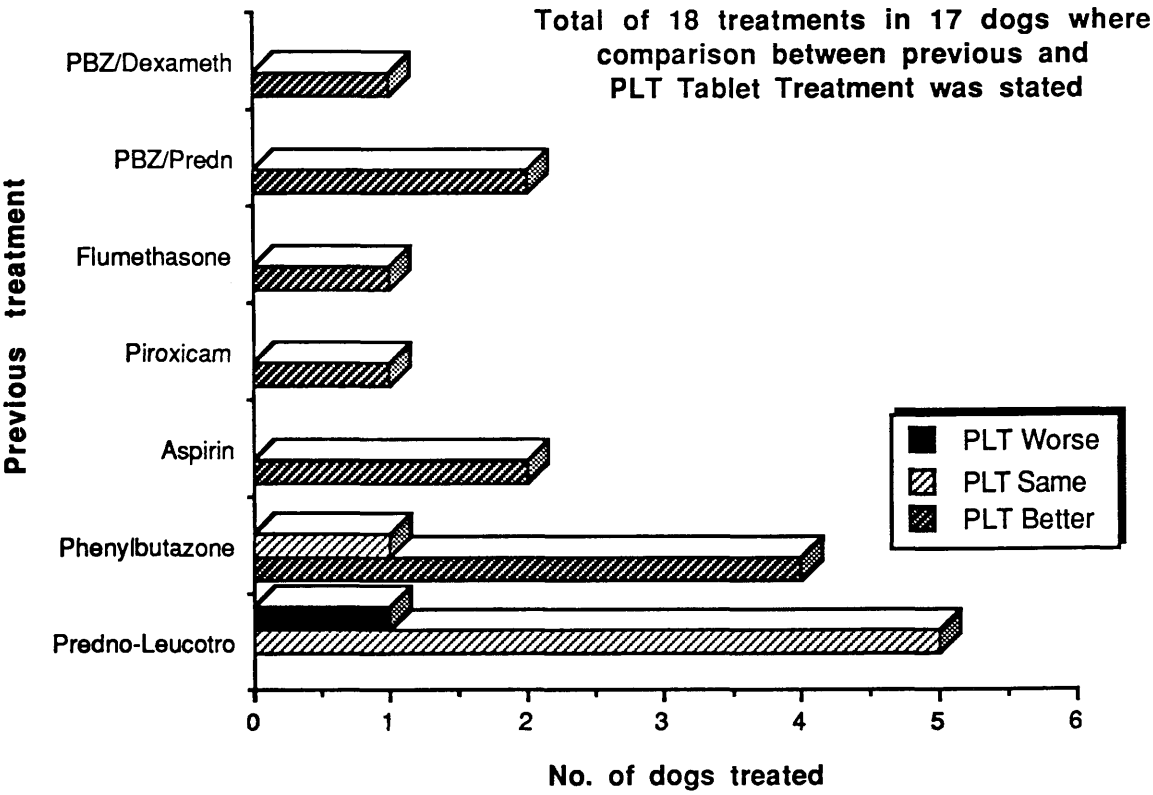
PREVIOUS TREATMENT

Case No.	Preparation/Drug	Dosage[mg/kg/day]	Recommendation	Duration	EFFECT
2	Prednisolone	0.14 e.o.d.	0.25-0.5	14 months	1
5	Piroxicam	0.57	0.3 e.o.d.	14 days	1
10	Voren Suspension [Dexamethasone]	[2mg] 0.056	1-2mg/dog	1 dose s/c	2
20	Predno-Leucotropin Tabs. Cinchophen 200mg	20	20 - 30	Constant	1-2
21	Predno-Leucotropin Tabs. Cinchophen 200mg	11.4	20 - 30	Constant	2
22	Predno-Leucotropin Tabs. Cinchophen 200mg	17.1	20 - 30	___	2
23	Phenylbutazone Opticorten [Dexamethasone]	12.0 0.01	2 - 20 0.05	Constant	2
24	Phenylbutazone	20	2 - 20	Constant	1
27	Phenylbutazone Prednisolone	15 0.25	2 - 20 0.25 - 0.5	Constant	1
30	Fluvet [Flumethasone]	0.0016 [1 tab]	0.5 - 4 tabs/dog	___	2
31	Phenylbutazone	13.3	2 - 20	6 months	2
36	Predno-Leucotropin Tabs. Cinchophen 200mg	26.7	20 - 30	___	0
	Aspirin	5	25	as requ.	2
37	Aspirin	10	25	___	1
41	Predno-Leucotropin Tabs. Cinchophen 200mg Prednisolone	20 0.10	20 - 30 0.1 - 0.15	4 months	1
	Phenylbutazone Prednisolone	15 0.19	2 - 20 0.25 - 5	2 weeks	1
44	Phenylbutazone	12	2 - 20	4 weeks	2
46	Predno-Leucotropin Tabs. Cinchophen 200 mg	20.0	20 - 30	30 days	2
48	Predno-Leucotropin Tabs. Cinchophen 200 mg	11.1	20 - 30	18 months	2 - 3
49	Aspirin	12 mg/kg as req.	25 ev. 8 hours	-	2
54	Predno-Leucotropin Tabs. Cinchophen 200 mg	20	20 - 30	14 days	0
56	Phenylbutazone	18.8	2 - 20	14 days	0
57	Predno-Leucotropin Tabs. Cichophen 200 mg	24	20 - 30	10 days	2
58	Phenylbutazone	6.3	2 - 20	14 days	2

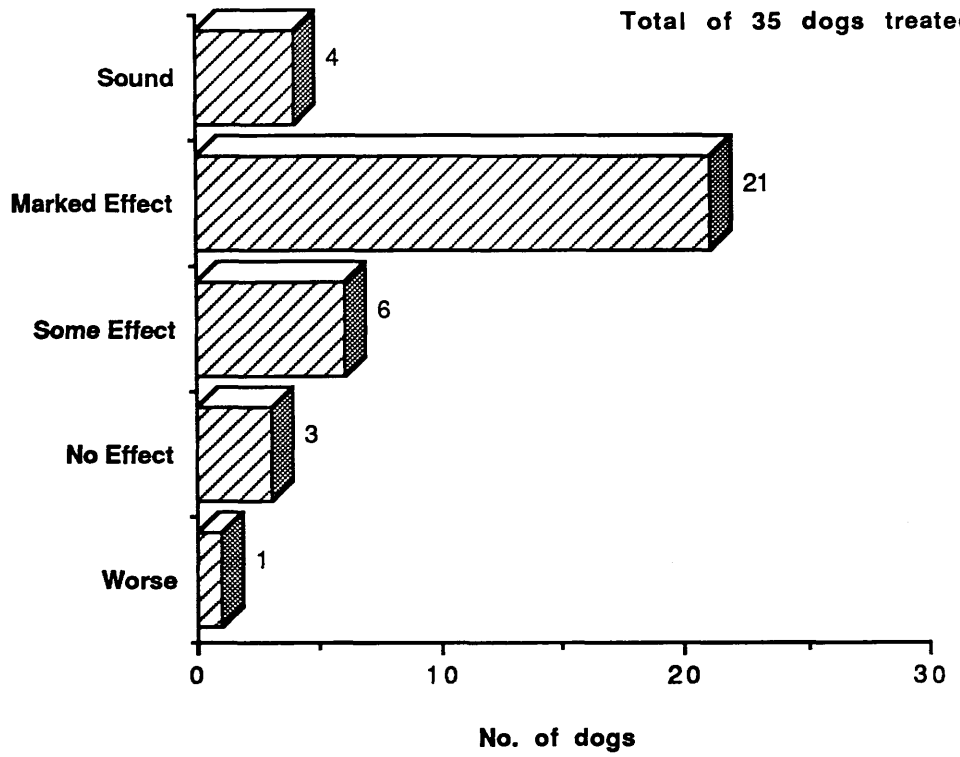
Previous Treatments and Their Effects



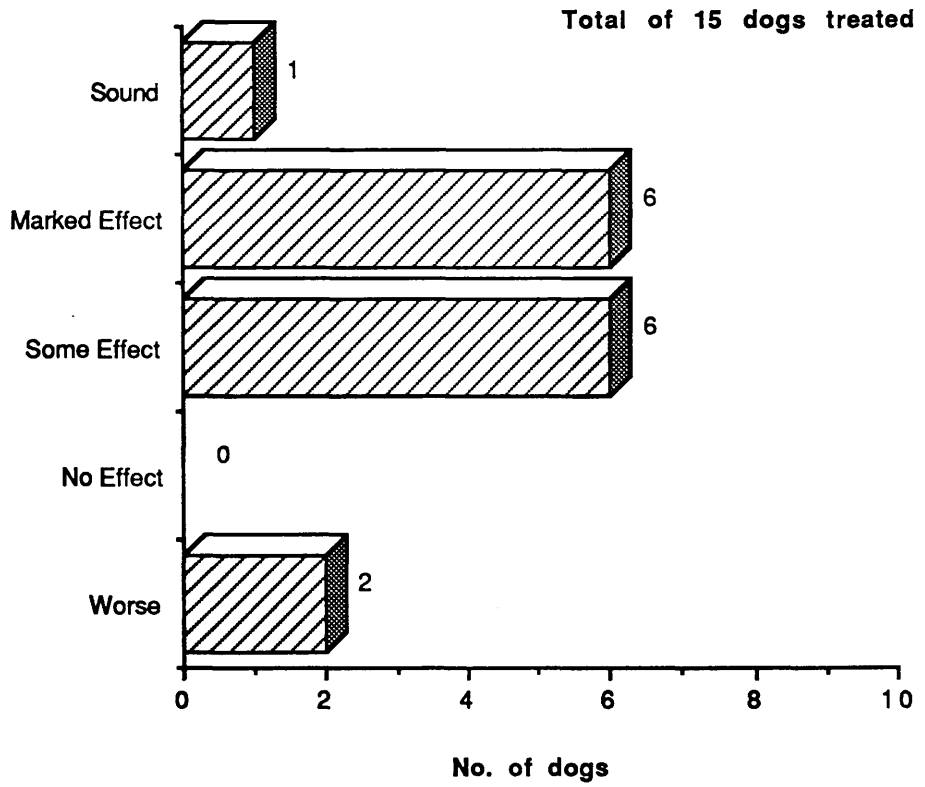
Comparison Between PLT Tablet Treatment and Previous Treatment Efficacy



PLT Treated Dogs: Overall Improvement Rating



Phenylbutazone Treated Dogs: Overall Improvement Rating



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Addendum

Note: **PLT Tablets** is the name used in the text for a new preparation containing cinchophen and prednisolone. The old preparation containing hexamine in addition to these compounds is called **Predno-Leucotropin Tablets** in this thesis although veterinarians and the manufacturers often use the abbreviation "**PLT**" to describe the product.