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A COMPARISON OF THE ANTIINFLAMMATORY ACTIVITY OF PIROXICAM AND ENTERIC-COATED ACETYLSALICYLIC ACID IN PATIENTS WITH RHEUMATOID ARTHRITIS

submitted by

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ABSTRACT

The antiinflammatory efficacy and side effects of a nonsteroidal antiinflammatory drug (NSAID), piroxicam, were compared to those of an enteric-coated formulation of acetylsalicylic acid, 'Entrophen', in patients with rheumatoid arthritis uncontrolled by their current NSAID therapy. Patients received both piroxicam and 'Entrophen' in a randomized, double-blind, crossover trial with 12 week treatment periods. Clinical evaluation of rheumatoid arthritis activity by grip strength measures, pain scale, duration of morning stiffness, erythrocyte sedimentation rate, articular index, and a composite systemic index, was unable to detect a difference in the efficacy of the two drugs in this population. Fewer, less severe side effects were reported during therapy with piroxicam as compared to 'Entrophen'. Responders to 'Entrophen' had a mean plasma salicylate level within the optimal antiinflammatory range; no relationship between drug level and response was detected for piroxicam.

ACKNOWLEDGEMENTS

The unfailing optimism and encouragement of Dr. W. McLean throughout this project were invaluable to its completion. Special thanks to Dr. R. McKendry for his interest in the project and confidence in my assessment of his patients.

The assistance of Dr. G. Anderson of the Department of Epidemiology, Faculty of Medicine, University of Ottawa, in statistical analysis of the data is acknowledged.

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LIST OF ABBREVIATIONS

BUN	blood urea nitrogen
°C	degrees centigrade
ESR	erythrocyte sedimentation rate
g	gram
G	gravity
hr	hour
kg	kilogram
L	litre
M	molar
mcg	microgram
mcg/mL	microgram per millilitre
mcm	micrometre
mg	milligram
mL	millilitre
mm	millimetre
mmHg	millimetres of mercury
N	normal
nm	nanometer
O.D.	optical density
%	percent
p	probability
r	Pearson's correlation coefficient
S.D.	standard deviation
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvate transaminase

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I. INTRODUCTION

Rheumatoid arthritis, a chronic inflammatory joint disease of unknown etiology, is rarely fatal, but the estimated three percent of the population who suffer from the disease frequently experience bone erosion and destruction which may result in disabling pain and joint deformities. Symptomatic relief of pain and inflammation, sometimes in conjunction with disease suppressants, remains the basis of therapy. For almost one hundred years, salicylates have maintained a preeminant position as the antiinflammatory drug of choice in rheumatoid arthritis, but dose-limiting side effects and complex pharmacokinetics prompted the search for an equally effective, but less troublesome agent, thus the inception and proliferation of a new class of drugs, the nonsteroidal antiinflammatory drugs (NSAIDs). Over the last decade, several have appeared on the market, each offering similar efficacy to acetylsalicylic acid (ASA) as the result of a common mechanism, but promising fewer side effects, and pharmacokinetic advantages of less complicated metabolism, or a longer half-life. One of the newest of these agents to be admitted to the Canadian market, piroxicam, has a pharmacokinetic advantage of a long half-life permitting once daily dosing, and a lower incidence of side effects than ASA. A comparison of the efficacy and side effects of piroxicam and 'Entrophen', an enteric-coated formulation of ASA, presently the NSAID of choice in Canada for rheumatoid arthritis, is necessary to establish the place of piroxicam in the therapeutic armamentarium of rheumatic disease.

II. REVIEW OF THE LITERATURE

A. RHEUMATOID ARTHRITIS AND PROSTAGLANDINS

Much of the pathogenesis of rheumatoid arthritis remains a mystery, but it is thought that in a host of appropriate genetic make-up an inciting factor stimulates an immune response which becomes localized to the synovial joints in a characteristic distribution. Synovial cell proliferation and immune complex formation herald the conversion of acute inflammatory changes to a chronic inflammatory process which relentlessly pursues a destructive course of bone erosion and subsequent joint deformity in a large number of patients.[1] Clinical manifestations of inflammation include stiffness, pain, joint swelling and tenderness to palpation, a weak grip strength, and loss of functional capacity.[2] Laboratory evidence of disease activity consists of relatively nonspecific correlates of inflammation such as an elevated erythrocyte sedimentation rate, alterations in acute phase reactants, anemia and lowered serum iron, and the presence of immunoglobulins specific for rheumatic disease.[3]

Although treatment has remained primarily symptomatic, aimed at reducing pain and inflammation with hopes of minimizing disease progression at an early stage, the discovery that NSAID's inhibit prostaglandin synthesis stimulated investigation of the role of prostaglandins in inflammation, possibly leading to the development of an agent which would specifically reverse the pathogenetic process of

rheumatic disease. Prostaglandins contribute to the cardinal features of inflammation, erythema, edema, and pain, by direct vasodilation, sensitization of vessel walls to the permeability effects of other mediators, and sensitization of pain receptors to pain-producing kinins, respectively.[4] It has been postulated that prostaglandins are chemotactic for the accumulation of monocytes, one of the aspects of the conversion of an acute inflammatory reaction to a chronic process, and that they enhance granuloma formation.[4] Recent investigations suggest prostaglandins may have bone resorbing properties, and may inhibit protein-polysaccharide synthesis in articular cartilege.[5] In addition, the biosynthesis of prostaglandins may be accompanied by the production of highly reactive oxygen species, the superoxide anion, hydroxyl radical, and singlet oxygen which may cause tissue injury.[6]

Although the contribution of prostaglandins to inflammation is multifactorial, their role in the pathogenesis of rheumatoid arthritis is uncertain. It has been shown that prostaglandin E_2, a potent antiinflammatory and bone resorbing prostaglandin is present in higher concentrations in the synovial fluid of patients with rheumatoid disease, than in those with traumatic or degenerative joint disease, and that treatment with a NSAID reduces synovial fluid prostaglandin levels to normal.[5] In a few patients studied, the reduction in prostaglandin levels appeared to correspond with clinical resolution of the inflammatory process.[5] In vitro experiments with synovial tissue cultures confirmed that rheumatoid tissue produced quantitatively more prostaglandin E than normal joint tissue. Medium from the synovial

tissue cultures possessed bone resorption-stimulating activity which could be inhibited by pretreatment with indomethacin.[5] On the basis of such evidence, it has been suggested that compounds with greater specificity for prostaglandin synthesis inhibition in articular tissues would be more effective therapeutic agents in rheumatic disease.[5]

B. PROSTAGLANDIN SYNTHESIS INHIBITION

The search for an effective, more specific antirheumatic drug, has resulted in the introduction of compounds with diverse chemical structures, but disappointingly similar efficacy in reducing pain and inflammation, and common side effects of gastrointestinal irritation, renal toxicity, inhibition of platelet aggregation, and delayed parturition.[7] Prostaglandin synthesis inhibition has been proposed as the common mechanism of antiinflammatory action of the NSAIDs, and is supported by *in vitro* evidence correlating the inhibition of rheumatoid synovial tissue prostaglandin E synthesis by NSAIDs with their efficacy in animal models of inflammation. Inhibition of prostaglandin E synthesis occurred at concentrations achieved with therapeutically effective doses of the NSAIDs studied, ASA and indomethacin.[5]

The proposed site of NSAID activity is the cyclooxygenase enzyme system of arachidonic acid metabolism. The arachidonic acid cascade, and sites of inhibition by NSAIDs, is shown in Figure 1. Arachidonic acid, the major prostaglandin precursor, is released from membrane phospholipids in response to a variety of stimuli, including those of

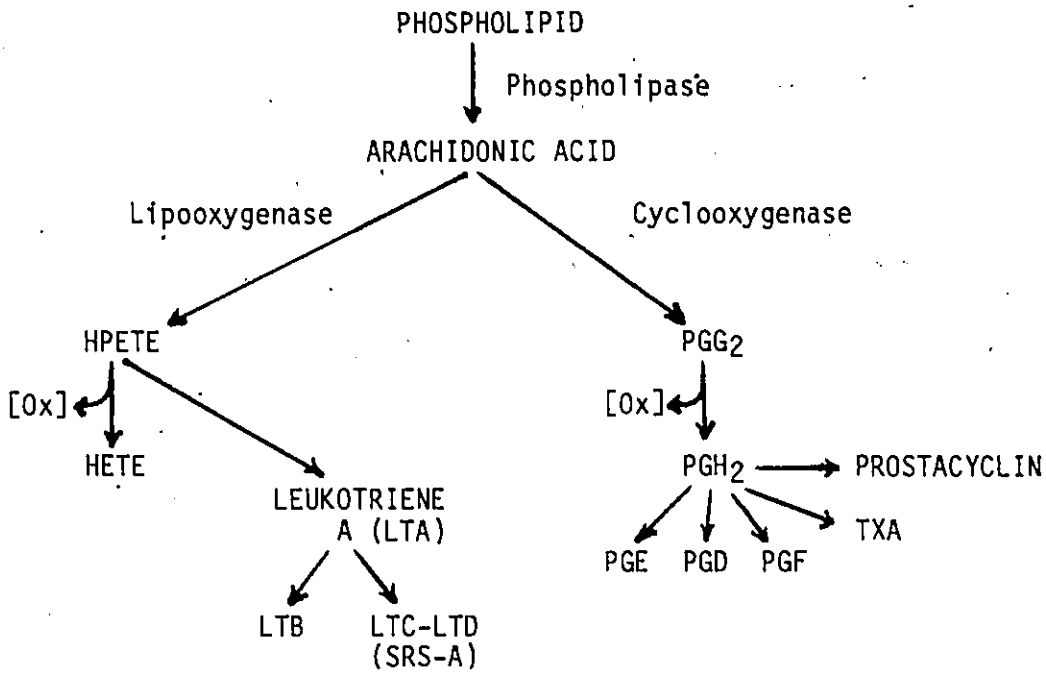
the inflammatory reaction, and is rapidly metabolized by two pathways: the lipooxygenase pathway, whose unstable hydroperoxyarachidonic acid products are currently under investigation, and the classic cyclooxygenase pathway of prostaglandin synthesis.[8] Cyclooxygenase tranforms arachidonic acid to unstable endoperoxide intermediates which are enzymatically, or nonenzymatically, converted to the stable prostaglandins E_2, F_2 , and D_2, or transformed to prostacyclin or thromboxanes. Inhibition of cyclooxygenase will thus diminish production of endoperoxides and all their derivatives, including prostaglandins, prostacyclin, and thromboxanes.[8] ASA appears to irreversibly acetylate the cyclooxygenase enzyme.[10] The mechanism of inhibition by other NSAIDs is unclear, although recent evidence from platelet studies suggests the inhibition is reversible.[11]

The consequences of cyclooxygenase inhibition depend on the distribution of the enzyme, and the physiological, and pathological roles of endoperoxide metabolites. Lipooxygenase has been detected only in platelets, lung, and white cells,[9] whereas the cyclooxygenase system appears to be ubiquitous in mammalian tissues. Preferential synthesis of different arachidonic acid metabolites between tissues may influence their proposed physiologic role as modulators of intra- and extracellular function. Investigation of the physiological role of prostaglandins has been facilitated by observing the effects of cyclooxygenase inhibition by NSAID's in vitro and in vivo, many which manifest as side effects during clinical use.

Prostaglandins appear to stimulate gastrointestinal motility,

FIGURE 1

The arachidonic acid cascade and site of inhibition by nonsteroidal antiinflammatory agents[13]



PG = Prostaglandin
[Ox] = toxic, unstable oxygen radical
HPETE = Hydroperoxyeicosatetraenoic acid
HETE = Hydroeicosatetraenoic acid
LT = Leukotriene
TXA = Thromboxane A
SRS-A = Slow-reacting substance of anaphylaxis

inhibit gastric acid secretion, and exert a cytoprotective effect on the stomach and upper intestine which is separate from their antisecretory effects.[12] Indirect evidence suggests that gastrointestinal irritation, blood loss, and ulceration secondary to NSAIDs may be due to the combined loss of prostaglandin cytoprotective effects, prostaglandin-mediated inhibition of gastric acid secretion, and a prostaglandin contribution to regional gastric perfusion.[13] Orally administered prostaglandin E_2 protects arthritis patients and healthy volunteers against indomethacin or aspirin-induced gastrointestinal blood loss.[14,15,16] Since oral prostaglandins do not appear to inhibit gastric acid secretion[17], it is suggested that interference with the cytoprotective effects of prostaglandins may be the major pathogenetic factor in NSAID-induced gastrointestinal bleeding.[15]

The major product of platelet arachidonic acid metabolism is thromboxane-A_2, a vasoconstrictor and the most potent platelet aggregating agent known.[18] Inhibition of cyclooxygenase by NSAID's prevents thromboxane-A_2 synthesis and interferes with the secondary phase of platelet aggregation. The mild hemostatic defect produced is usually manifest by a prolonged bleeding time, but rarely results in clinically overt bleeding episodes.[18]

Sodium and water retention with edema formation, frequently seen with indomethacin, and occasionally with other NSAIDs, may reflect an inhibitory effect on prostaglandin production by the kidney.[13] Vasodilatory prostaglandins are thought to act in a protective manner to maintain renal blood flow and glomerular filtration rate under condi-

tions of altered circulatory dynamics. In addition, a natriuretic role unrelated to their vasodilatory effect, a direct action on renin-secreting cells, and perhaps a role as endogenous modulators of the water permeability response to vasopressin, have all been postulated as functions of renal prostaglandins.[19,20] The effects of NSAID's on renal function are reversible; they are most apparent in patients with underlying renal disease or abnormalities of renal perfusion, such as heart failure, ascites or lupus erythematosis, where prostaglandins appear to contribute significantly to the maintenance of renal function.[13,19]

A number of arachidonic acid metabolites appear to modulate lung function, and may participate in pathophysiologic mechanisms. Of the cyclooxygenase pathway, prostacyclin, the major vasoactive product formed in vascular tissue, is a potent pulmonary vasodilator and may inhibit intrapulmonary platelet aggregation; thromboxane-A_2, as well as inducing platelet aggregation and vasoconstriction may promote bronchoconstriction by contracting airway smooth muscles; prostaglandins D_2 and F_2 are potent pulmonary vasoconstrictors and bronchoconstrictors; prostaglandin E_2 may have bronchodilator properties, pulmonary vasodilator properties in the fetus, and is necessary to maintain patency of the fetal ductus arteriosus.[21] Inhibition of fetal cyclooxygenase during maternal ingestion of NSAIDs may contribute to the syndrome of primary pulmonary hypertension of the newborn.[21]

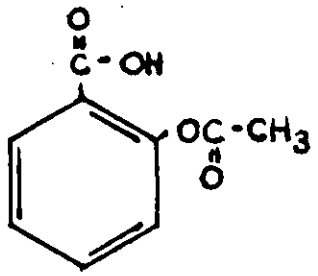
The alternate lipooxygenase pathway produces leukotrienes which are potent mediators of acute and subacute hypersensitivity reactions. By altering tone and permeability of microvasculature in skin and other tissues, leukotrienes may act as pathophysiological mediators in the bronchospasm and mucosal edema of bronchial asthma and anaphylaxis. Hypersensitivity to NSAID's as a group may be manifest by a syndrome of asthmatic attacks in patients with vasomotor rhinitis, nasal polyposis, and bronchial asthma, or as a syndrome of urticaria and angioedema. It is postulated that, by inhibiting cyclooxygenase, the NSAIDs remove bronchodilatory prostaglandins, or shift arachidonic acid metabolism to the leukotriene pathway with subsequent bronchospasm and mucosal edema, or manifestations of cutaneous hypersensitivity.[13,21]

Prolongation of gestation and delayed parturition accompanying administration of NSAIDs to pregnant women near term is also likely related to reduction of prostaglandins, which appear to be important regulators of the onset of labour, and to stimulate uterine contraction during parturition.[22]

These side effects are common to all the nonsteroidal antiinflammatory agents presently available for clinical use. Since differential inhibition of prostaglandin synthesis among tissues has not been shown, manufacturers' claims of fewer side effects may be misleading. With a common mechanism of action, and similar side effects, choice of an antiinflammatory drug rests on demonstrated clinical efficacy, individual patient response, and in some cases, compliance factors and cost.

FIGURE II

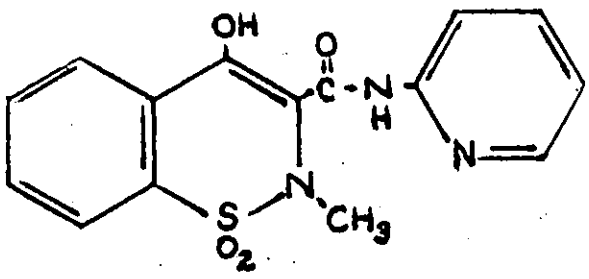
Structure of acetylsalicylic acid (ASA)



2-acetyl-orthohydroxybenzoic acid

FIGURE III

Structure of piroxicam



4-hydroxy-2-methyl-N-(2-pyridyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide

C. ACETLYSALICYLIC ACID (ASA)

The standard to which other NSAIDs are compared is ASA (Figure 2). Because of its efficacy, low cost, and low toxicity when properly administered, it has maintained the status of drug of choice in rheumatoid arthritis since its introduction in 1899.

1. Mechanism

The mode of action of ASA in reducing inflammation was unknown as late as ten years ago, and remains controversial despite extensive investigation of its prostaglandin synthesis inhibiting activity, and other less tenable hypotheses. The "prostaglandin hypothesis" was formulated with the appearance of three classical papers describing the ability of ASA and indomethacin to inhibit prostaglandin synthesis in a cell-free guinea pig lung homogenate[23], human platelets[24], and a perfused dog spleen system.[25] The inhibitory action of ASA on prostaglandin production has been confirmed, and demonstrated in almost all laboratory species, numerous biological preparations, and humans, using a variety of assay techniques.[26] The parent drug, acetylsalicylic acid, is thought to be the most active entity although it is rapidly hydrolysed to the salicylate anion *in vivo*. Sodium salicylate has only weak activity against prostaglandin synthetase *in vitro*, although it may be as potent as ASA *in vivo*; this discrepancy cannot adequately be explained.[4,26] ASA has been shown to irrevers-

ibly inactivate the enzyme cyclooxygenase by acetylating its active site, thereby blocking conversion of arachidonic acid to cyclic endoperoxide precursors of the active prostaglandins.[10] The acetylation reaction is inhibited by the enzyme substrate, arachidonic acid, and by substrate analogues, including other NSAIDs.[10] Pharmacological actions of ASA attributed to prostaglandin synthesis inhibition include antiinflammatory activity, antipyretic effects, and analgesia.[4,8] Most of its side effects have been linked to this common mechanism of action as well.[4,7]

Prostaglandin synthesis inhibition cannot fully explain all the therapeutic actions of salicylates, particularly the antiinflammatory properties; thus, alternative or additional mechanisms have been proposed. Current major lines of research include investigation of:[26]

1. inhibition of aspects of lymphocyte function
2. inhibition of leukocyte and platelet function
5. inhibition of superoxide anion production
4. displacement of endogenous antiinflammatory substances from plasma proteins.

These hypotheses are currently less tenable than the prostaglandin hypothesis.[26] Indeed, until the physiological and pathophysiological roles of prostaglandins are clarified, it is impossible to rule out their involvement in these alternative hypotheses of ASA's antiinflammatory activity.

2. Pharmacokinetics

Although antiinflammatory effects of ASA are attributed primarily to the parent compound, consideration of the pharmacokinetics of the drug includes the disposition of both ASA and its active hydrolysis product, the salicylate anion. Absorption of ASA occurs both in the stomach, where the low pH facilitates passive diffusion of the undissociated molecule, and in the small intestine, where the large surface area provides the optimum site for drug absorption despite the higher pH.[27,28] Absorption is generally rapid, with peak concentrations occurring 30 to 60 minutes after uncoated plain or buffered ASA, although pharmaceutical formulation, gastric and intestinal pH, gastric motility, and gastric contents determine the rate and extent of absorption.[27] Food tends to slow absorption as do large, single doses of salicylate.[27,28] Rowland and Riegelman noted that bioavailability of ASA from an oral solution was only 68% of an equivalent intravenous dose, whereas that of salicylic acid was essentially complete.[29] The reduced bioavailability of the parent compound, ASA, can be accounted for by hydrolysis to salicylic acid in the gut wall, and during first pass of the drug through the liver.[29]

Enteric-coated formulations, intended to reduce gastric intolerance to ASA, are currently the dosage form of choice in rheumatic disease, but have been the subject of controversy with regard to their absorption characteristics. Enteric coatings are intended to dissolve readily in intestinal fluids; thus the absorption of a well-formulated tablet is a

function of gastric emptying, which in turn, is subject to modification by numerous factors. Leonards and Levy demonstrated that enteric-coated ASA had poorly reproducible absorption characteristics as compared to a solution.[30] Bioavailability of salicylate, determined by the urinary excretion method, was equivalent for the two dosage forms, however, and this has been confirmed in subsequent investigations.[31,32] Enteric-coated ASA appears to behave as a "slow-release" preparation with absorption delayed up to two hours after ingestion, and peak plasma levels occurring at six to nine hours.[33,34]

Once absorbed, intact acetylsalicylic acid is rapidly hydrolysed in the blood and liver to the pharmacologically active salicylate anion, with a disposition half-life of 15 minutes.[29,35] ASA can be detected in the blood up to two hours following oral administration of 650 mg in solution.[29] The steady-state volumes of distribution for ASA (650 mg) and salicylic-acid (500 mg) following their respective intravenous doses are similar, although that of ASA (mean 11.3 L) is greater than that of salicylic acid (mean 9.4 L), possibly due to the greater affinity of salicylic acid for plasma albumin.[35] Graham et al. found the volume of distribution of salicylic acid following a single oral dose of 1200 mg of soluble ASA, 11.2 + 2.3 L, to be poorly correlated with body weight or concentration of plasma albumin.[36] A trend to increasing volume of distribution with increasing dose is apparent from various studies in adults and children, and may be a consequence of saturable binding of salicylic acid to plasma albumin.[36,37]

Salicylate distributes to the joint fluid in rheumatoid arthritis patients with a mean transport time of 14 minutes following first appearance of salicylate in blood.[38] On chronic dosing, concentrations in joint fluid accumulate to equal those of free salicylate in the plasma.[38]

At low plasma concentrations (13.8 mcg/mL), 94% of salicylate is bound, mainly at two primary, high affinity sites, and several secondary binding sites on the albumin molecule.[39] Saturation of binding sites occurs within the therapeutic range in normal, uremic, and rheumatoid arthritis patients; thus, an increase in plasma level of salicylate above 150 mcg/mL is accompanied by a disproportionate increase in the free fraction of drug.[39,40] Reduction in plasma albumin levels may compound this effect.[39] Saturable protein binding may account for relatively constant total salicylate clearance over the therapeutic range, because increasing the unbound fraction compensates for the decreasing clearance of unbound drug.[41] It has been suggested that unbound, rather than total concentration of salicylate, should be correlated with clinical effects; however, Ekstrand et al. found no correlation between unbound plasma salicylate and therapeutic effect in rheumatoid arthritis.[39]

Because it is rapidly hydrolysed during absorption, in the plasma, and on passage through the liver, the metabolism and elimination of ASA essentially concerns that of salicylic acid. Salicylic acid is eliminated from the body by renal excretion, and by biotransformation to salicyluric acid, salicyl phenolic and acyl glucuronides, and gentisic

acid.[42] Renal excretion of free salicylate is the summation of glomerular filtration, active proximal tubular secretion, passive tubular secretion, and passive tubular reabsorption. Alkaline urine enhances ionization of salicylate and excretion can increase markedly as urine pH increases from five to eight.[28]

Both major pathways of elimination, salicylurate and phenolic glucuronide formation, are saturable within the therapeutic range.[42] When the amount of salicylate in the body is about 600 mg the half-maximal capacity for formation of saturable metabolites is reached, and salicylate concentrations increase nonlinearly with increasing dose.[28] Clearance thus decreases as the dose is increased, and although the concept of half-life can be misleading in the presence of zero-order kinetics, the apparent elimination half-life of the drug increases from three hours after a 250 mg dose to 20 or 30 hours following full antirheumatic doses of four to six grams daily.[28,43] Furst et al. suggest that total clearance of salicylate may be constant over the therapeutic range of salicylate concentrations, 150 to 300 mcg/mL, and attribute this to saturable protein binding such that the increasing fraction of unbound drug compensates for decreasing clearance.[41] Despite this observation, clinical implications of nonlinear elimination kinetics of salicylates are clear: the steady-state level will increase more than proportionately with an increasing dose rate; the time required to attain steady state lengthens with increasing dose, and it may take a week to attain steady-state with antirheumatic doses of four to six grams daily; there can be a great deal of latitude with respect

to the size of and interval between fractional doses, as long as the total daily dose is appropriate.[42,43]

Because saturation of important metabolic pathways occurs at therapeutic doses of salicylate, monitoring plasma concentrations has been suggested to guide dosing, particularly in rheumatoid arthritis where potentially toxic doses are required to attain maximal antiinflammatory effects. While there has been no formal study relating suppression of inflammation to plasma concentrations of salicylate, clinical evidence indicates that plasma concentrations between 200 to 300 mcg/mL are usually required for clinically significant antiinflammatory activity.[36,44] This likely represents the range in which most patients experience dose-limiting side effects, rather than optimal antiinflammatory response. Ekstrand et al. could find no correlation between clinical response and either unbound or total plasma salicylate in eight patients with rheumatoid arthitis, although the small number of patients in combination with relatively insensitive measures of clinical response in arthritis, may account for this observation.[40]

3. Clinical Studies

Until the studies of Fremont-Smith[45] and Boardman[46], there was little published evidence of salicylate antiinflammatory activity, and thus salicylates were used in rheumatoid arthritis primarily for their analgesic effects.[45] Fremont-Smith et al.[45], in an open

study using buffered aspirin in doses of 3.6 to 7.5 g daily, demonstrated a reduction in rheumatic disease activity, including diminished joint size, increased range of motion and grip strength, followed by an exacerbation of symptoms when the drug was withdrawn. Boardman and Hart[46] attempted to differentiate reduction of swelling, an index of antiinflammatory activity, from the analgesic effect of high (5.3 g) and low (2.6 g) daily doses of aspirin in a double-blind, cross-over comparison with placebo. Outcomes were compared to similar treatment groups receiving a known antiinflammatory agent, prednisone 7.5 mg daily, or acetaminophen 6 g daily, a strictly analgesic drug, in the same placebo-controlled, cross-over manner. High-dose salicylate, like prednisone, produced a reduction in joint size as compared with low dose or placebo, where no change was noted; although grip strength improved, the difference from low-dose or placebo was not significant. The analgesic, acetaminophen, did not reduce joint swelling or significantly increase grip strength, although patient preference for active drug over placebo suggested analgesia may be an important component of relief.[46]

Subsequent clinical trials have repeatedly confirmed the findings of these early investigators, and ASA remains the standard to which all nonsteroidal antiinflammatory agents are compared, since none can be shown to be more efficacious in rheumatoid arthritis.[7]

Enteric-coated ASA was introduced in an attempt to reduce gastric irrtation that inevitably accompanied large doses of ASA, but acceptance was hesitant following criticisms of unpredictable absorption. Formulation changes since the early 1960's when shellac coatings were

used have resulted in a product from which ASA is reliably absorbed.[32]

Significant improvement over placebo in rheumatoid arthritis has been demonstrated for enteric-coated ASA.[47] When compared with regular ASA, efficacy of the two formulations was equivalent, and serum levels achieved with enteric-coated ASA were equal to, or higher than those with regular ASA.[32] A greater patient acceptance of the enteric-coated product was noted, perhaps because of the ease in swallowing a smooth tablet as compared to a regular ASA tablet.[32]

4. Side Effects

In the initial study of salicylate therapy in rheumatoid arthritis, Fremont-Smith declined to use a double-blind design since typical side effects of ASA at antiinflammatory doses, tinnitis, deafness, and perspiration or nausea, would have alerted both physician and patient to the prescribed treatment.[45] Indeed, these are the most common manifestations of central nervous system and gastrointestinal toxicity at therapeutic doses; however, hypersensitivity reactions, hematologic abnormalities, and hepatic and renal dysfunction have been reported.

Central nervous system effects of salicylates are dose-related, and consist of stimulation followed by depression. Toxic effects are largely prevented by therapeutic plasma drug level monitoring, although headaches, vertigo, tinnitis and deafness are common in the antiinflammatory range, 200 to 300 mcg/mL; tinnitis and hearing loss may be due to increased labyrinthine pressure or an effect on the hair cells

of the cochlea, and any hearing loss is reversible upon withdrawal of the drug.[28,48] Uncoupling of oxidative phosphorylation in skeletal muscle may occur in this concentration range, and may stimulate respiration, although plasma carbon dioxide tension does not change.[48] An increase in oxygen consumption and metabolic rate may cause sweating.[48] Centrally mediated nausea and vomiting, and hyperventilation secondary to direct stimulation of the respiratory center, are noted above 300 mcg/mL.

Frank salicylate intoxication, arbitrarily designated levels above 450 mcg/mL, may be accompanied by respiratory alkalosis (a consequence of hyperventilation), metabolic acidosis (secondary to uncoupling of oxidative phosphorylation), fever and concomittant dehydration, convulsions or coma, and cardiovascular collapse as levels over 800 mcg/mL are attained. Treatment of salicylate overdose consists of restoring water and electrolyte balance, correcting acid-base disturbances, and perhaps attempting to increase elimination of the drug by alkalinization of the urine or hemodialysis.[49]

Hepatic dysfunction has been reported rarely following chronic administration of salicylates, usually in children with juvenile rheumatoid arthritis (JRA).[50] The typical clinical findings are elevated serum enzymes, SGOT, SGPT and alkaline phosphatase, occasional hepatomegaly, and mild periportal inflammation.[50] Cessation of therapy is not required unless symptoms of severe hepatic dysfunction are evident. Since transaminase elevations rarely occur in nonrheumatic individuals receiving salicylates, it has been suggested that rheumatic

disease, particularly JRA, may predispose patients to drug-induced hepatic injury.[50]

Acute administration of ASA may produce a transient increase in urinary excretion of epithelial cells, elevations of blood urea nitrogen (BUN) and serum creatinine levels, and proteinuria.[51] Chronic use of salicylates, usually in combination with other analgesics, has been linked with the production of a form of chronic interstitial nephritis, "analgesic nephropathy". The causative agent and pathogenesis of analgesic nephropathy is controversial, however.[52] A recent study by Emkey et al. supported other literature demonstrating that salicylate, after prolonged use in rheumatoid arthritis, does not cause serious renal disease.[51]

Hematologic toxicities of salicylates include anemia, which may be due to gastrointestinal blood loss; rare leukopenia or thrombocytopenia; and the well-publicized "platelet-inhibition".[53] ASA irrversibly acetylates platelet cyclooxygenase, thereby inhibiting platelet thromboxane synthesis and preventing the secondary phase of platelet aggregation which is dependent on thromboxane release.[18] 96% inhibition of thromboxane synthesis is achieved with a dose of 325 mg, and lasts for the life of the platelet.[18] A mild hemostatic defect, accompanied by prolonged bleeding time but no alteration of standard coagulation tests, is evident for up to 72 hours following administration of a single dose.[54] The platelet antiaggregatory effects of ASA have been used therapeutically to prevent platelet aggregation associated with thromboembolic events.[18] The salicylate

anion likely also impairs platelet aggregation by virtue of its ability to inhibit prostaglandin synthesis; however, the effect is reversible and of short duration.[4]

Gastrointestinal complaints, including occult bleeding and ulceration, are common during therapeutic use of ASA, and have stimulated both the development of less irritating formulations of ASA, and the search for more well-tolerated antiinflammatory alternatives. Investigation of the pathogenesis of gastric injury suggests that inhibition of prostaglandin synthesis in the gastric mucosa removes cytoprotective properties of prostaglandins, and predisposes to injury by gastric acid.[55] Indeed, oral administration of prostaglandin E_2 to normal subjects or rheumatoid arthritis patients treated with ASA prevents fecal blood loss.[15,16] A contributory role of gastric acid cannot be denied, since exogenous or endogenous hydrochloric acid is required for ulcer formation in animals;[55] it is suggested that increased back diffusion of acid through a weakened mucosal barrier causes cellular damage which produces histamine release from mast cells and perpetuation of acid-mediated injury.[56] ASA-induced gastrointestinal bleeding may be reduced by concurrent administration of cimetidine which reduces histamine-mediated gastric-acid secretion and raises intragastric pH.[57]

Prostaglandin inhibition may not be the sole mechanism of toxicity, however. In one study, administration of equi-potent doses of ASA and piroxicam, a representative NSAID, resulted in fewer gastrointestinal complaints and no pathologic changes of the gastric mucosa with

piroxicam as compared to ASA. ASA produced gastrointestinal complaints, and erythema, gastritis or erosions in virtually all subjects. Fecal blood loss increased significantly with ASA treatment, but did not differ from control with piroxicam.[50] Direct irritant effects of ASA appear to be related to the low intragastric pH which may facilitate penetration of unionized salicylate into mucosal cells where interference with intracellular metabolism may cause structural alteration of the gastric mucosa and alter transmembrane ion transport.[56]

Enteric-coated formulations of ASA were developed to circumvent the problem of gastric mucosal damage by releasing ASA in the neutral pH of the intestine, thereby minimizing contact with the gastric mucosa. Assessment of mucosal damage by endoscopy[59] or detection of radiolabelled red cells in the feces[60] confirms that enteric-coated ASA preparations protect against gastric mucosal injury. At therapeutic blood levels, fecal blood loss was similar following administration of an enteric-coated or intravenous form of ASA, but significantly less than following buffered or plain ASA.[60] Detection of blood in the feces following intravenous ASA supports the theory of a systemic contribution to the pathogenesis of mucosal injury.[60]

Notably lacking in the literature is a clinical comparison of the antirheumatic efficacy and side effects of enteric-coated ASA with one of the newer nonsteroidal agents, or a specific comparison of their gastric irritant potential.

D. PIROXICAM

1. Mechanism

Piroxicam is the most recent nonsteroidal antiinflammatory alternative to ASA to be released on the Canadian market (Figure 3). Although structurally unrelated to NSAIDs in current use, it possesses pharmacological properties characteristic of this class of drugs: heat, redness, swelling and pain are suppressed by piroxicam in traditional animal models of inflammation used to screen for antiinflammatory properties.[61] Piroxicam was inactive in tests used to measure opiate-like analgesic activity.[61] Its antiinflammatory effects are thought to be mediated to a large extent by prostaglandin synthesis inhibition; results of *in vitro* mechanism studies suggest piroxicam is a relatively specific inhibitor of cyclooxygenase at clinically achievable concentrations. The inhibition appears to be competative and reversible, readily overcome by addition of substrate, arachidonic acid, in tissue culture.[62] The effect of piroxicam on human prostaglandin production *in vivo* has not been studied, however, a short report by Spector et al. documented significant decreases in serum prostaglandins E_1, E_2 and F_2 within two hours of drug administration to asthmatic patients with aspirin sensitivity.[63]

2. Pharmacokinetics

Piroxicam can be detected in blood within 30 minutes of oral administration, and average peak serum concentrations of 2.0 and 4.0 mcg/mL are reached 2.5 to 3.0 hours following administration of single 20 and 30 mg doses respectively.[64,65] Plateau serum concentrations of 5.0 to 7.0 mcg/mL are achieved after 5 to 7 days dosing with 20 mg daily,[65] and this has been quoted as the optimal antiinflammatory range, although blood levels and efficacy have not been monitored concurrently in the same patient.[65,66] Synovial fluid concentrations approach 40% of steady state serum concentrations.[62,66]

Piroxicam is 99.3% bound to plasma proteins and the apparent volume of distribution, 0.140 L/kg, is similar to that of other acidic and highly protein-bound NSAIDs which are limited to the approximate space of the extracellular fluid.[67]

The overall elimination half-life of 37 to 45 hours is independent of dose.[66,67] Renal clearance of unchanged piroxicam accounted for 10.4% of total plasma clearance in one study,[67] although unpublished observations suggest that two to five % is a more usual range of excretion of unchanged piroxicam.[65] The remainder of the drug is eliminated in the urine following metabolism: hydroxylation of the pyridyl ring, with the product excreted alone or as the glucuronide conjugate, appears to be the major pathway.[61,65] Deamidation, decarboxylation, and ring contraction are minor pathways.[61]

3. Clinical Studies

The antiinflammatory and analgesic effects of piroxicam have been studied in rheumatoid arthritis, osteoarthritis, gout, ankylosing spondylitis, post-partum pain, and acute musculoskeletal pain. In rheumatoid arthritis patients treated for 12 weeks with either piroxicam 20 or 30 mg or placebo, a significant improvement over baseline was noted in grip strength, duration of morning stiffness, walking time, self-assessment of pain, and number of swollen and tender joints in both piroxicam groups, but not in the placebo group.[68] When piroxicam 20 mg daily was compared to 40 mg daily, there was a small but consistent advantage for the 40 mg dose; however, gastrointestinal side effects are more prevalent at 40 mg daily and preclude chronic use of this dose.[66,69]

Comparative studies of piroxicam with other agents in rheumatoid arthritis suggest that piroxicam, 20 or 30 mg daily, is at least as effective as therapeutic doses of ASA, naproxen, and ibuprofen,[61,70] more effective than indomethacin, but less effective than phenylbutazone. There are problems with some studies, however, particularly in the lack of double-blind technique, free access to ASA, and tabulation of results, which limit the validity of the conclusions. It appears that piroxicam is at least as effective as current antiinflammatory therapy for rheumatoid arthritis. Clinical studies to date have not been designed to assess the impact of once-daily dosing of piroxicam on compliance of rheumatoid arthritis patients.

4. Side Effects

Central nervous system and gastrointestinal side effects are the most common complaints during therapy with NSAIDs, including piroxicam. Headache, vertigo, and insomnia have been reported.[61] Gastrointestinal irritation, described as epigastric discomfort, nausea, indigestion, heartburn, abdominal pain or flatulence has occurred in an average of 19 percent of patients receiving piroxicam during clinical trials.[69] Gastrointestinal ulceration, both gastric and duodenal, has been reported, although rarely. A significant dose-response relationship is apparent with piroxicam for both subjective gastrointestinal side effects and ulceration, over the dose range of 10 to 40 mg daily.[6] Since a 40 mg dose of piroxicam produces no additional clinical benefits over 20 mg daily, and is accompanied by a disproportionately greater incidence of gastrointestinal side effects, it is recommended that a dose of 30 mg daily not be exceeded.[66] Prostaglandin synthesis inhibition may account for the consistent incidence of gastrointestinal side effects reported with NSAIDs, including piroxicam.[7] In comparative trials with uncoated ASA, piroxicam has been more well-tolerated with respect to gastrointestinal side effects; similar comparative trials have not been carried out with enteric-coated ASA.

Miscellaneous symptoms difficult to attribute to the drug have been described: fatigue, rash, itching, and pedal edema.[61] Laboratory abnormalities occurring during therapy are rare, but consistently

involve an increased BUN which subsides to normal on stopping therapy, and/or mild elevations in transaminase (SGOT, SGPT) levels.[61,19] Drug-induced hepatitis was diagnosed in one subject with abnormal liver function tests.[71] Elevations of BUN have been reported with other NSAIDs; data suggest that a reversible functional effect of NSAIDs, perhaps involving inhibition of prostaglandin synthesis in the kidney, may be the cause, rather than a direct renal toxic effect.[69]

E. SUMMARY AND OBJECTIVES

In summary, symptomatic treatment with NSAIDs remains an important modality in the management of rheumatoid arthritis, a chronic inflammatory disease of unknown etiology. Prostaglandins appear to play a role in the pathogenesis of inflammation, and although their contribution to the pathogenesis of rheumatoid arthritis is uncertain, inhibition of prostaglandin synthesis is thought to be one of the mechanisms of NSAID activity in arthritis. Enteric-coated ASA is currently the antiinflammatory agent of choice in Canada, and although tolerance, particularly to gastrointestinal irritation, appears to be better with piroxicam, efficacy and tolerance as compared to an enteric-coated formulation of ASA has not been assessed. Such a study is necessary to determine the place of piroxicam in the therapy of rheumatoid arthritis.

The objectives of this study are threefold:

i) To compare the pharmacological activity of an enteric-coated formulation of ASA, 'Entrophen', with that of a new NSAID, piroxicam, in rheumatoid arthritis, by measurement of clinical indices of disease activity.

ii) To compare the incidence of spontaneously reported side effects of the drugs.

iii) To determine if a relationship between clinical efficacy and steady state blood levels of the drugs can be detected.

III METHODOLOGY

A. PATIENT SELECTION

The study was carried out at the Rheumatology Clinic of the Ottawa General Hospital under the medical supervision of Dr. R.J. McKendry (R.J.M.) who acted as a blind observer with D.W.. Dr. W. McLean (W.M.) served as the unblinded investigator. Patients were selected for the study by R.J.M. from a population of rheumatoid arthritis outpatients. Informed consent was obtained prior to entry in the study, and it was understood by all patients that they could voluntarily terminate their participation in the study at any time.

Patients were included in the study based on the following criteria:

i) male or female between 21 and 70 years of age

ii) informed consent was obtained (Appendix I)

iii) active definite, or classical rheumatoid arthritis as defined by the American Rheumatism Association (Appendix II)[12]

iv) active disease as defined by the presence of two or more of the following:

five or more joints tender or painful on motion;

five or more swollen joints;

45 minutes or more morning stiffness;

erythrocyte sedimentation rate greater than 1.5 times normal

v) not satisfactorily controlled on present antiinflammatory therapy.

Patients were not eligible for participation in the study if any of the following criteria were met:

i) pregnant women, nursing mothers, or women of child-bearing age who were not following adequate contraceptive precautions and/or whose intent it was to become pregnant during the study period

ii) patients who required other medications which may have obscured the pharmacologic effect of the study drugs, including:

other nonsteroidal antiinflammatory agents;

chloroquine or penicillamine;

concomitant, gold or corticosteroids (maximum prednisone 10 mg daily or equivalent) which had not been administered in a fixed stable maintenance regimen during the preceding three months

iii) patients who required medications which may interact with the study medications, including:

anticoagulants;

urinary acidifiers or alkalinizers;

uricosurics;

barbiturates

iv) patients in whom joint surgery was contemplated

v) anemia or any other hematological disorder such as leukopenia or thrombocytopenia, which, in the opinion of the attending physician (R.J.M.), precluded entry into the study

vi) significant liver or renal disease (creatinine clearance less than 30 mL/minute) which may have altered the pharmacokinetics of the study drugs

vii) active gastrointestinal disease, which included the presence of peptic ulceration and gastrointestinal bleeding or a past history of these conditions

viii) known or suspected allergy to either of the study medications, or other nonsteroidal antiinflammatory agents

ix) patients with diseases closely related to rheumatoid arthritis (Appendix III)

B. STUDY DESIGN

The study was a double-blind, randomized, crossover trial which began with a washout period to assess disease activity in the absence of antiinflammatory medication. Three days prior to the first clinic visit, all previous NSAIDs were stopped; acetaminophen or propoxyphene were allowed on an "as needed" basis for pain. At the first clinic visit, a history and physical examination preceded baseline clinical assessment of disease activity, baseline laboratory analyses, including serum (piroxicam) and plasma (salicylate) drug determinations, were carried out. Randomization to either the 'Entrophen' or piroxicam

treatment groups was determined by random numbers, and assigned by the unblinded investigator, W.M. Sufficient medication was supplied to last until the next appointment, and the patient instructed to record the use of other analgesics or supplementary medications (Appendix IV). The patient was seen at the same time of day weekly for four weeks during the dose-adjustment period, then at eight and twelve weeks. At the end of the initial treatment period, study medications were stopped for three days to reproduce the initial washout period, and the crossover period commenced in the same manner as the initial treatment period.

Piroxicam ('Feldene', Pfizer Canada, Ltd.) and matching placebo were supplied as 10 mg capsules. 'Entrophen' (Charles E. Frosst Co. enteric-coated ASA) and placebo, were supplied as 650 mg tablets. Each patient was required to take two medications, one placebo, and one active drug, in accordance with the dosage adjustment schedule outlined below and in Appendix V. Piroxicam, with an elimination half-life of 40 hours, required once daily administration at 8:00 a.m. 'Entrophen' was taken four times daily at 8:00 a.m., 12:00 p.m., 6:00 p.m., and 10:00 p.m. Since both medications are potentially irritating to the gastrointestinal tract, patients were encouraged to take the medication with meals or a snack.

To permit dosage adjustment within a double-blind study design, a system of four different dosage schedules was devised as follows:

Schedule	Piroxicam (10 mg Active Drug or Placebo)	'Entrophen' (650 mg ASA or Placebo)
I	1 capsule	5 tablets
II	2 capsules	6 tablets
III	2 capsules	7 tablets
IV	2 capsules	8 tablets

All patients were started at Schedule 2, and the dosage adjusted either down to Schedule 1 or up to Schedule 3 or 4 in the first three weeks of the treatment period based on clinical evidence of antiinflammatory activity. Drug levels were not used to adjust dosages since the antiinflammatory response to piroxicam has not been clearly correlated with a range of serum concentrations.[65,70]

C. ASSESSMENT

1. Clinical Assessment of Disease Activity

At each visit, standard clinical assessments of rheumatoid arthritis disease activity were performed by a blinded investigator, D.W., under the supervision of R.J.M. These included a count of joints tender or painful when subjected to passive movement; a count of swollen joints as determined by inspection and palpation; the patient's perceived duration of morning stiffness elicited by questioning; grip strength, recorded for each hand as the average of three consecutive measurements using a Davis bag. In addition, each patient was classi-

fied according to his/her American Rheumatism Association functional class (Appendix VI).

2. Laboratory Assessment of Disease Activity

Rheumatoid factor was measured upon entry into the study as one of the diagnostic criteria for rheumatoid arthritis, but was not used as a measure of response to therapy. Erythrocyte sedimentation rate was measured at each visit as a laboratory correlate of inflammatory activity.

3. Indices of Disease Activity

The Lansbury articular and systemic indices were calculated as measures of disease activity. The articular index was devised by Lansbury to reflect the extent of joint inflammation on the basis of a weighted joint count in which joint size was taken into account.[73,74] Each joint that was tender on passive motion was assigned a value based on the relative area of its articulating surface, and the values summed to produce the articular index.[75] The average area of the articulating surfaces used by Lansbury in his original calculations[74] and the simplified values which he recommended later [73,75], which were used to calculate the articular index in this study, are shown in Appendix VII.

A systemic index, incorporating manifestations of rheumatoid activity present in the majority of cases of active disease, was devised by Lansbury to serve as a guide to the general trend of disease activity.[76] Erythrocyte sedimentation rate, pain, grip strength, morning stiffness, and the articular index were evaluated by Lansbury in a series of untreated arthritis patients, and the average of the abnormal findings for each measure assigned a value of 100.[76] To calculate a systemic index, the values of the measures for any patient were expressed as a percentage of Lansbury's original untreated values, summed, and divided by five. The resulting number represented the patient's disease activity relative to that of an untreated patient.[76,77] This systemic index was shown to accurately reflect disease activity and response to therapy in patients with rheumatoid arthritis.[73]

The systemic index was calculated in this study by using the table in Appendix VIII to assign percentage values for the measures, which were then summed to give the systemic indices.[77] A sample calculation is shown.

4. Pain

Patient perception of pain was recorded at each visit using a graphic rating scale[78] (Appendix IX). Patients were asked to indicate the intensity of their pain as an average of the preceding 24 hours without access to their ratings of previous visits. For purposes

of statistical analysis, pain ratings were converted to a numerical score, based on the distance from "No pain" in centimeters.

Acetaminophen or propoxyphene were allowed on an "as needed" basis for additional pain relief, and patients were asked to record supplementary analgesic use in a daily diary (Appendix IV).

5. Side Effects

Since clinical acceptance of a drug is frequently based on side effects when no difference in the efficacy of two drugs can be detected, side effects experienced during treatment were recorded. At each visit, having not been informed of the side effects to expect, patients were asked to describe any side effects which they attributed to the medication. Side effects were classified as "mild" if they disappeared with continued treatment or were tolerated with no alteration of dose; "moderate" if they were tolerated with a reduction in dose; or "severe" if they necessitated discontinuation of therapy.

6. Compliance

Returned medications were counted as a measure of compliance. Drug levels also served as a check on compliance.

D. LABORATORY ANALYSIS

1. Serum Piroxicam Concentration

Serum piroxicam determinations were carried out at the Pfizer Canada, Ltd. plant in Arnprior, Ontario, using a high pressure liquid chromatography assay.[79]

Blood for assay was drawn by direct venipuncture at a consistent time for each patient, and the time of the last dose of piroxicam recorded. Serum was separated by centrifugation and frozen at -20°C for up to eight weeks before assay.

The internal standard, isoxicam (4-hydroxy-2-methyl-N-5-methyl-3-oxazolyl-2H-1,1-benzothiazine-3-carboxamide-1, 1-dioxide) was prepared as an aqueous solution in 0.1N sodium hydroxide at a concentration of 1.0 mg/ mL, and diluted with distilled water to a working dilution of 100 mcg/ mL.

In disposable 16 mm x 100 mm culture tubes, 10 mL of serum were fortified with 10 mcg of internal standard, mixed with 0.5 mL of 0.1N sulfuric acid to precipitate serum protein, and extracted with 5.0 mL of diethylether on a vortex mixer (Thermolyne Maxi-Mixer, Fisher Scientific Co., Ottawa) for 30 seconds. After centrifugation (Beckman TJ6, Beckman Instruments, Montreal), the solvent layer was transferred to another tube, and evaporated to dryness using a vortex evaporator (Buchler Vortex Evaporator, Fisher Scientific Co., Ottawa). The residue was reconstituted in 1.0 mL of 0.1 M tris (hydroxymethyl) aminomethane

and held in the buffer no longer than two days before assay.

A Hewlett-Packard 1084B high pressure liquid chromatograph with recorder and integrator (Hewlett Packard, Avondale, Pennsylvania), equipped with a variable wavelength detector (range 190 to 600 nm) and semi-automatic injector (0 to 200 mcL), was fitted with a 300 mm x 3.9 mm internal diameter 10 mcm Micro Bondapak-CN column (Waters Canada, Mississauga). The mobile phase of acetonitrile-water-acetic acid (25:70:5) was heated to 75°C, filtered, degassed, and used at a flow rate of 1.2 mL per minute. The detector was set to monitor at 355 nm. Samples of 100 mcL were injected at eight minute intervals. Column effluent was recycled back into the mobile phase reservoir (800 mL) and the mobile phase replaced every two days.

Calibration curves, constructed by determining the response from known amounts of piroxicam and 10 mcg internal standard added to control serum, demonstrated assay linearity over the range of 0.5 to 20.0 mcg/mL. For daily validation, six samples, fortified in the mid-range (50 mcg/mL) were processed with each group of test samples, two at the beginning of the run, two at mid-run, and two at the end of the run. The mean ratio of piroxicam to the internal standard integrator area counts from fortified samples, was determined, then the piroxicam concentration in test samples was calculated from the expression:

$$\text{Concentration (mcg/mL)} = \frac{\text{area counts drug}}{\text{area counts standard}} \times \frac{C}{\text{mean ratio}}$$

where C represents the concentration (mcg/mL) of piroxicam in the fortified sample.

Assay recovery of piroxicam and the internal standard were 73.6 and 71.3% respectively. Acetaminophen and salicylate at concentrations of 100 mcg/mL did not interfere with the assay. Of known human and animal metabolites of piroxicam, only the 5'-hydroxylated metabolite yielded a chromatographic peak; however, recovery was poor, and the retention time did not interfere with detection of piroxicam. The relative mean standard deviation for piroxicam was 3.1 over a concentration range of 0.5 to 20.0 mcg/mL.

2. Salicylate Plasma Concentrations

Assay of salicylate plasma concentrations was done using the colorimetric method of Trinder[80] in the Special Biochemistry Laboratory of the Ottawa General Hospital.

Blood for assay was drawn by direct venipuncture into a citrated tube at a consistent time for each patient, and the time of the last dose of 'Entrophen' recorded. Plasma was separated by centrifugation, and frozen at -20°C for up to 24 hours before assay.

The colorimetric reagent contained mercuric chloride and hydrochloric acid to precipitate plasma proteins, and ferric nitrate to develop the color. Ferric ions complex with salicylate to produce a violet color, and nitrate eliminates inhibition of the reaction by phosphates and oxalates. 20 g mercuric chloride were dissolved in 425 mL water, heating if necessary. After cooling, 60 mL of 1N hydrochloric acid and 20 g ferric nitrate ($Fe(NO_3)_3$-$9H_2O$) were added, and the

stock solution made up to 500 mL with distilled water.

A commercial salicylate control, Wellcontrol (Burroughs Wellcome Inc., Lots W1K8463, W1K9035) was used to test the assay procedure daily. For a stated concentration of 400 mcg/mL, the coefficient of variation ranged from 3.3 to 3.9 for Lot W1K8463 (October 1980 to March 1981) and from 2.3 to 2.4 for Lot W1K9035 (April to October 1981).

To 12 mL test tubes containing 2.5 mL ferric nitrate reagent, were added either 0.5 mL water to prepare a blank, 0.5 mL of commercial control to prepare a standard, or 0.5 mL of plasma to prepare the test sample. The tubes were capped with parafilm, mixed for ten seconds on a vortex mixer (Thermolyne Maxi-Mix, Fisher Scientific Co., Ottawa), then centrifuged for ten minutes at 2000 x G (CRU 5000, Damon-IEC Division, Burlington). The supernatent was carefully removed and placed in small cuvettes. Optical density (O.D.) was read at 540 nm against the blank in a Bausch and Lomb Spectronic-70 spectrophotometer (Beckman Instruments, Montreal).

The concentration of salicylate in the sample was calculated as:

$$\text{Concentration salicylate (mcg/mL)} = \frac{\text{O.D. Test}}{\text{O.D. Standard}} \times 400$$

Recovery of salicylate from the plasma was 100 percent.

3. Laboratory Tests

Prior to beginning the study medications, and at weeks eight and 12 of the treatment periods, the following laboratory analyses were done to

monitor possible drug-related toxicity:

Hematology: red blood cell count, hemoglobin, hematocrit, total white blood cell count and differential, platelet count, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC);

Urinalysis: sugar, protein, pH, microscopic analysis of centrifuged urinary sediment;

Biochemistry: random sugar, blood urea nitrogen, serum creatinine, SGOT, alkaline phosphatase, total bilirubin, total protein, albumin.

At all other visits (weeks two, three, and four), only ESR and hemoglobin were measured.

E. DROPOUTS

Informed consent was accepted with the understanding that the patient was free to terminate his/her participation in the study at any time. Mandatory termination of participation in the study was dependent upon:

development of an allergic reaction to either of the study medications;

development of side effects or laboratory abnormalities, which, in the opinion of the attending physician (R.J.M.) would preclude continuation of the study;

noncompliance with the treatment regimen or conditions of the study

F. STATISTICAL ANALYSIS

Statistical analysis was undertaken in consultation with the Department of Epidemiology, Faculty of Medicine, University of Ottawa. The "Statistical Package for Social Sciences" (SPSS) computer program was used to facilitate computation where possible.

1. Efficacy

To evaluate the efficacy of 'Entrophen' and piroxicam in this sample of rheumatoid arthritis patients, Student's t-test for paired samples was used to compare week 12 with baseline values of the outcome measures: pain, joint tenderness, articular index, morning stiffness, ESR, grip strength, and systemic index. Patients dropping out of a treatment due to side effects or lack of efficacy were not included in the analysis of that treatment.

The antiinflammatory efficacy of 'Entrophen' and piroxicam was compared using both parametric and nonparametric statistical methods. Student's t-test for paired samples was used to compare the change in disease activity during piroxicam therapy with that during 'Entrophen' therapy in patients completing both phases of the trial. The change in disease activity was defined as the difference between week 12 and pretreatment values of the aforementioned outcome measures.

Since outcome measures in rheumatoid arthritis may not be normally distributed, and are only moderately sensitive to changes in disease

activity[81], nonparametric analysis of the data was undertaken as well. The change in disease activity during treatment, defined as the difference between the value of the composite systemic index at baseline and the final visit, was compared between 'Entrophen' and piroxicam using the Wilcoxan signed rank sum test.[82] For patients completing both treatments, the comparison was made at week 12. Dropouts were included in the analysis by comparing the change in disease activity occurring during a comparable length of treatment. For example, if a patient completed treatment with piroxicam but dropped out of 'Entrophen' treatment at week 4, the change in disease activity to week 4 would be compared.

2. Side Effects

The total number of side effects recorded for each drug were tabulated according to their classification of "mild", "moderate", or "severe". The proportional distribution of side effects in these categories was compared between the two tests using the chi-square test for a 2 x 3 contingency table.[83]

3. Drug Levels

Pearson correlation coefficients were calculated to examine the relationship between drug levels and each of the outcome measures at each visit. The average drug level at the last week of treatment in

"responders", defined as those with an improvement in the systemic index of 20 points or greater, was compared to that of "nonresponders" using Student's t-test for independent samples.

4. Other

The adequacy of the between-treatments washout period was tested using Student's t-test for paired samples to compare washout values of the outcome measures with those at baseline.

Pearson correlation coefficients were calculated for pairs of outcome measures at each visit, to test for relationships between the various outcome measures.

IV RESULTS

A. PATIENT CHARACTERISTICS

Fifteen patients (12 female, 3 male), with a mean age of 52.9 years (range 31 to 73 years), and a mean duration of rheumatoid arthritis of 10.8 years (range 1 to 30 years), were entered in the study. Seven patients had other conditions which did not affect their entry into the study, and four patients continued to receive medications unrelated to the treatment of rheumatoid arthritis. Three patients were receiving prednisone or an equivalent which had been administered in a stable dose of 10 mg of prednisone equivalent for the preceding three months. Fourteen patients had used other NSAID's in the past for their arthritis, including ASA in 11 patients. Six patients had a remote history of gold treatment. Patient characteristics are shown in Table I. A summary of baseline disease activity, assessed after the initial washout period, is shown in Table II.

Of the 15 patients entered in the trial, seven completed both phases of the crossover, three patients completed at least one phase and dropped out of the other, and three patients were unable to complete treatment with either drug. Two patients tried only one of the study medications: Patient 1 refused to continue in the trial, having successfully completed the first treatment period with piroxicam, Patient 13 was dropped from the trial when a severe flare of disease activity prompted alteration of her immunosuppressive therapy. The

outcomes of each patient are summarized in Table III.

B. EFFICACY

The antiinflammatory efficacy of 'Entrophen' and piroxicam in this rheumatoid arthritis population was assessed in patients who completed 12 weeks of therapy with either agent. Disease activity at week 12 was compared to baseline, and the results are summarized in Tables IV and V. Both agents produced statistically significant ($p \leq 0.05$) changes in the articular and systemic indices. 'Entrophen' produced a statistically significant change ($p=0.035$) in the pain scores, while piroxicam reduced the count of tender joints ($p=0.002$). No other measure of arthritis disease activity was altered to a statistically significant degree by treatment.

To directly compare the efficacy of 'Entrophen' and piroxicam, the change in disease activity from baseline to week 12 was evaluated in the seven patients completing both treatments. The results are summarized in Table VI. No statistically significant difference between treatments could be detected in this manner.

When the change in systemic index from baseline to the final common visit in patients trying both drugs was compared nonparametrically, however, a statistically significant difference could be shown between the two treatments. 'Entrophen' produced a greater improvement in the composite systemic index than piroxicam when all patients were included in the analysis (Table VII, $p=0.0060$); when patients 9 and 10 were

excluded because of possible interference from underlying rheumatic diseases (Table VIII, p=0.0162); and when only patients completing both phases of the trial were analysed (Table IX, p=0.0292).

When other measures of disease activity were compared by the Wilcoxan signed rank sum test in patients completing the trial, 'Entrophen' produced a greater improvement over piroxicam in only the pain rating.

C. SIDE EFFECTS

The spectrum of side effects experienced by patients during the study is shown in Table XVI. During piroxicam therapy, a total of 14 adverse effects were experienced by seven patients. Gastrointestinal discomfort, headache, and swelling of the face and extremities were severe enough to require discontinuation of therapy in one patient, but the remainder were rated as mild. During 'Entrophen' therapy, 27 side effects were recorded in 11 patients. Side effects leading to discontinuation of therapy in three patients included gastrointestinal discomfort (two patients), tinnitis with reduced hearing (three patients), and swelling of the face and extremities, experienced by the same patient who discontinued piroxicam therapy. Eleven side effects were rated as mild, and ten as moderate. Gastrointestinal and central nervous system effects were prominant with both agents.

When the proportional distribution of side effects rated as "mild", "moderate", or "severe" was compared between the two drugs, a signifi-

cant difference was noted between piroxicam and 'Entrophen'. The calculations are shown in Table XVII. 'Entrophen' appears to produce a greater incidence of, and more severe side effects, than piroxicam.

D. DRUG LEVELS

For any visit, including week 12, there was no correlation between the change from baseline in any outcome measure, and the drug level (Table XVIII, Table XIX).

When the mean drug level of responders was compared to that of nonresponders, there was a significant difference for 'Entrophen' treatment, but not for piroxicam, as shown in Table XX.

E. OTHER

1. Test for Adequacy of the Washout

When Student's t-test for paired data was used to compare the mean values of outcome measures at pretreatment baseline assessment, and after the washout period, a statistically significant improvement from baseline was detected for both the articular and systemic indices. No statistically significant change was noted in other outcome measures. The results are shown in Table XXI.

The washout may have been incomplete for some patients crossing over from piroxicam to 'Entrophen' treatments, since detectable serum

levels of piroxicam were measured in three patients (patients 4, 6, 9), two of which were above the minimum antiinflammatory drug concentration of 5.00 mcg/mL.[70] (Table XXVII).

2. Correlations Between Outcome Measures During 'Entrophen' or Piroxicam Therapy

No consistent correlations were evident between weekly pain ratings or morning stiffness estimations, and other outcome measures when the relationships between the outcome measures were evaluated. As would be expected, a consistently high correlation between articular index and the count of tender joints, from which it was derived, was found ($r = 0.6406$ to 0.9423, $p = 0.005$ to 0.000).

A significant correlation between ESR and grip strength was noted, particularly during piroxicam treatment. The results are shown in Table XXII. Systemic index was most consistently correlated with ESR and grip strength during both treatments, as shown in Table XXIII and XXIV.

3. Compliance

Compliance did not appear to be a problem for most patients with either 'Entrophen' or piroxicam, as shown in Tables XXV and XXVI. Patients 12 and 14 appeared to have a consistent problem with compliance to 'Entrophen' therapy, but not with piroxicam, which was reflected in both pill count and plasma salicylate levels.

TABLE I

Patient Characteristics at Entry into the Study

Patient Number	Age (Yrs)	Sex	Duration of Arthritis (Yrs)	RF	ANF
1	63	M	4	1:80	Negative
2	31	F	6	1:320	Negative
3	65	F	5	1:640	Negative
4	59	F	30	1:320	Negative
5	43	M	1	1:320	1:40
6	46	F	19	Negative	Negative
7	57	F	25	1:320	1:40
8	46	F	10	1:160	1:40
9	32	F	2	Negative	Negative
10	57	F	4	Negative	1:80
11	73	F	4	Negative	1:40
12	61	F	26	Negative	1:40
13	58	F	9	Negative	Negative
14	51	F	7	1:320	1:80
15	52	M	10	1:160	1:80
Summary:	52.9 ± 11.7	F: 12 M: 3	10.8 ± 9.5	Negative: 6 Positive: 9	Negative: 7 Positive: 8

TABLE I, continued

Patient Characteristics at Entry into the Study

Patient Number	Past Use of ASA	Past Use of NSAID (#)	Past Use of Suppressants	Concurrent Arthritis Medications	Concurrent Disease	Concurrent Other Medications
1	Yes	1	Gold[1]	No	No	No
2	Yes	1	No	No	Hypothyroid goitre, Heart Murmur	No
3	Yes	1	No	No	Benign thyroid nodules	Premarin
4	Yes	No	No	No	Anemia, gallstones	Lorazepam
5	No	1	No	No	No	No
6	Yes	1	No	No	No	No
7	Yes	Numerous	Gold Penicillamine Chloroquin	Methylpred-nisolone 7.5 mg/d	Depression	Amitriptyline
8	Yes	1	Gold[2]	No	No	No
9	Yes	1	No	No	No	No

TABLE I, continued

Patient Characteristics at Entry into the Study

Patient Number	Past Use of ASA	Past Use of NSAID (#)	Past Use of Suppressants	Concurrent Arthritis Medications	Concurrent Disease	Concurrent Other Medications
10	No	2	No	No	Hypertension Hypothyroid Glaucoma	
11	No	3	No	No	No	No
12	No	4	Gold?[3]	No	Hypertension	Dyazide
13	Yes	1	Gold Penicillamine	Azathioprine Prednisone	Degenerative Disk Disease	- -
14	Yes	Numerous	No	Prednisone 5 mg BID	No	-
15	Yes	1	Gold?[3]	No	Dysphagia	No

1. Gold = test dose of gold only
2. Gold = discontinued 4 months prior to study secondary to proteinuria
3. Gold? = uncertain history of gold therapy

Summary	Yes: 11 No : 4	0: 1 1: 9 2: 5	Yes: 6 No : 9	Yes: 3 No : 12	Yes: 8 No : 7	Yes: 3 No : 12

TABLE II

Summary of Disease Activity after Initial Washout at Entry into the Study

	Systemic Index	Pain Rating	Tender Joints (Number)	Articular Index	Duration Morning Stiffness (hours)	ESR (mm/hr)	Average Grip Strength (mmHg)
Minimum	19	0.0	8	36	0.00	21	56
Maximum	132	12.3	39	182	9.99'	52	237
Mean	91	8.0	23	106	2.06	39	123
S.D.	35	4.1	11	52	2.58	10	51

'9.99 signifies "all day"

TABLE III

Patient Outcomes Following 'Entrophen' and/or Piroxicam Treatments

Patient Number	Outcome 'Entrophen'	Outcome Piroxicam	Comments
1	C	C	
* 2	N	C	Refused to try 'Entrophen' after successful completion of piroxicam treatment
3	C	C	
4	D	C	Dropout due to side effects
5	C	C	
6	D	D	Dropout of both treatments due to inadequate disease control
7	D	C	Dropout due to side effects
8	C	D	Dropout due to inadequate disease control
9	C	C	
10	C	C	
11	C	C	
12	C	C	
* 13	N	D	Dropped out of trial before trying 'Entrophen' due to severe flare of disease activity, and reactivation of degenerative disk disease

TABLE III, continued

Patient Outcomes Following 'Entrophen' and/or Piroxicam Treatments

Patient Number	Outcome 'Entrophen'	Outcome Piroxicam	Comments
14	D	D	Dropped out of both treatments due to side effects
15	D	D	Dropped out of both treatments due to inadequate disease control

C = Completed full 12 weeks of treatment

D = Dropped out before completing 12 weeks of treatment

N = Did not try the medication

* = Patients were excluded from final analysis since they did not try both medications

TABLE IV

Change in Disease Activity During Completed Piroxicam Treatments

Variable	Number of Patients[1]	Baseline Mean	Week 12 Mean (S.D.)	Mean Change	p
Pain	10	7.3 (4.1)	8.6 (2.6)	-1.3 (4.3)	0.356
Tender Joints (Number)	10	25 (14)	16 (14)	9 (7)	0.002*
Articular Index	10	103 (14)	64 (15)	36 (31)	0.006*
Duration A.M. Stiffness (Hrs)	10	0.95 (0.32)	0.56 (0.61)	0.39 (0.56)	0.054
ESR (mm/hr)	9[2]	38 (10)	41 (10)	-4 (6)	0.105
Average Grip Strength (mm Hg)	10	139 (57)	167 (92)	28 (48)	0.100
Systemic Index	9[2]	77 (27)	63 (18)	15 (19)	0.044*

[1]Patients 1, 2, 3, 4, 5, 7, 9, 10, 11, 12 completed a full 12 week course with piroxicam

[2]ESR not available for patient 3 at Week 12, so systemic index was not calculable

*Statistically significant at $p < 0.05$

TABLE V

Change in Disease Activity During Completed 'Entrophen' Treatments

Variable	Number of Patients[1]	Baseline Mean	Week 12 Mean (S.D.)	Mean Change	p
Pain	8	10.1 (2.9)	7.3 (3.6)	2.9 (2.8)	0.035*
Tender Joints (Number)	8	22 (12)	15 (9)	7 (9)	0.080
Articular Index	8	101 (72)	78 (58)	23 (22)	0.033*
Duration A.M. Stiffness (Hrs)	8	0.76 (0.76)	0.60 (0.40)	0.16 (0.73)	0.573
ESR (mm/hr)	8	36 (13)	32 (12)	4 (9)	0.283
Average Grip Strength (mm Hg)	7[2]	144 (87)	160 (82)	16 (18)	0.080
Systemic Index	7[2]	78 (30)	59 (20)	19 (18)	0.045*

[1]Patients 1, 3, 5, 8, 9, 10, 11, 12 completed a full 12 week course of therapy with 'Entrophen'

[2]Grip strength measurement not available for patient 5 at baseline so systemic index could not be calculated

*Statistically significant at $p < 0.05$

TABLE VI

T-tests Comparing the Change in Disease Activity Between 'Entrophen' and Piroxicam in Patients Completing Both Phases of the Trial

Variable	N[1]	Drug	Change in Activity (Mean of Differences)	Standard Error	Mean Difference (E-P)	Standard Error	p
Pain	7	E[2]	0.57	2.51	1.32	3.34	0.709
		P[3]	-0.75	1.63			
Tender Joints (Number)	7	E	8.8	3.9	4.4	6.3	0.511
		P	13.3	4.1			
Articular Index	7	E	27.2	9.6	-12.5	16.8	0.490
		P	39.7	14.2			
A.M. Stiffness (Hours)	7	E	0.142	0.325	-0.000	0.306	1.000
		P	0.142	0.057			
ESR (mm/hr)	6[4]	E	5.0	4.1	10.2	7.0	0.208
		P	-5.2	3.4			
Grip Strength (mmHg)	6[5]	E	16.2	9.1	-20.6	14.5	0.228
		P	36.8	15.0			
Systemic Index	5[6]	E	18.0	8.7	13.6	8.2	0.174
		P	4.4	5.8			

[1]Patients 1, 3, 5, 9, 10, 11, 12 completed 12 weeks treatment with both agents
[2]E = 'Entrophen'
[3]P = Piroxicam
[4]ESR not available for patient 3 at baseline of piroxicam treatment
[5]Grip strength not available for patient 5 at baseline of 'Entrophen' treatment
[6]Systemic index could not be calculated for patients 5 and 3

TABLE VII

Comparison of the Change in Systemic Index Produced by 'Entrophen' and Piroxicam by the Wilcoxan Signed Rank Sum Test[82]

Patient[1]	Week of Comparison	Change in Index-E[2]	Change in Index-P[3]	Difference (E-P)	Rank	Signed Rank
1	12	20	22	-2	1	-1.5
3	12	38	19	19	8	8
4	2	0	3	-3	3	-3.5
6	1	11	-13	24	9	9
7	3	9	11	-2	2	-1.5
8	4	21	-17	38	11	11
9	12	0	-11	11	7	7
10	12	14	11	3	4	3.5
11	12	50	5	45	12	12
12	12	6	-5	11	6	6
14	2	34	3	31	10	10
15	8	-12	-19	7	5	5

[1]Patient 2 and 13 excluded because they only tried piroxicam
Patient 5 excluded because baseline systemic index could not be calculated

[2]E = 'Entrophen'

[3]P = Piroxicam

Sum+ = 71.5

Sum- = -6.5

$$E(\text{Sum+}) = \tfrac{1}{2}(12)(13) = 39$$

$$\text{Var(Sum+)} = (12)(13)(25) - \frac{1}{48}\left[(2^3-2) + (2^3-2)\right]$$

$$= \frac{}{24} \quad = 162.5 - 0.25 = 162.25$$

$$\text{SE(Sum+)} = \sqrt{\text{Var}} = 12.738$$

$$\mu = \frac{71.5 - 39 - 0.5}{12.738} = 2.512 \qquad p = 0.0060$$

TABLE VIII

Comparison of the Change in Systemic Index Produced by 'Entrophen' and Piroxicam by the Wilcoxan Signed Rank Sum Test[82]
Excluding Patients 9 and 10

Patient[1]	Week of Comparison	Change in Index-E[2]	Change in Index-P[3]	Difference (E-P)	Rank	Signed Rank
1	12	20	22	-2	1	-1.5
3	12	38	19	19	6	6
4	2	0	3	-3	3	-3
5	12	23	23	0	-	
6	2	11	-13	24	7	7
7	3	9	11	-2	2	-1.5
8	4	21	-17	38	9	9
11	12	50	5	45	10	10
12	12	6	-5	11	5	5
14	2	34	3	31	8	8
15	8	-12	-19	7	4	4

[1]Patient 2 and 13 excluded because they only tried piroxicam
[2]E = 'Entrophen'
[3]P = Piroxicam

Sum+ = 49
Sum- = 6

$E = \frac{1}{4}(10)(11) = 27.5$

$Var = \frac{(10)(11)(21)}{24} - \frac{1}{48}(2^3-2) = 96.125$

$SE = \sqrt{Var} = 9.804$

$\mu = \frac{49 - 27.5 - 0.5}{9.804} = 2.141$ $\quad p = 0.0162$

TABLE IX

Comparison of the Change in Systemic Index Produced by 'Entrophen' and Piroxicam, in Patients Completing the Trial, by the Wilcoxan Signed Rank Sum Test[82]

Patient[1]	Week of Comparison	Change in Index-E[2]	Change in Index-P[3]	Difference (E-P)	Rank	Signed Rank
1	12	20	22	-2	1	-1
3	12	38	19	19	5	5
9	12	0	-11	11	3	3.5
10	12	14	11	3	2	2
11	12	50	5	45	6	6
12	12	6	-5	11	4	3.5

[1]Patient 5 completed both phases of treatment but baseline Systemic Index could not be calculated for the 'Entrophen' treatment
[2]E = 'Entrophen'
[3]P = Piroxicam

Sum+ = 20
Sum- = -1

$E(\text{Sum+}) = \frac{1}{4}(7)(6) = 10.5$

$\text{Var}(\text{Sum+}) = \frac{(7)(6)(13)}{24} - \frac{1}{48}(2^3-2)$

$= 22.75 - 0.125 = 22.625$

$SE(\text{Sum+}) = \sqrt{\text{Var}} = 4.757$

$u = \frac{20 - 10.5}{4.757} - 0.5 = 1.892$

$p = 0.0292$

TABLE X

Comparison of the Change in Pain Rating Produced by 'Entrophen' and Piroxicam, in Patients Completing the Trial, by the Wilcoxan Signed Rank Sum Test[82]

Patient	Week of Comparison	Change in Index-E[1]	Change in Index-P[2]	Difference (E-P)	Rank	Signed Rank
1	12	3.0	0.5	2.5	3	3
3	12	4.3	0.0	4.3	4	4
5	12	2.0	3.0	-1.0	1	-1
9	12	0.0	-7.0	7.0	6	6
10	12	1.0	3.0	-2.0	2	-2
11	12	8.0	0.0	8.0	7	7
12	12	2.0	-4.0	6.0	5	5

[1]E = 'Entrophen'
[2]P = Piroxicam

Sum+ = 25
Sum- = -3

$E(\text{Sum+}) = \frac{1}{4}(7)(8) = 14$

$\text{Var}(\text{Sum+}) = \frac{(7)(8)(15)}{24}$

$= 35$

$SE(\text{Sum+}) = \sqrt{\text{Var}} = 5.916$

$u = \frac{25 - 14}{5.916} - 0.5 = 1.775$

$p = 0.0379$

TABLE XI

Comparison of the Change in ESR Produced by 'Entrophen' and Piroxicam, in Patients Completing the Trial, by the Wilcoxan Signed Rank Sum Test[82]

Patient	Week of Comparison	Change in Index-E[1]	Change in Index-P[2]	Difference (E-P)	Rank	Signed Rank
1	12	-9	3	-12	4	-4
5	12	13	-21	33	6	6
9	12	7	-3	10	3	3
10	12	5	-2	7	2	2
11	12	18	-7	25	5	5
12	12	-4	0	-4	1	-1

[1]E = 'Entrophen'
[2]P = Piroxicam

Sum+ = 16
Sum- = -5

$E(\text{Sum+}) = \frac{1}{4}(6)(7) = 10.5$

$\text{Var}(\text{Sum+}) = \frac{(6)(7)(13)}{24}$

$= 22.75$

$SE(\text{Sum+}) = \sqrt{\text{Var}} = 4.77$

$u = \frac{16 - 10.5 - 0.5}{4.77} = 1.048$

$p = 0.1474$

TABLE XII

Comparison of the Change in Articular Index Produced by 'Entrophen' and Piroxicam, in Patients Completing the Trial, by the Wilcoxan Signed Rank Sum Test[82]

Patient	Week of Comparison	Change in Index-E[1]	Change in Index-P[2]	Difference (E-P)	Rank	Signed Rank
1	12	25	35	-10	1	-1
3	12	103	16	87	6	6
5	12	30	98	-68	5	-5
9	12	6	28	-22	2	-2
10	12	22	-8	30	3	3
11	12	171	33	138	7	7
12	12	9	52	-41	4	-4

[1]E = 'Entrophen'
[2]P = Piroxicam

Sum+ = 16
Sum- = 12

$E(\text{Sum+}) = \frac{1}{4}(7)(8) = 1.4$

$\text{Var}(\text{Sum+}) = \frac{(7)(8)(15)}{24}$

$= 35$

$SE(\text{Sum+}) = \sqrt{\text{Var}} = 5.916$

$u = \frac{16 - 14 - 0.5}{5.916} = 0.254$

$p = 0.3997$

TABLE XIII

Comparison of the Change in Tender Joints Produced by 'Entrophen' and Piroxicam, in Patients Completing the Trial, by the Wilcoxan Signed Rank Sum Test[82]

Patient	Week of Comparison	Change in Index-E[1]	Change in Index-P[2]	Difference (E-P)	Rank	Signed Rank
1	12	12	7	5	4	3.5
3	12	1	14	-13	6	-6
5	12	9	14	-5	3	-3.5
9	12	4	6	-2	1	-1
10	12	1	-2	3	2	2
11	12	26	5	21	7	7
12	12	1	10	-9	5	-5

[1]E = 'Entrophen'
[2]P = Piroxicam

Sum+ = 12.5
Sum- = 15.5

$E(\text{Sum+}) = \frac{1}{4}(7)(8) = 14$

$\text{Var}(\text{Sum+}) = \frac{(7)(8)(15)}{24} - \frac{1}{48}(2^3-2)$

$= \frac{35}{} - 0.125 = 34.875$

$\text{SE}(\text{Sum+}) = \sqrt{\text{Var}} = 5.906$

$u = \frac{12.5 - 14 - 0.5}{5.906} = -0.337$

$p = 0.3780$

TABLE XIV

Comparison of the Change in Morning Stiffness Produced by 'Entrophen' and Piroxicam, in Patients Completing the Trial, by the Wilcoxan Signed Rank Sum Test[82]

Patient[1]	Week of Comparison	Change in Index-E[2]	Change in Index-P[3]	Difference (E-P)	Rank	Signed Rank
1	12	1	0.25	0.75	4	4
5	12	0	0.25	-0.25	2	-2
9	12	-0.5	0.00	-0.50	3	-3
10	12	0.9	0.05	0.85	5	5
11	12	0.15	0.30	-0.15	1	-1
12	12	-0.9	0.0	-0.90	6	-6

[1]Patient 3 excluded since she could not specify a duration of morning stiffness
[2]E = 'Entrophen'
[3]P = Piroxicam

Sum+ = 9
Sum- = 12

$E(\text{Sum+}) = \frac{1}{4}(6)(7) = 10.5$

$\text{Var}(\text{Sum+}) = \frac{(6)(7)(13)}{24}$

$= 22.75$

$SE(\text{Sum+}) = \sqrt{\text{Var}} = 4.77$

$u = \frac{9 - 10.5 - 0.5}{4.77} = -0.4193$

$p = 0.3375$

TABLE XV

Comparison of the Change in Grip Strength Produced by 'Entrophen' and Piroxicam, in Patients Completing the Trial, by the Wilcoxan Signed Rank Sum Test[82]

Patient[1]	Week of Comparison	Change in Index-E[2]	Change in Index-P[3]	Difference (E-P)	Rank	Signed Rank
1	12	46	83	-37	4	-4
3	12	67	-10	77	6	6
9	12	-2	61	-63	5	-5
10	12	-3	23	-26	3	-3
11	12	15	8	7	1	1
12	12	25	9	16	2	2

[1]Patient 5 excluded since baseline grip strength was missing for 'Entrophen' treatment
[2]E = 'Entrophen'
[3]P = Piroxicam

Sum+ = 9
Sum- = 12

$E(\text{Sum+}) = \frac{1}{4}(6)(7) = 10.5$

$\text{Var}(\text{Sum+}) = \frac{(6)(7)(13)}{24}$

$= \sqrt{22.75}$

$SE(\text{Sum+}) = \text{Var} = 4.77$

$u = \frac{9 - 10.5 - 0.5}{4.77} = -0.4193$

$p = 0.3375$

TABLE XVI

Number of Patients Experiencing Side Effects
During Treatment with 'Entrophen' and Piroxicam

Side Effects	Number of Patients with Side Effects					
	Piroxicam			'Entrophen'		
	Mild	Moderate	Severe	Mild	Moderate	Severe
GASTROINTESTINAL						
cramps/gas	1					
constipation	1			2		
discomfort	2		1	1	3	2
CENTRAL NERVOUS SYSTEM						
tinnitis, hearing				1	6	3
drowsiness	1			1	1	
lightheaded/dizzy	2					
headache	1		1			
insomnia				1		
OTHER-						
short of breath				3		
flushing				1		
rash	1					
swelling			1			1
petechiae/bruises easily	1			1		
nosebleed	1					
TOTAL	11	0	3	11	10	6

TABLE XVII

Chi-square Test[83] for a Difference in the Proportional Distribution of Side Effects Between Piroxicam and 'Entrophen' Treatments

	Piroxicam		'Entrophen'		Totals
Mild	O = 11	E = 7.5	O = 11	E = 14.5	22
Moderate	O = 0	E = 3.4	O = 10	E = 6.6	10
Severe	O = 3	E = 3.1	O = 6	E = 5.9	9
Totals	14		27		41

$$\chi^2 = \frac{(O - E)^2}{E} = \frac{(11 - 7.5)^2}{7.5} + \frac{(11 - 14.5)^2}{14.5} + \frac{(0 - 3.4)^2}{3.4} + \frac{(10 - 6.6)^2}{6.6} + \frac{(3 - 3.1)^2}{3.1} + \frac{(6 - 5.9)^2}{5.9}$$

$$= 1.63 + 0.84 + 3.4 + 1.75 + 0.0032 + 0.0017$$

$$= 7.623$$

DF = 2 $p < 0.025$

Where O = observed counts
E = expected counts
DF = degrees of freedom

TABLE XVIII

Relationship Between Piroxicam Level and Outcome Measures During Treatment

Variable	Correlation Coefficient "r" (p)					
	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12
Pain	0.5576 (0.020)	-0.4187 (0.068)	-0.2444 (0.210)	-0.3984 (0.079)	0.0018 (0.498)	0.0883 (0.404)
Tender Joints	-0.4695 (0.045)	-0.2594 (0.185)	0.0581 (0.425)	0.1479 (0.307)	0.0222 (0.473)	0.6501 (0.021)
Articular Index	-0.3014 (0.147)	0.0094 (0.487)	-0.0933 (0.381)	0.0210 (0.472)	-0.0712 (0.413)	0.3032 (0.197)
Morning Stiffness	0.0750 (0.399)	-0.1693 (0.290)	-0.5534 (0.039)	-0.3575 (0.127)	-0.4951 (0.061)	-0.3981 (0.127)
ESR	0.3473 (0.112)	-0.1049 (0.361)	0.0049 (0.494)	0.2833 (0.163)	0.0801 (0.407)	0.1622 (0.338)
Grip Strength	-0.1273 (0.332)	-0.0048 (0.494)	0.0377 (0.451)	-0.0715 (0.404)	-0.3704 (0.118)	-0.3379 (0.170)
Systemic Index	-0.0939 (0.375)	-0.2510 (0.228)	-0.3928 (0.092)	0.1896 (0.267)	0.4955 (0.073)	0.2119 (0.292)

TABLE XIX

Relationship Between Salicylate Level and Outcome Measures During Treatment

Variable	Correlation Coefficient "r" (p)					
	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12
Pain	0.1992 (0.267)	0.1054 (0.372)	0.0472 (0.445)	-0.5717 (0.042)	-0.5169 (0.077)	-0.2094 (0.326)
Tender Joints	0.0012 (0.499)	0.3231 (0.153)	0.1305 (0.351)	-0.0306 (0.467)	-0.2272 (0.278)	-0.5379 (0.106)
Articular Index	-0.0196 (0.476)	0.0807 (0.402)	0.0072 (0.492)	-0.0242 (0.474)	-0.1661 (0.335)	-0.0028 (0.498)
Morning Stiffness	0.6691 (0.012)	-0.2744 (0.207)	-0.2074 (0.283)	-0.2433 (0.264)	-0.2738 (0.256)	-0.1764 (0.353)
ESR	0.4177 (0.088)	-0.1972 (0.270)	0.0213 (0.475)	0.0172 (0.481)	-0.0501 (0.449)	-0.5293 (0.111)
Grip Strength	-0.1818 (0.296)	0.0144 (0.483)	-0.3130 (0.174)	-0.1139 (0.377)	-0.3583 (0.172)	-0.2273 (0.312)
Systemic Index	0.0961 (0.396)	-0.0996 (0.385)	0.2281 (0.278)	0.3118 (0.207)	-0.2549 (0.271)	-0.1858 (0.345)

TABLE XX

Comparison of Drug Levels in Responders and Nonresponders to 'Entrophen' and Piroxicam

'Entrophen' Treatment

Responders				Nonresponders			
Patient	Final Week	Change in Systemic Index	Level (mcg/mL)	Patient	Final Week	Change in Systemic Index	Level (mcg/mL)
1	12	20	112	4	2	5	0
3	12	38	242	6	2	-11	M
5	12	23	313	7	3	9	156
8	12	25	247	9	12	0	161
11	12	50	300	10	12	14	0
14	3	30	174	12	12	6	118
				15	8	-12	129
			$\bar{x}$ = 231				$\bar{x}$ = 94 ($p < 0.02$)

M = missing

Comparison of Drug Levels in Responders and Nonresponders to 'Entrophen' and Piroxicam

Piroxicam Treatment

Responders				Nonresponders			
Patient	Final Week	Change in Systemic Index	Level (mcg/mL)	Patient	Final Week	Change in Systemic Index	Level (mcg/mL)
1	12	22	5.66	2	12	8	3.91
4	12	20	10.89	3	12	-21	30.29
5	12	40	6.23	6	8	4	4.31
7	12	36	4.19	8	4	-17	6.44
				9	12	-11	6.28
				10	12	3	5.74
				11	12	5	5.77
				12	12	- 5	14.03
				13	5	-56	6.23
				14	2	3	7.01
				15	7	-19	31.94
			$\bar{x}$ = 6.74				$\bar{x}$ = 11.09 ($p > 0.10$)

TABLE XXI

Test for Adequacy of the Washout: Pretreatment Baseline Compared to Washout Disease Activity

Variable	N[1]	Baseline	Washout Means (S.D.)	Difference	p
Pain	13	7.9 (4.4)	9.2 (2:9)	1.3 (4.4)	0.321
Tender Joints (Number)	13	24 (11)	21 (15)	-4 (9)	0.190
Articular Index	13	111 (55)	94 (58)	-17 (27)	0.036*
Morning Stiffness (Hours)	13	1.16 (1.21)	0.67 (0.72)	-0.49 (1.13)	0.160
ESR (mm/hr)	13	39 (11)	38 (20)	-1 (20)	0.873
Grip Strength (mmHg)	12[2]	125 (53)	130 (72)	5 (38)	0.687
Systemic Index	12[2] (31)	91 (29)	80 (14)	-11	0.028*

[1]All Patients except 2 and 13 crossed over
[2]Grip strength not available for Patient 5 at time of washout so systemic index could not be calculated
*Statistically significant $p < 0.05$

TABLE XXII

Relationship Between ESR and Grip Strength
During 'Entrophen' and Piroxicam Treatments

Drug	Correlation Coefficient "r" (p)					
	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12
Piroxicam	-0.6572 (0.994)	-0.5747 (0.020)	-0.5952 (0.012)	-0.5893 (0.013)	-0.5012 (0.058)	-0.8287 (0.003)
'Entrophen'	-0.6003 (0.020)	-0.9071 (0.000)	-0.3123 (0.175)	-0.1318 (0.358)	-0.4206 (0.130)	-0.4955 (0.129)

TABLE XXIII

Relationship Between Systemic Index and and Measures During Treatment with Piroxicam

Variable	Correlation Coefficient "r" (p)					
	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12
Pain	0.3973 (0.071)	0.3376 (0.142)	0.3371 (0.119)	0.6366 (0.010)	0.6356 (0.024)	0.3026 (0.214)
Tender Joints	0.3325 (0.113)	0.1698 (0.299)	0.2413 (0.203)	0.4825 (0.047)	0.3372 (0.170)	0.5960 (0.045)
Articular Index	0.4939 (0.031)	0.4046 (0.096)	0.4262 (0.064)	0.5460 (0.027)	0.5217 (0.061)	0.6708 (0.024)
Morning Stiffness	0.8970 (0.000)	0.3736 (0.129)	0.3955 (0.102)	0.1595 (0.320)	-0.2263 (0.279)	0.3182 (0.202)
ESR	0.6682 (0.003)	-0.4170 (0.089)	0.2565 (0.188)	0.5909 (0.017)	-0.1223 (0.368)	-0.8722 (0.001)
Grip Strength	-0.6123 (0.008)	-0.3373 (0.142)	-0.6655 (0.005)	-0.6978 (0.004)	-0.3890 (0.133)	-0.7074 (0.017)

TABLE XXIV

Relationship Between Systemic Index and
and Measures During Treatment with 'Entrophen'

Variable	Correlation Coefficient "r" (p)					
	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12
Pain	0.2771	0.4193	0.1718	0.2572	0.6588	0.6597
	(0.205)	(0.100)	(0.329)	(0.252)	(0.038)	(0.053)
Tender Joints	0.3196	0.3211	0.5684	0.4816	0.2455	0.8970
	(0.169)	(0.168)	(0.055)	(0.095)	(0.279)	(0.003)
Articular Index	0.2567	0.4287	0.5938	0.5317	0.5230	0.9461
	(0.223)	(0.094)	(0.046)	(0.070)	(0.092)	(0.001)
Morning Stiffness	0.1109	0.3231	0.1034	0.4892	0.1865	0.1365
	(0.380)	(0.181)	(0.396)	(0.109)	(0.344)	(0.385)
ESR	0.3750	0.5859	0.5616	0.4949	0.8402	-0.0933
	(0.128)	(0.029)	(0.058)	(0.088)	(0.005)	(0.421)
Grip Strength	0.0401	-0.3432	-0.5457	-0.0503	-0.4766	-0.1818
	(0.453)	(0.151)	(0.064)	(0.449)	(0.116)	(0.348)

TABLE XXV

Serum Levels and Compliance at Each Week of Treatment with Piroxicam

Patient	Serum Concentration mcg/mL (% Compliance)					
	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12
1	0.00(100)^{2*}	0.00(100)^{2}	0.00(100)^{3}	3.80(100)^{3}	5.87(100)^{3}	5.66(100)^{3}
2	4.71(100)^{2}	5.58(100)^{3}	5.50(57) ^{4}	5.17(96) ^{4}	4.76(100)^{4}	3.91(105)^{4}
3	0.00(100)^{2}	4.88(100)^{2}	10.04(100)^{3}	10.83(114)^{3}	19.58(95) ^{3}	30.29(98)**
4	5.52(100)^{2}	9.38(107)^{2}	10.38(100)^{3}	N/A(100)^{3}	13.90(95) ^{3}	10.89(100)^{3}
5	0.00(100)^{2}	10.01(100)^{2}	10.63(100)^{3}	12.20(100)^{4}	7.61(102)^{4}	6.23(100)^{4}
6	1.36(100)^{2}	3.50(100)^{3}	3.82(100)^{4}	5.81(107)^{4}	4.31(100)^{4}	
7	3.79(100)^{2}	1.76(100)^{3}	0.00(100)^{4}	3.07(100)^{4}	6.87(100)^{4}	4.19(100)^{4}
8	6.57(100)^{2}	10.23(100)^{3}	6.73(100)^{4}	6.44(100)^{4}		
9	5.32(100)^{2}	0.00(100)^{3}	6.75(100)^{4}	7.30(100)^{4}	11.36(96) ^{4}	6.28(89) ^{4}
10	5.27(100)^{2}	3.95(100)^{3}	7.12(100)^{4}	5.39(93) ^{4}	6.42(100)^{4}	5.74(100)^{4}
11	11.19(93) ^{2}	18.67(100)^{2}	16.57(100)^{4}	12.78(100)^{4}	10.04(100)^{2}	5.77(102)^{4}
12	14.01(100)^{2}	17.11(114)^{2}	17.72(114)^{2}	17.44(114)^{2}	20.02(89) ^{2}	14.03(86) ^{2}
13	0.00(100)^{2}	8.57(100)^{3}	9.00(100)^{4}	13.28(100)^{4}		
14	5.67(100)^{2}	7.01(63) ^{1}				
15	10.22(86) ^{2}	8.72(114)^{3}	0.00(29) ^{2}	10.47(100)^{2}	31.94(89) ^{2}	

* Dosage schedule 1, 2, 3, 4 as outlined in "Methodology", indicated by a superscript

** Exacerbation of arthritis uncontrolled by medications prompted unscheduled increase in piroxicam to 30 mg daily by R.M. for 1 week at end of therapy

N/A Not Available

TABLE XXVI

Plasma Salicylate Levels and Compliance at Each Week of Treatment with 'Entrophen'

Patient	Plasma Salicylate Level mcg/mL (% Compliance)					
	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12
1	52(N/A)^{2*}	128(N/A)^{3}	209(N/A)^{4}	219(N/A)^{4}	152(N/A)^{4}	114(N/A)^{4}
3	278(100)^{2}	287(98)^{3}	291(100)^{3}	315(117)^{3}	238(102)^{2}	242(98)^{2}
4	0(45)^{2}					
5	111(100)^{2}	196(102)^{3}	213(100)^{4}	283(100)^{4}	254(100)^{4}	313(100)^{4}
6	N/A(102)^{2}	N/A(37)^{1}				
7	253(105)^{2}	129(114)^{1}	156(83)^{1}			
8	200(102)^{2}	277(92)^{3}	327(97)^{4}	339(100)^{4}	320(98)^{3}	247(100)^{3}
9	319(107)^{2}	181(80)^{1}	152(100)^{1}	183(100)^{1}	114(98)^{1}	161(102)^{1}
10	106(83)^{2}	122(100)^{3}	192(91)^{4}	169(114)^{4}	41(96)^{4}	0(95)^{4}
11	347(126)^{2}	268(109)^{2}	239(97)^{1}	238(94)^{1}	293(97)^{1}	300(96)^{1}
12	281(45)^{2}	371(81)^{3}	235(76)^{2}	235(66)^{2}	178(67)^{2}	119(56)^{2}
14	67(58)^{2}	0(41)^{1}	174(66)^{1}	0(53)^{1}		
15	216(95)^{2}	132(86)^{3}	222(96)^{3}	323(96)^{4}	129(97)^{3}	

* Dosage schedule 1, 2, 3, 4 as outlined in "Methodology", indicated by a superscript

N/A Not available

TABLE XXVII

Piroxicam and Salicylate Levels at the End of The Washout in Patients* Crossing Over

Patients Receiving Entrophen First		Patients Receiving Piroxicam First	
Patient	Entrophen Level (mcg/mL)	Patient	Piroxicam Level (mcg/mL)
1	0	4	11.55
3	16	6	6.70
5	0	7	0.00
8	0	9	1.80
10	0	12	0.00
11	0		
14	0		
15	0		

* Patients 2 and 13 received piroxicam in the first treatment and did not cross-over to receive 'Entrophen'

V. DISCUSSION

A. PATIENT CHARACTERISTICS

The patient population of this study was representative of the general rheumatoid arthritis population, with a female to male ratio of 4.1, and a mean age of 52.9 years. The mean duration of rheumatoid arthritis, 10.8 years, suggests a relatively chronic disease process was represented. The mean duration of disease activity of the 12 female patients was 11.4 years (range 2 to 30 years) as compared to 5.0 years (range 1 to 10 years) in the three male patients. This may reflect an observation that females are more prone to develop a more chronic form of arthritis than males.[84]

Consistent with the chronic nature of the disease process in this population, 10 patients had previously taken at least one NSAID, as well as some form of ASA, and five had tried at least two different NSAIDs before entering the study. Four patients had never tried ASA, although may have used other NSAIDs in the past. This history of antiinflammatory drug use was not unexpected since, for ethical reasons, patients had been selected from a population of rheumatoid arthritis patients not responding to antiinflammatory drug therapy at the time of admission to the study.

The phenomenon of varying interindividual response to NSAIDs [85,86] justified the selection of patients unresponsive to previous therapy; however, the need for remittive agents, as opposed to another

trial of NSAIDs at this point in the course of the disease, must be considered. The point at which a patient is considered unresponsive to antiinflammatory drug therapy and becomes a candidate for remittive therapy (gold or penicillamine) is variable, depending on the rate of disease progression, the patient's expectation of treatment, and the physician's attitude to NSAIDs and remittive therapy.[86,87,88] Two patients (7, 13) had a history of previous trials with remittive agents, including penicillamine and chloroquin, and four other patients had a remote history of exposure to gold, three of whom had received a test dose only (1, 12, 15), and one of whom was discontinued due to proteinuria (8). Eight of 15 patients (2, 3, 5, 6, 8, 10, 14, 15) eventually received remittive therapy after terminating the study. It appears the disease activity may have been severe enough to render a portion of the study population refractory to NSAIDs. A more responsive population may have been recently diagnosed rheumatoid arthritis patients undergoing initial treatment; however, the unpredictable course of arthritis in the first six months precluded study of patients in this group.[2,72]

Since ASA is the drug most frequently recommended by Canadian physicians for symptomatic treatment of arthritis,[87,89] it was not surprising that 11 of 15 patients had a history of previous ASA use. As defined by the selection criteria, these patients were unresponsive to previous antiinflammatory therapy; in a study comparing the pharmacological effects of two drugs by measuring the clinical response, the lack of response to one study agent in the past would constitute a

bias against that agent. However, suboptimal dosing of ASA could not be ruled out, and use of uncoated ASA could have necessitated discontinuing the drug prematurely due to side effects despite antiinflammatory response. This could not be confirmed by questioning the patient. Even a newly diagnosed, untreated rheumatoid arthritis population may have yielded patients previously exposed to ASA through self-medication.

Three patients (7, 13, 14) received steroids throughout the study in a stable dose of less than 10 mg of prednisone, or its equivalent, daily. The antiinflammatory, but not the analgesic properties of piroxicam and 'Entrophen' may have been obscured by concurrent steroid administration in these patients.

Patient 13 was receiving immunosuppressive therapy with azathioprine, in addition to steroids. In retrospect, this patient was of questionable suitability for entry into the study, since, although not an exclusion criteria, she had degenerative disk disease which flared early in the study necessitating hospitalization. During hospitalization, her immunosuppressive therapy was altered, and she was subsequently dropped from the study. Immunosuppressive therapy should represent an exclusion criteria for a study such as this, since these patients characteristically have advanced disease unresponsive to conventional medical management, and the need for alteration of immunosuppressive therapy is unpredictable due to hematologic toxicities.

Baseline disease activity, recorded after the initial washout period, varied considerably between patients as shown in Table II. The

mean values of the outcome measures approximated those reported by Lansbury to be characteristic of previously untreated patients,[75,76] but tended to reflect a less severe disease process. This may be the result of incomplete washout of previous therapy in some patients who were unable to tolerate a drug-free period of greater than three days.

Concurrent disease, recognized in eight patients at entry to the study, did not pose problems during the study except in patient 13, where a flare of degenerative disk disease contributed to her withdrawal from further treatment. However, the appearance of secondary rheumatic diseases, in some patients at the end of the study, suggest that the rheumatoid arthritis in this population may not have been as homogeneous as initially assessed, and may complicate interpretation of the data. Although all patients had been diagnosed as having had rheumatoid arthritis for at least six months, after completing the trial, a revised diagnosis of psoriatic arthritis was proposed for patient 9; patient 10 was investigated for kidney problems possibly secondary to systemic lupus erythematosis (SLE), a diagnosis which was never substantiated. Patients 4, 7, 10 and 11 had evidence of degenerative joint changes on X-ray. These patients were not excluded from the study however, since degenerative joint changes are not uncommon in rheumatoid arthritis and the major component of their disease was potentially responsive to the agents under study.

It is important that only a single disease, true rheumatoid arthritis, be tested.[73] Clinical experience, unconfirmed by controlled trials, suggests, for example, that the newer NSAID's are

more effective than ASA in the spondyloarthropathies (Reiter's syndrome, ankylosing spondylitis, psoriatic arthritis)[90]; in addition, the controversial role of inflammation in degenerative joint disease raises doubts as to the antiinflammatory effectiveness of NSAID's in this condition.[2,72] It is the nature of rheumatoid disease, however, that a population labelled as "rheumatoid arthritis" may consist of a group of similar diseases which will be defined in the future.[73] At present, the results of any study of rheumatoid arthritis must be interpreted with the heterogeneity of the disease in mind. It might even be hypothesized, for example, that subsets of patients defined by their response to specific NSAID's may represent subclinical differences in the disease process.

The exclusion of patients 9 and 10 from comparison of the change in disease activity between the two agents by the Wilcoxan signed rank sum test did not change the outcome; a statistically significant difference between the two treatments remained.

B. EFFICACY

The pharmacological effects and clinical efficacy of two antiinflammatory agents with prostaglandin synthesis inhibiting properties can be compared both directly by measuring the response of prostaglandin levels in an appropriate tissue during therapy, and indirectly by monitoring clinical manifestations of inflammation. Although reduction in synovial fluid prostaglandin levels during NSAID

treatment of rheumatoid arthritis has been shown to correspond weakly with clinical resolution of the inflammatory response in a few patients,[5] the evidence supporting the role of prostaglandin synthesis inhibition in the antiinflammatory effects of NSAIDs is largely circumstantial.[13] Thus, the pharmacological effects of NSAIDs in rheumatoid arthritis are more practically compared indirectly by measurement of the resolution of clinical manifestations of inflammation, stiffness, pain, joint swelling and tenderness, and functional capacity. Clinical response to NSAIDs in rheumatoid arthritis can be equated to a reduction in stiffness and pain, and the number of swollen and tender joints, as well as an improvement in functional capacity which frequently parallels an increase in grip strength.[2]

To take advantage of the quantitative nature of the data collected in this study, Student's t-test for paired data was used to assess the change in disease activity during treatment with 'Entrophen' or piroxicam, and then to compare the change in disease activity produced by the study drugs in patients who completed full courses of therapy with each. Piroxicam and 'Entrophen' both produced statistically significant improvement in the articular index and systemic index over a 12 week treatment period. Since the articular index is a component of the systemic index, the significant improvement in the systemic index may have simply reflected the significant improvement in articular index. No consistent correlation between articular index and systemic index was noted, however, when the relationships between outcome

measures were tested (Table XII). It is likely that the improvement in the systemic index was independent of the improvement in the articular index. Lansbury advocated the use of a systemic index, with or without the inclusion of the articular index, as a measure of the systemic activity of rheumatoid arthritis,[74,76] and showed that even without including joint findings, it was capable of detecting a true clinical remission.[73] This reinforces the concept of rheumatoid arthritis as a systemic disease,[72] rather than one with manifestations confined solely to the joint. 'Entrophen' and piroxicam appear to be useful agents for the symptomatic relief of systemic aspects of rheumatoid arthritis, in addition to their ability to control joint inflammation.

Piroxicam, but not 'Entrophen', produced a statistically significant reduction in the number of tender joints. Since the articular index is directly derived from the count of tender joints, and there was a consistently high correlation between the count of tender joints and the articular index when the relationship between outcome measures was tested, it is curious that 'Entrophen' did not also produce a statistically significant improvement in the count of tender joints. The explanation may lie in the calculation of Lansbury's articular index as a weighted sum of involved joints depending on the area of the articulating surface. For example, in calculating Lansbury's articular index, an involved knee would be assigned a value of 24 as compared to an interphalangeal joint which would be given a value of 1, or the wrist which would have a value of 4. A small change in the absolute number of tender joints not reaching statistical significance, could result in a

sufficiently large change in articular index to reach statistical significance if the joints involved have a relatively large articulating surface, for example, the hips, knees or wrists. Lansbury advocated the use of a weighted articular index as a more accurate measure of the total pool of joint inflammation, as compared to a simple joint count. Since both drugs produced a statistically significant reduction in the articular index, or total pool of joint inflammation, the reduction in number of tender joints by piroxicam, but not 'Entrophen' is of questionable significance.

'Entrophen', but not piroxicam, produced a statistically significant reduction in the patients' perception of pain as measured by the pain scale. The etiology of pain in rheumatoid arthritis is rooted in inflammation, where swelling of intra-articular tissues compresses pain-sensitive nerve tissue, and the presence of prostaglandins sensitizes nerve endings to the effects of pain mediators at the inflammatory site.[13] Piroxicam and ASA, inhibitors of prostaglandin synthetase, potentially ameliorate the pain of rheumatoid arthritis by reducing prostaglandin production, thereby preventing perpetuation of edema and swelling, and sensitization of pain receptors by prostaglandins. Since both agents are prostaglandin-synthesis inhibitors, and effectively reduced evidence of inflammation in these patients, as shown by a significant decrease in the systemic and articular indices, it is difficult to account for the differing effect of the two drugs on pain perception. Perhaps 'Entrophen' has additional analgesic properties unrelated to prostaglandin-synthesis inhibition at

the site of inflammation. A mechanism other than prostaglandin-synthesis inhibition may be postulated, or perhaps inhibition of prostaglandin synthesis at another site may be involved. It has been suggested that analgesics with prostaglandin-synthesis inhibiting properties may act centrally at a site in the brain or spinal cord, as well as peripherally.[91] Penetration to, or specificity for, proposed central sites may be a factor in their contribution to the analgesic activity of this class of drugs. Further studies are required to investigate this aspect of the NSAIDs analgesic properties.

The change in other outcome measures, duration of morning stiffness, ESR, and average grip strength, did not reach statistical significance during treatment with either drug. This may have been a function of the small number of patients in the study, and does not rule out a favourable effect of 'Entrophen' or piroxicam on components of disease activity represented by these measures.

When Student's t-test was used to compare the change in disease activity between 'Entrophen' and piroxicam in patients completing both phases of the trial, no significant difference between drugs was noted for any of the outcome measures. This suggests that, although both drugs reduced disease activity, as shown by a significant decrease in systemic index, there was no statistically significant difference in the ability of the drugs to do so. This is not surprising in light of previous studies which have failed to find a difference in the efficacy of NSAIDs, even with large numbers of patients collected in multicenter trials.[85]

The ability of the t-test to detect a statistically significant difference between treatments in this study population was very low, however. Because of the relatively insensitive nature of outcome measures in rheumatoid arthritis, it is not unreasonable to assume, for the purposes of calculating the power of the t-test with this data, that at least a 70% difference between agents would have to be present to be detectable in clinical practise. In retrospective analysis, the ability of the t-test to detect a 70% difference between drugs based on the change in any outcome measure during treatment, ranged from 6.8% to 66.3%. The outcome criteria most likely to predict a difference between drugs, number of tender joints, articular index, and system index, would only detect a significant difference 47% (tender joints, systemic index) and 66% (articular index) of the time. The calculations are outlined in Table XXVII. Thus, the utility of the t-test to evaluate this data is questionable. The power of a statistical test, defined as the probability of detecting a significant difference at the predetermined level of significance "p",[93] depends on the magnitude of the difference that actually exists and the standard deviation.[94] This, in turn, depends both on inherent variability of the study population and measurement error, as well as on the number of patients under study.[94] Aspects of the study affecting both determinants of standard deviation combined to produce large standard deviations for both study drugs, and minimized the usefulness of the t-test. These will be discussed further as limitations of the study.

TABLE XXVII

Power of the T-Test to Detect a 70% Difference Between 'Entrophen' and Piroxicam in their Ability to Improve Outcome Criteria

Outcome Measure	μ^1	σ^2	5% Level[3]	$\bar{x}$ alt[4]	β	(Power) 1-β
Pain	0.5667	6.139	4.703	0.9634	0.932	0.068
Tender Joints	8.8333	9.496	15.23	13.2499	0.522	0.478
Articular Index	27.1667	23.404	42.9350	46.183	0.367	0.663
Morning Stiffness	0.1417	0.797	0.6787	0.2409	0.911	0.089
ESR	5.000	10.139	11.8311	8.500	0.790	0.210
Strength Grip	16.2000	20.143	29.953	27.54	0.614	0.386
Systemic Index	18.000	19.442	31.099	30.600	0.525	0.475

μ^1 = mean outcome measure change following ASA administration

σ^2 = standard deviation of the mean of outcome measure change following ASA administration

[3]5% level = value cutting off upper 5% of the curve

[4]$\bar{x}$ alt = mean outcome measure change required to show a 70% difference from that seen with ASA

See Appendix IX for an explanation of the calculations.

Outcome measures in rheumatoid arthritis may not be normally distributed,[81] and this may have affected the performance of the t-test as well, since normal distribution is an underlying assumption in calculation of the t-statistic. For this reason, non-parametric analysis of the data was undertaken. The change in the composite systemic index during treatment, representing the change in total disease activity, was the basis of comparison. All patients completing at least two weeks of treatment with both drugs were included in the analysis, and the change in disease activity over a similar duration of treatment, was compared between the two treatments. Response to nonsteroidal antiinflammatory agents should be apparent within seven to fourteen days,[7] and both drugs, despite their long half-lives, would be expected to have reached steady state serum concentrations by this time. The Wilcoxan signed rank sum test was able to detect a difference between the change in disease activity recorded during treatment with the two agents ($p=0.01151$). 'Entrophen' produced a greater change in disease activity than did piroxicam (Table VII). Exclusion of patients 9 and 10 from analysis on the basis of possible underlying confounding rheumatic diseases did not change the outcome ($p=0.0263$) (Table VIII).

Although these data meet criteria for the use of distribution-free methods of statistical analysis, namely a small sample size, and nonnormality of distribution,[96] it is curious that a statistically significant difference between treatments could be detected, when previous studies with larger numbers of patients were unable to detect

differences between various NSAIDs. Statistically significant differences cannot always be equated with clinical superiority of one agent over another, however. Factors inherent in the study population and study design, discussed below as limitations of the study, prevent interpretation of the results to favour the efficacy of one agent over the other, particularly in clinical practise.

C. SIDE EFFECTS

A similar spectrum of side effects was reported for both agents, many of which are currently thought, but not proven, to be attributable to inhibition of prostaglandin synthesis.[13] These include gastrointestinal complaints; central nervous system toxicity including drowsiness, dizziness, headache and insomnia; platelet inhibition, which may have resulted in petechiae and bruising in one patient, and a nosebleed in another. Mild shortness of breath was reported by three patients receiving 'Entrophen', none of whom had a history of allergic disorders or asthma. Shortness of breath was not consistently reported at every visit by these patients, suggesting it was of minimal significance to the patients or not present constantly, in which case, contribution of the drug could be questionable. One patient experienced swelling of the ankles, hands, and face with both drugs, and this may have represented prostaglandin-mediated renal dysfunction with subsequent edema.

Gastrointestinal distress was more common with 'Entrophen' than piroxicam, which was unexpected because the enteric-coated formulation is intended to prevent gastrointestinal irritation resulting from direct contact of ASA with gastric mucosa.[59,60] Centrally mediated nausea may appear at plasma salicylate concentrations around 270 mcg/mL;[48] however in this study, nausea was not always reported with plasma salicylate levels greater than 270 mcg/mL, and patients complaining of nausea did not have plasma levels above 270 mcg/mL.

Tinnitis was the side effect reported most frequently during 'Entrophen' therapy, requiring a reduction in dose in six patients, and discontinuation in three. Six of the ten patients complaining of tinnitis, including the three who dropped out because of it, experienced the tinnitis soon after beginning treatment with 3.9 g (six 'Entrophen' tablets) of ASA daily. Tinnitis resulted in noncompliance and undetectable plasma salicylate levels in the patients who dropped out (4, 6, 14); the three patients tolerating a reduced dose of 3.25 g of ASA a day, had plasma salicylate levels of 319 mcg/mL, 347 mcg/mL, and 371 mcg/mL (patients 9, 10, 11 respectively) at 3.9 g of ASA daily. Tinnitis is not usually apparent until the upper therapeutic range of 250 to 300 mcg/mL is reached, and can be avoided by a gradual increase in dose accompanied by monitoring plasma salicylate levels.[27]

Tinnitis, and the consequent noncompliance and discontinuation of 'Entrophen' treatment by three patients, may have been prevented in this study by starting with a lower dose of 'Entrophen' and titrating to maximal antiinflammatory levels. Because of the risks of unblinding

the investigators, adjustment of dose according to serum levels was not allowed.

Overall, "Entrophen" appeared to produce a greater number of side effects and of greater severity than piroxicam. The proportional distribution of side effects into "mild", "moderate", and "severe" categories was significantly different between the two drugs when compared by chi-square analysis. Although the number of observations was low, the trend to a lower incidence of less severe side effects with piroxicam may have ramifications in clinical practise where the choice of an antiinflammatory agent for mild to moderate rheumatoid arthritis may rest on side effects.[85]

D. DRUG LEVELS

For any visit, including that at Week 12, there was no correlation between the change from baseline in any outcome measure, and either mean salicylate or piroxicam levels. This could be due both to unpredictable interindividual response to the drugs, and varying interindividual drug concentration. Drug levels varied widely between patients, reflecting interindividual differences in drug absorption, distribution, metabolism, and elimination. This was particularly evident with piroxicam: at the maximum daily dose of 20 mg, serum levels ranged from 5 to 30 mcg/mL in different patients (Table XXV). Although the protocol allowed a greater opportunity for individualization of 'Entrophen' dosing, only four of eight patients completing treatment

with 'Entrophen' had antiinflammatory levels of 200 to 300 mcg/mL on completion of therapy. Patients 1 and 12 had achieved therapeutic salicylate levels at some point during therapy, and noncompliance may explain their low levels at the end of the trial; patient 9 was unable to tolerate doses of 'Entrophen' producing optimal antiinflammatory plasma concentrations; patient 10 was apparently compliant by pill count, but her levels were consistently low, decreasing further toward the end of treatment (Table XXVI).

Lansbury found a change in the systemic index of 20 points or greater to reflect a clinically evident change in disease activity.[73] When response to drug therapy was defined as a 20 point or greater change in the systemic index, the mean plasma salicylate level of responders, 231 mcg/mL, was within the optimal antiinflammatory range, and was statistically significantly greater than that of nonresponders, 94 mcg/mL ($p < 0.02$). No statistically significant difference was detected between mean piroxicam levels in responders, 5.27 mcg/mL, or nonresponders, 11.68 mcg/mL ($p < 0.10$) (Table XX).

E. LIMITATIONS OF THE STUDY

A number of factors limiting the conclusions which can be drawn from this study have already been alluded to. They include aspects of the patient population studied, elements of study design, and the choice of outcome criteria in rheumatoid arthritis.

1. Patient Population

The inherent variability in a population of rheumatoid arthritis patients may be larger than for other disease states because of the heterogeneity of the symptom complex and the uncertain relationship of rheumatoid arthritis to other rheumatic diseases.[72,72] The phenomenon of varying interindividual response to NSAID's complicates the study of NSAIDs in such a population. A sufficiently large number of patients can overcome the limitation of population variability for the purposes of statistical analysis. Fifteen patients may not have represented a sufficient number for adequate comparison of two NSAIDs in this rheumatoid arthritis population.

2. Outcome Measures

In addition to the inherent variability in a study population, measurement error affects interpretation of the study results. Evaluation of the response of rheumatoid arthritis is indirect, limited to observation of clinical manifestations of inflammation.[73] Clinical tests of inflammation, whether subjective, objective, or a combination of the two, have been criticized both for their degree of subjectivity, and their insensitivity to changes in the inflammatory process.[2] The need for standardized evaluative criteria, capable of reliable, objective measurement, and accurately reflecting the general state of rheumatoid disease in the majority of cases, has long been

recognized.[70,71,72] After a study of numerous manifestations of rheumatoid arthritis and their correlation with disease trends, Lansbury recommended that morning stiffness, fatigue, aspirin request, grip strength, and ESR be adopted as acceptable criteria for measuring systemic activity of rheumatoid arthritis.[72] Together with a measure of joint involvement, a standardized, reproducible method of assessing rheumatoid arthritis is possible.[72,73] Of these, morning stiffness, pain as measured by a pain scale rather than by aspirin request, grip strength, and ESR, as well as a count of tender joints and calculation of an articular index have become the standard criteria for evaluation of antiinflammatory drug therapy in rheumatoid arthritis.

i) Stiffness

Stiffness experienced in the joints or muscles is suggestive of inflammation, and is almost universal in all forms of inflammatory arthritis, and thus duration of morning stiffness was recorded as a measure of inflammation. Stiffness is difficult to quantify, however, and although it appears easiest for the patient to specify an approximate duration rather than degree of stiffness, it is largely a subjective measure. Patient 3, for example, was unable to identify an aspect of her disease which she would call "morning stiffness", whereas Patient 14 could not identify a point at which he was no longer stiff, and consistently estimated the duration of his stiffness as "all day."

ii) Pain

The graphic pain rating scale, a composite of the visual analogue and descriptive pain scales,[76] was used to assess the degree of pain experienced by patients in this study. Although pain is a subjective sensation, pain scales are an acceptable method of quantifying pain.[76] Patients were asked to mark the average severity of pain experienced in the preceding 24 hours, without access to previous ratings. It was felt that a more accurate assessment of pain was possible if the patient was uninfluenced by access to previous ratings, although some investigators feel a comparison to previous ratings may be more valuable.[73] The major criticism of the graphic rating scale is that the sensitivity of the visual analog scale is lost by adding descriptors.[76] In addition, equal intervals between descriptors are assumed, when this may not be true for many patients.[76] Downie, however, investigated the degree of correlation between pain scores registered on four different rating scales: the simple descriptive scale, the numerical rating scale, and the vertical and horizontal visual analogue scales[74] and found a high correlation between any two scales.[74] It has been suggested that addition of descriptors to the visual analogue scale may improve patient comprehension without significant loss of sensitivity.

This protocol may have underestimated the pain score, since the majority of patients were seen on a Monday, and the average rating of their pain experienced the day before, a Sunday, was requested. Pain ratings from a weekday, during which the patient undertook a full complement of daily activities, may have more accurately represented the average pain experienced. It was felt the patient would more easily recall the level of pain experienced in the preceding 24 hours, however than at a point more distant in the past. Daily pain ratings, recorded by the patient in a log book, may have solved the problem, but the question of compliance with such methods could not be overlooked.

iii) Grip strength

Grip strength is measured as an indicator of loss of functional capacity associated with progressive arthritis.[2,73] It reflects a composite of articular and periarticular stiffness possibly secondary to inflammation, joint pain, muscle strength, irreversible deformity and patient motivation.[75] Because multiple factors are involved which may take a considerable time to recover during therapy, the test may not be suitable for trials under three months duration.[2] Fluctuations can be expected during the treatment period, since rapid deterioration due to muscle weakness or a solitary painful joint is more clearly monitored

than changes produced by improvement. Fluctuations unrelated to disease activity are minimal since Lee et al. showed day to day, and week to week variation in grip strength in stable arthritis with no change in disease activity, to be of the same magnitude as intraobserver error, which is less than the change expected from an effective antirheumatic drug.[2,94]

The Davis bag was used to measure grip strength in this study since patients find it easier to grip than a folded sphygmomanometer cuff, and the problem of variability in folding the cuff from visit to visit was avoided. Consequently, grip strength measurements were higher than one would expect if a sphygmomanometer cuff had been used.[2] Although a report of diurnal variation in grip strength measurements could not be confirmed,[75] evaluation was conducted at roughly the same time of day during each visit to avoid the effect of time.

The utility of the grip strength measurement can be questioned in patients without significant disease activity in the hands, however, all patients in this study had at least one swollen and tender joint in each hand indicating measurable disease activity. Patient 7 had significant hand deformities which may have affected sensitivity of the grip strength measurement; however, a change of at least 20 mmHg, usually

considered significant,[2] was recorded over the study period, suggesting measurable residual function of the hands was present.

iv) Erythrocyte sedimentation rate

Although potentially a more objective measurement of the rheumatoid process than clinical assessment, laboratory correlates of disease activity are both nonspecific, and less sensitive to overt clinical changes than other measures.[75] Rheumatoid factor (RF) and antinuclear factor (ANF) were both measured prior to initiating therapy, but were not used to monitor disease activity. High titres of RF, primarily an IgM immunoglobulin directed against endogenous gammaglobulin, occur in 75% of rheumatoid arthritis patients, and correlate broadly with chronicity and complications in rheumatoid arthritis.[2,98] Fluctuation of RF titre is not sensitive to acute changes in the inflammatory response, however, and it was measured as a diagnostic criteria rather than as an outcome measure. Antinuclear factor, an IgM immunoglobulin directed against antigenic components of nucleic acids, is elevated in only 30% of patients with rheumatoid arthritis, but the overlap of arthritis syndromes and other collagen diseases or systemic lupus erythematosis necessitates measurement of ANF in rheumatoid arthritis patients. ANF is not an appropriate laboratory parameter with which to follow

the course of inflammation.[98]

Erythrocyte sedimentation rate (ESR) is a nonspecific correlate of inflammation in which changes in fibrinogen and macroglobulin during an inflammatory process, produce rouleauxd formation and increased sedimentation of red blood cells.[25] Elevation of ESR tend to reflect the extent of systemic disease rather than joint involvement, and fluctuations lag behind changes in clinical indices.[2,75] Because it is invariably elevated in rheumatoid arthritis, ESR has confirmatory value in the diagnosis of active disease, and is useful to monitor remissions, particularly during therapy with remission-inducing agents. Although response to NSAID's may be minimal, the ESR is a component of a systemic index which has been shown to adequately monitor response to antiinflammatory drug therapy.[2,73]

More recent studies suggest that C-reactive protein correlates more closely with acute changes in clinical activity than ESR in patients on NSAID's, and its use has been recommended over ESR.[99,100] C-reactive protein was not measured in this study.

v) Joint count, articular index

The count of tender joints, and articular index derived from

it, are objective measures of rheumatic disease activity. Interobserver error may be significant, however, depending on the technique and pressure used to elicit pain.[101] Intraobserver error may also be present, particularly if the technique for eliciting pain is refined with time.[101] A learning process may have been present over the duration of the study as D.W. was an inexperienced observer at the beginning of the study.

3. Study Design

A double-blind, crossover trial with randomized assignment of patients to treatment groups was the basic study design used. Double-blind techniques and randomization procedures are necessary to lend maximal statistical validity to a trial,[94] however the necessity of a crossover design, particularly in a disease such as rheumatoid arthritis, is disputed.[103] A comparison of treatments on the same subject is expected to be more precise by reducing the contribution of subject to subject variability to the standard deviation, and therefore requires fewer subjects than a between-subjects comparison to produce statistically significant results. Distinguishing treatment effects from both time and carryover effects, however, can be difficult or impossible in rheumatoid arthritis.[103]

During the course of chronic inflammatory disease, there is a progressive change of function, usually for the worse, but with

intermittent periods of improvement, and there is no evidence that antiinflammatory agents alter the course of the disease.[2,87] Therefore it cannot be assumed that a return to baseline disease activity will occur between treatment periods, and assessment of the benefit of therapy may change with the duration of the disease. In short-term studies, progression of disease may be sufficiently minimal to justify a crossover design, however, it is conceivable that progression of disease activity could occur in the time required to complete a crossover trial with two 12-week treatment periods. Random assignment of patients to treatment groups may have overcome some of the difficulties presented by the nature of the disease, since progression of disease activity would affect variability in response to both drugs equally.

There is evidence that, in this study, a complete return to baseline disease activity did not occur during the washout period, since a statistically significant improvement over baseline was noted in both the articular index and composite systemic index at the end of the washout period. When pharmacokinetics of the study agents are considered, carryover effects in the early stages of the second treatment period could not be ruled out. Piroxicam, with an average half-life of 37 hours,[70] would require at least seven days for complete washout; although difficult to estimate due to the saturable pharmacokinetics of salicylates, 'Entrophen' could require a similar washout period.[28] The washout period allowed was considerably shorter, since a flare of disease activity invariably required introduction of the second agent after a three day washout.

It is questionable that significant antiinflammatory concentrations of these agents would remain at the end of a three day washout, however. The antiinflammatory effects of NSAID's appear to require higher serum concentrations than analgesia. For piroxicam, the analgesic effect is apparent at 2 mcg/mL, and an optimal antiinflammatory effect appears to require steady state concentrations greater than 5 mcg/mL.[70] Similarly, analgesia is apparent at salicylate concentrations around 100 mcg/mL, while steady state plasma levels of 200 to 300 mcg/mL are generally accepted as correlating with clinical antiinflammatory effects.[28,36,44]

Detectable piroxicam levels were found in Patients 4, 6 and 9 at the end of the washout period, and of these Patient 4 and 6 had levels well within the antiinflammatory range, 11.55 mcg/mL and 6.70 mcg/mL respectively. Residual antiinflammatory effects could have obscured the baseline disease activity in these two patients. Salicylate was detected in the plasma of Patients 3 and 9 at washout, although the levels, 16 mcg/mL and 41 mcg/mL respectively, were below those associated with significant analgesia. It is unlikely these levels would have affected baseline disease activity. Carryover effects in the remainder of the treatment period were negligible, minimized by the duration of treatment. The possibility of an antiinflammatory effect persisting after elimination of the drug cannot be excluded, either.

A dosage adjustment phase was incorporated into the protocol to reflect the clinical practice of adjusting the dose of medication to clinical response in the first few weeks of therapy. The importance of

dose adjustment is to account for interindividual variation in drug response, and provide effective doses with minimal side effects. Because antiinflammatory plasma concentrations have not been clearly established for either agent, dose was titrated to clinical antiinflammatory response, rather than to a range of plasma concentrations. The unblinded investigator was permitted to suggest a decrease in dose if he noted the serum levels were outside a previously established acceptable range.

Patients were started on the optimum dose of piroxicam, 20 mg daily, or an equivalent dose of 'Entrophen', six 650 mg tablets daily.[70] Upward dosage adjustment of piroxicam was not permitted, since no additional antiinflammatory benefits have been shown at 30 mg daily, although there is a dose-related increase in gastrointestinal side effects.[70] Increments of the 'Entrophen' dose, to a maximum of eight 650 mg tablets daily, were allowed since some patients require high doses to achieve antiinflammatory salicylate plasma concentrations.[70] This dosage adjustment protocol may have produced a bias against piroxicam, since an increased dose of piroxicam was not allowed if there was poor clinical response to the initial dose. Although antiinflammatory plasma concentrations have not been clearly defined for either agent,[65,70] titration of patients to a predetermined desirable range of plasma concentrations, under the guidance of the unblinded investigator, may have been a more equitable way of handling the dose adjustment period.

Alternatively, a bias against 'Entrophen' may have been created with this protocol, since 3.9 g of ASA frequently produce sufficient blood levels to cause side effects requiring a reduction in dosage, or refusal to continue treatment, as discussed earlier. ASA could have been introduced at a subtherapeutic dosage and increased slowly to avoid side effects early in treatment.

Experience from the study suggests that the dosage adjustment period could have been improved by starting with a piroxicam dose of 10 mg daily, thus allowing an increase to 20 mg daily if necessary. The 'Entrophen' dose could have been started at five 650 mg tablets daily to prevent side effects from occurring early in therapy, titrating to an effective dose with minimal side effects.

VI CONCLUSIONS

With respect to the three objectives of the study, the following conclusions can be drawn from analysis of the data presented:

1. Piroxicam and 'Entrophen' appear to be effective agents for the symptomatic treatment of inflammatory manifestations of rheumatoid arthritis in some patients. This observation is limited to that population of rheumatoid arthritis patients with established disease who are unresponsive to previous NSAID therapy.

2. Piroxicam appears to produce fewer, less severe side effects than 'Entrophen'. This may be significant in clinical practise where the side effect spectrum may dictate the choice of one agent over another with similar efficacy. Subjective gastrointestinal side effects are common with 'Entrophen' despite the enteric coating; objective evidence of gastrointestinal ulceration or bleeding was not sought in this study.

3. The practice of titrating ASA dosage to salicylate plasma concentrations of 200 to 300 mcg/mL seems justified since responders to 'Entrophen' therapy had salicylate levels in this range as compared to nonresponders who had a lower mean salicylate level. A relationship between drug level and response to piroxicam was not evident.

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APPENDIX I

INFORMED CONSENT FORM

CLINICAL DRUG TRIALS - INFORMED CONSENT FORM

I, _____ agree to take part in a clinical trial to assess the value of _____ in the treatment of _____.

I understand that although _____ has been used as an investigational drug in the treatment of some patients with _____, it is not yet approved for use in Canada.

Dr. _____ has explained to me the nature of the trial and the known side effects of the trial drug _____.

I understand that I may withdraw from the trial at any time.

Patient _____

Witness _____

Date _____

APPENDIX II

American Rheumatism Association Classification for Diagnosis of Rheumatoid Arthritis[72]

A. Classical Rheumatoid Arthritis

The diagnosis requires seven of the following criteria. In criteria 1 through 5, the joint signs or symptoms must be continuous for at least six weeks.

1. Morning stiffness.
2. Pain on motion, or tenderness in at least one joint.
3. Swelling in at least one joint.
4. Swelling of at least one other joint.
5. Symmetrical joint swelling.
6. Subcutaneous nodules.
7. Roentgenographic changes typical of rheumatoid arthritis.
8. Positive demonstration of "rheumatoid factor."
9. Poor mucin precipitate from synovial fluid.
10. Characteristic histologic changes of the synovium.
11. Characteristic histologic changes in nodules.

B. Definite Rheumatoid Arthritis

This diagnosis requires five of the above criteria. Joint signs or symptoms of criteria 1 through 5 must be continuous for at least 6 weeks.

APPENDIX III

Diseases Closely Related to Rheumatoid Arthritis for the Purposes of Exclusion Criteria

systemic lupus erythematosis

periarteritis nodosa, erythema nodosum

scleroderma, dermatomyositis

rheumatic fever

ankylosing spondylitis

gout

Reiter's syndrome

sarcoidosis

acute infectious arthritis

joint tuberculosis or syphilis

leukemia not lymphoma

agammaglobulinemia

hypertrophic pulmonary osteoarthropathy

multiple myeloma

psoriasis

inflammatory bowel diseases known to be associated with arthropathies

APPENDIX IV

Representative Page from a Patient Diary

Patient No:_____
No du patient:_____

WEEK __ of Therapy
SEMAINE de traitement no __

	Medications/Médicament	Amount Taken/Quantité absorbée
Day/Jour 1		
Day/Jour 2		
Day/Jour 3		
Day/Jour 4		
Day/Jour 5		
Day/Jour 6		
Day/Jour 7		

APPENDIX V

Medication Regimens of the Piroxicam and 'Entrophen' Treatment Groups

A. Piroxicam (P) Group

	8:00 a.m. (Breakfast)	12:00 noon (Lunch)	6:00 p.m. (Dinner)	10:00 p.m. (Snack)
Schedule 1	P 1 Cap. ASA 2 Pbo.	— 1 Pbo.	— 1 Pbo.	— 1 Pbo.
Schedule 2	P 2 Caps. ASA 2 Pbo.	— 1 Pbo.	— 1 Pbo.	— 2 Pbo.
Schedule 3	P 2 Caps. ASA 2 Pbo.	— 2 Pbo.	— 1 Pbo.	— 2 Pbo.
Schedule 4	P 2 Caps ASA 2 Pbo.	— 2 Pbo.	— 2 Pbo.	— 2 Pbo.

B. ASA Group

	8:00 a.m.	12:00 noon	6:00 p.m.	10:00 p.m.
Schedule 1	P 1 Pbo. ASA 2 Tabs.	— 1 Tab.	— 1 Tab.	— 1 Tab.
Schedule 2	P 2 Pbo. ASA 2 Tabs.	— 1 Tab.	— 1 Tab.	— 2 Tabs.
Schedule 3	P 2 Pbo. ASA 2 Tabs.	— 2 Tabs.	— 1 Tab.	— 2 Tabs.
Schedule 4	P 2 Pbo. ASA 2 Tabs.	— 2 Tabs.	— 2 Tabs.	— 2 Tabs.

Note: Cap = Active capsule
Tab = Active tablet
Pbo = Placebo

APPENDIX VI

American Rheumatism Association Functional Class

Class I - Complete

Ability to carry out all usual activities without handicaps.

Class II - Adequate

Adequate for normal activities despite handicaps of discomfort or limited motion at one or more joints.

Class III - Limited

Limited only to little or none of the duties of usual occupation or self care.

Class IV - Incapacitated, largely or wholly bedridden, or confined to wheelchair with little or no self care.

APPENDIX VII

Size of the Articulating Surfaces of Joints and Their Values Used to Calculate Lansbury's Articular Index[73,75]

Joint	Number	Size of Articulating Surface of Each Joint (cm^2)	Value to Calculate Articular Index (Each Joint)
Temporo-mandibular	2	4	2
Acromio-clavicular	2	4	1
Sterno-clavicular	2	12	4
Shoulder	2	45	12
Elbows	2	52	12
Wrists	2	15	4
Metacarpal-phalangeal (MCP)	5	4	1
Distal and proximal interphalangeal (PIP,DIP)	18	4	1
Hip	2	82	24
Knee	2	104	24
Ankle	2	35	8
Tarsus	2	35	8
Bunion	2	8	2
Interphalangeal (IP)	16	2	1

Sample Calculation:

Joints Tender on Passive Motion	Value	Total	
L - Sternoclavicular	1 x 4	4	
R,L - Shoulder	2 x 12	24	
R,L - Wrists	2 x 4	8	Articular Index =
3 MCP's	3 x 1	3	107
4 IP's	4 x 1	4	
L - Hip	1 x 24	24	
R - Knee	1 x 24	24	
R - Ankle	1 x 8	8	
L,R - Bunion	2 x 2	4	
4 IP's	4 x 1	4	
		107	

APPENDIX VIII

Percentage Value of Outcome Measures Used to Calculate Lansbury's Systemic Index[75]

Morning Stiffness Hrs	%	Pain Scale Scale	%	Grip Strength (Av) mmHg	%	Articular Index	%	Westergren ESR mm/hr	%
0.25	1	1	3	300	0	5	1	10	0
0.4	2	2	6	290	1	10	2	15	2
0.5	3	3	9	280	2	15	3	20	3
0.75	4	4	12	270	3	20	4	25	5
1.0	6	5	16	260	4	25	5	30	7
1.5	9	6	19	250	5	30	6	35	8
2.0	11	*7	22	240	6	35	7	40	10
2.5	14	8	25	230	7	40	8	45	12
3.0	17	9	29	220	8	45	9	50	13
*3.5	20	10	32	210	9	50	10	55	15
4.0	23	11	35	200	10	55	11	60	17
4.5	26	12	38	190	11	60	12	65	18
5.0	29	13	41	180	12	65	13	*70	20
5.5	31	14	43	170	13	70	14		
6.0	34	15	46	160	14	75	15		
6.5	37	16	50	150	15	80	16		
7.0	40			140	16	90	18		
7.5	43			130	17	*100	20		
8.0	46			120	18	110	22		
9.0	52			110	19	120	24		
				*100	20	130	26		
				90	21	140	28		
				80	22	150	30		
				70	23	160	32		
				60	24	170	34		
				50	25	180	36		
				40	26	190	38		
				30	27	200	40		
						210	42		
						220	44		
						240	46		

Note: Each percentage value is given at one-fifth its true value so that a Systemic Index may be obtained simply by adding up the percentage values.

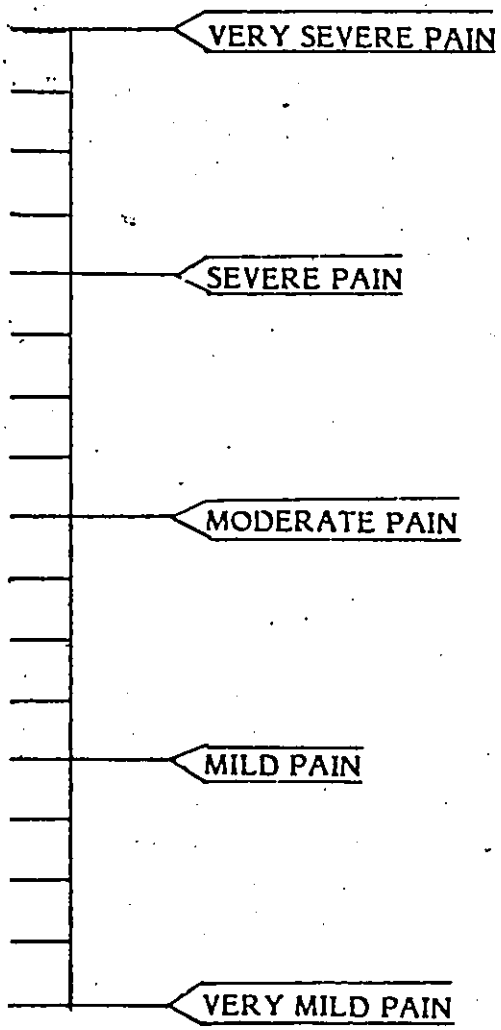
Since each percentage value given is one-fifth its true value, the 20 percent level represents the value assigned "100" in the original scheme.. These values are denoted * and represent the average value of the measures as evaluated in Lansbury's original population of untreated patients.

APPENDIX IX

Pain Scale

PAIN SCALE I have pain YES ☐ NO ☐

Mark an X on the line indicating how much pain you have had within the past 24 hours.



APPENDIX X

Calculation of the Power of the T-Test to Detect a Difference Between Treatments

The "power" of a statistical test is defined as the probability of detecting a significant difference at the predetermined level of significance, "p". The power is calculated as $1-\beta$ where β is the "βerror", the chance of finding "no significant difference" when, indeed one does exist. That is, the chance of accepting a false null hypothesis.

To calculate β, population parameters must be known, from which the upper 5% level of the population is determined(1); then, using parameters of the test population, the portion of the curve falling below the upper 5% level of the underlying population is determined.(2) This is the "βerror". The acceptable βerror depends on the study, but most commonly a 10-15% chance of accepting a false null hypothesis is reasonable.[102]

μ = population mean
σ = population std. deviation
$Z_{0.05}$ = critical ratio when p = 0.05 Z = 1.65
$\bar{X}_1$ = value of population cutting off upper 5%
Z_2 = critical ratio corresponding to point of sample curve falling below X_1

(1) $Z_{0.05} = \dfrac{\bar{X}_1 - \mu}{\sigma/\sqrt{n}}$

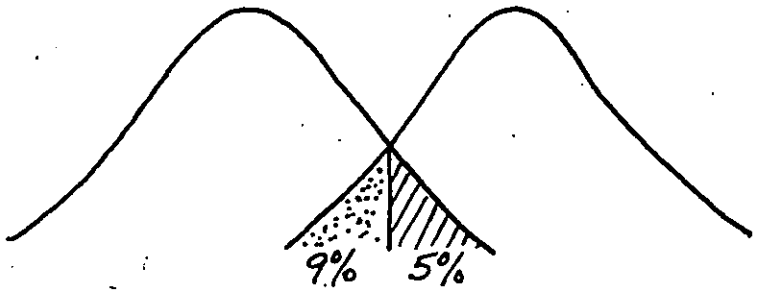
(2) $Z_2 = \dfrac{\bar{X}_2 - \bar{X}_1}{\sigma/\sqrt{n}}$

$1-\beta$ = area in tail of normal distribution corresponding to

APPENDIX X, continued

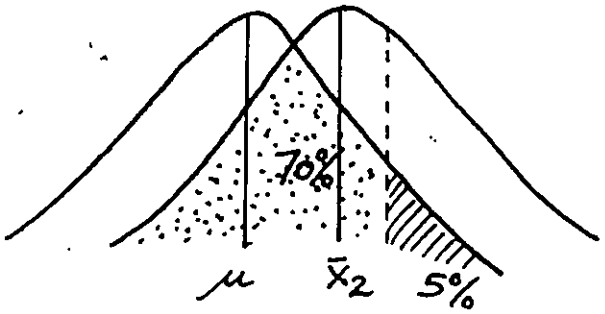
For the purposes of estimating the power of the t-test to distinguish between two treatments yielding data such as that gathered in this study, the mean change in disease activity during treatment with 'Entrophen', and its standard deviation, represented μ and σ respectively. (Table XVIII) $\bar{X}_2$, the mean of the alternative population, was assigned a value of 1.7 times μ, since the ability of the test to detect at least a 70% difference between treatments was desired.

Invariably, the value cutting off the upper 5% of the underlying population included (was greater than) the mean of the alternative population, suggesting that there was a greater than 50% chance of being unable to detect even a 70% difference between treatments with this data and study population (Table XVIII). The ideal situation, and the situation represented by this study are illustrated below:



β = 0.09 (9%)
Ideal Situation

$P = 0.05$



β = 0.70 (70)
$1-\beta$ = 30% chance of detecting a significant difference

This Study (assuming a normal distribution)

APPENDIX XI

ESR (mm/hr): Original Data from 'Entrophen' Treatment

Patient	Baseline	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12
1	25	33	22	24	N/A	35	34
3	49	45	45	45	42	38	40
4	24	26	N/A				
5	29	29	30	22	23	29	16
6	23	23					
7	52	52	52	53			
8	49	48	51	44	33	33	39
9	27	27	22	24	24	19	20
10	42	44	42	N/A	45	34	37
11	44	47	48	46	44	34	26
12	47	50	32	49	52	N/A	51
14	34	33	45	43	35		
15	46	50	48	N/A	46	48	
Mean (S.D.)	37.8 (11.0)	39.0 (10.6)	39.7 (11.2)	38.9 (12.0)	38.2 (10.1)	33.8 (8.1)	30.4 (11.9)

*Patients 2 and 13 did not try 'Entrophen'

N/A = Not available

APPENDIX XII

Morning Stiffness (Hours): Original Data from 'Entrophen' Treatment

Patient	Baseline	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12
1	2	2	1	0.75	0.25	1	1
3	Patient could not specify duration of morning stiffness						
4	2	2	2				
5	1	1	1.5	1	1	1	1
6	0.5	0					
7	0	0	0	0			
8	0.5	0.5	0.3	0.25	0.2	0.2	0.2
9	0	0.1	0.2	0.25	0.2	0.25	0.5
10	1.5	0.5	0.2	0.5	0.75	0.5	0.4
11	0.25	0	0.2	0.1	0.1	0.1	0.1
12	0.1	1	1	1	0	1	1
14	4	0	0.1	1	0.5		
15	Patient could not specify a point when morning stiffness ended						
Mean (S.D.)	1.08 (1.23)	0.65 (0.77)	0.65 (0.69)	0.54 (0.41)	0.38 (0.35)	0.60 (0.40)	0.60 (0.40)

*Patients 2 and 13 did not try 'Entrophen'

APPENDIX XIII

Pain Rating: Original Data from 'Entrophen' Treatment

Patient	Baseline	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12
1	12.0	10.0	8.0	8.5	8.0	9.8	9.0
3	12.3	12.3	12.3	12.3	9.7	8.3	8.0
4	8.0	8.0	8.0				
5	14.0	12.0	12.0	12.0	12.0	12.0	12.0
6	11.0	9.0					
7	13.0	11.5	11.5	9.5			
8	9.0	10.0	8.0	6.0	4.0	5.0	4.0
9	8.0	15.0	11.0	7.0	7.0	7.0	8.0
10	12.0	10.0	5.0	12.0	12.0	12.0	11.0
11	12.0	0.0	4.0	4.0	4.0	8.0	4.0
12	5.0	7.0	7.0	8.0	6.0	8.0	3.0
14	4.0	0.0	0.0	4.0	4.0		
15	6.0	8.0	10.0	8.0	8.0	11.0	
Mean (S.D.)	9.1 (4.2)	8.4 (4.1)	8.1 (3.7)	8.0 (3.2)	7.5 (3.1)	9.5 (2.3)	7.3 (3.6)

*Patients 2 and 13 did not try 'Entrophen'

APPENDIX XIV

Average Grip Strength (mm Hg): Original Data from 'Entrophen' Treatment

Patient	Baseline	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12
1	160	240	264	272	259	300	206
3	95	124	120	130	140	139	162
4	136	144	N/A				
5	N/A	231	274	229	239	245	208
6	159	148					
7	51	59	53	45			
8	68	61	74	87	46	85	84
9	298	288	296	296	284	298	296
10	158	N/A	N/A	172	184	149	155
11	63	90	72	73	101	96	78
12	114	111	123	111	122	117	139
14	101	110	105	92	106		
15	182	170	152	166	146	111	
Mean (S.D.)	132.9 (64.8)	148 (72.4)	153.3 (91.0)	152.1 (83.3)	162.7 (77.0)	171.1 (86.1)	166.0 (71.3)

*Patients 2 and 13 did not try 'Entrophen'

N/A = Davis Bag Not Available

APPENDIX XV

Tender Joints (Number): Original Data from 'Entrophen' Treatment

Patient	Baseline	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12
1	28	18	11	13	10	11	16
3	37	60	64	53	22	52	36
4	2	3	2				
5	27	42	33	44	25	29	18
6	32	22					
7	34	20	21	20			
8	8	6	7	7	7	3	7
9	10	6	5	6	3	6	6
10	34	55	14	46	57	46	33
11	39	13	12	13	7	7	13
12	13	13	19	14	12	12	12
14	21	7	5	8	6		
15	11	9	7	5	7	8	
Mean (S.D.)	22.8 (12.6)	21.1 (19.1)	16.7 (17.2)	21.1 (17.9)	15.6 (16.2)	19.3 (18.4)	17.6 (11.2)

*Patients 2 and 15 did not try 'Entrophen'

APPENDIX XVI

Articular Index: Original Data from 'Entrophen' Treatment

Patient	Baseline	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12
1	106	80	58	53	68	65	81
3	166	141	149	133	81	135	63
4	36	40	36				
5	167	139	141	187	101	130	137
6	188	161					
7	136	117	123	125			
8	47	61	38	42	39	33	36
9	12	6	5	10	3	6	6
10	176	168	77	177	204	175	154
11	182	114	112	113	79	83	111
12	32	24	36	47	32	22	23
14	69	41	42	48	39		
15	51	47	44	31	44	75	
Mean (S.D.)	105.2 (66.3)	87.6 (55.1)	71.8 (47.7)	87.8 (61.4)	69.0 (55.4)	80.4 (56.9)	76.4 (54.5)

*Patients 2 and 13 did not try 'Entrophen'

APPENDIX XVII

Systemic Index: Original Data from 'Entrophen' Treatment

Patient	Baseline	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12
1	89	73	51	49	NC-E	58	69
3	115	96	98	94	74	77	62
4	65	NC-G	65				
5	NC-G	86	85	92	74	83	82
6	94	81					
7	107	NC-E	100	98			
8	77	84	70	62	56	54	52
9	33	54	41	31	31	27	33
10	106	NC-G	NC-G	NC-E	107	99	92
11	111	56	71	70	60	71	61
12	54	65	61	112	58	NC-E	48
14	83	33	49	63	53		
15	132	136	139	NC-E	130	144	
Mean (S.D.)	88.8 (28.2)	81.2 (24.9)	74.9 (29.1)	74.6 (26.2)	73.8 (31.3)	76.6 (34.7)	62.4 (18.8)

*Patients 2 and 13 did not try 'Entrophen'

NC-G = Not Calculable - Grip Strength Missing

NC-E = Not Calculable - ESR Missing

APPENDIX XVIII

ESR (mm/hr): Original Data from Piroxicam Treatment

Patient	Baseline	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12
1	29	28	30	37	36	28	26
2	35	42	41	42	46	49	50
3	40	34	42	44	42	48	N/A
4	44	42	48	49	44	38	42
5	17	17	21	19	27	37	38
6	21	33	37	26	26	18	
7	52	54	N/A	52	51	52	52
8	26	33	49	48	47		
9	24	24	26	27	27	N/A	27
10	40	47	44	43	48	42	42
11	37	30	41	35	N/A	40	44
12	50	49	52	51	51	50	50
13	38	43	45	38	50		
14	N/A	50	43				
15	40	50	53	40	48	44	
Mean (S.D.)	35.2 (10.5)	38.4 (10.9)	40.9 (9.5)	39.4 (9.9)	41.8 (9.5)	40.5 (10.2	43.0 (8.4)

N/A = Not Available

APPENDIX XIX

Morning Stiffness (Hours): Original Data from Piroxicam Treatment

Patient	Baseline	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12
1	0.75	0.5	1	0.75	1	0.5	0.5
2	3	2	2	1	1	1	2
3	Patient could not specify a duration of morning stiffness						
4	0.5	0.5	0.5	0.5	0.5	0.25	0.17
5	1	0.5	0.5	0.5	0.5	0.5	0.75
6	0.5	0.5	0.75	0.5	0.5	0.5	
7	2.5	2.5	2	2	2	2	0.75
8	0.1	0.1	0.1	0.1	0.2		
9	0.1	0	0	0	0.25	0.25	0.1
10	0.3	0.4	0.4	0.4	0.4	0.2	0.25
11	0.4	0.1	0.1	0.1	0.1	0.25	0.1
12	1	1.5	0	0.5	4	0	1
13	4	8	4	All Day	All Day		
14	2	All Day	1				
15	Patient could not specify when morning stiffness ended						
Mean	1.24	2.35	0.95	1.70	2.04	0.55	0.56
(S.D.)	(1.24)	(4.10)	(1.14)	(3.91)	(3.92)	(9.58)	(0.61)

All Day = 14 hours for the purpose of calculating a mean

APPENDIX XX

Pain Rating: Original Data from Piroxicam Treatment

Patient	Baseline	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12
1	9.0	8.5	8.5	8.5	8.5	8.5	8.5
2	8.3	8.3	8.3	7.4	12.4	7.4	7.4
3	12.0	8.0	8.0	8.0	8.0	8.0	12.0
4	8.4	4.3	8.3	8.4	8.4	4.0	4.0
5	13.0	9.0	9.0	9.0	7.0	11.0	10.0
6	11.0	9.0	12.0	9.0	8.0	8.0	
7	11.0	11.0	10.0	10.0	12.0	5.0	5.0
8	7.0	8.0	9.0	10.0	9.0		
9	0.0	12.0	11.0	4.0	7.0	11.0	7.0
10	11.0	11.0	8.0	10.0	10.5	14.0	8.0
11	8.0	4.0	8.0	8.0	4.0	8.0	8.0
12	4.0	5.0	4.0	1.0	2.0	4.0	8.0
13	8.0	12.0	8.0	11.5	16.0		
14	4.0	8.2	4.0				
15	10.6	9.0	8.0	4.0	7.5	12.0	
Mean (S.D.)	8.4 (3.5)	8.5 (2.5)	8.6 (1.8)	7.8 (2.9)	8.6 (3.5)	8.4 (3.2)	8.6 (2.6)

APPENDIX XXI

Average Grip Strength (mm Hg): Original Data from Piroxicam Treatment

Patient	Baseline	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12
1	217	287	282	292	173	280	300
2	145	176	181	194	158	179	175
3	108	115	N/A	115	114	114	98
4	138	112	122	126	141	158	89
5	208	291	254	274	279	228	261
6	130	161	149	138	142	122	
7	62	62	63	42	66	67	48
8	67	73	72	58	74		
9	237	237	N/A	295	300	272	298
10	165	181	170	155	144	217	188
11	68	110	83	85	83	93	76
12	105	139	137	127	125	105	114
13	56	48	64	33	40		
14	76	68	76				
15	95	132	136	177	145	119	
Mean (S.D.)	125.1 (59.4)	146.1 (77.1)	137.6 (70.6)	150.8 (87.6)	141.7 (73.5)	162.8 (71.7)	164.2 (89.6)

N/A = Davis Bag Not Available

APPENDIX XXII

Tender Joints (Number): Original Data from Piroxicam Treatment

Patient	Baseline	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12
1	12	7	9	9	5	3	5
2	11	5	9	7	9	7	4
3	51	26	28	26	22	27	37
4	9	5	6	2	4	4	4
5	24	15	11	11	16	13	10
6	27	30	32	33	34	33	
7	36	19	18	16	17	14	15
8	5	6	6	8	7		
9	12	10	9	9	8	13	6
10	40	29	29	30	39	39	42
11	22	6	10	11	8	19	17
12	25	18	16	25	14	22	15
13	14	22	12	17	34		
14	11	15	6				
15	13	9	7	9	6	12	
Mean (S.D.)	20.8 (13.2)	14.8 (8.9)	13.9 (8.9)	15.2 (9.6)	15.4 (12.4)	17.2 (11.3)	15.5 (13.6)

APPENDIX XXIII

Articular Index: Original Data from Piroxicam Treatment

Patient	Baseline	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12
1	66	54	26	26	15	20	31
2	71	8	54	60	61	32	60
3	133	97	55	101	80	107	117
4	84	45	47	40	44	44	41
5	155	44	86	85	97	109	57
6	163	172	188	188	190	192	
7	123	86	95	88	111	95	84
8	37	41	41	43	39		
9	36	12	11	21	22	40	8
10	155	128	128	150	208	164	163
11	127	97	131	86	97	149	94
12	71	32	39	85	37	64	19
13	83	104	75	88	152		
14	58	89	58				
15	77	83	59	72	66	99	
Mean (S.D.)	95.9 (43.0)	72.8 (44.8)	74.0 (48.1)	80.9 (45.6)	87.1 (60.4)	92.9 (55.2)	67.4 (37.9)

APPENDIX XXIV

Systemic Index: Original Data from Piroxicam Treatment

Patient	Baseline	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12
1	62	48	46	44	56	41	40
2	80	62	69	64	83	60	72
3	97	71	NC-G	76	71	78	NC-E
4	73	55	70	69	67	45	53
5	83	44	57	55	52	76	60
6	91	88	104	91	87	87	
7	112	105	NC-E	10	108	NC-E	74
8	57	64	73	78	74		
9	19	52	NC-G	23	33	NC-E	30
10	91	87	78	90	106	96	80
11	84	57	83	72	NC-E	87	79
12	71	61	53	62	69	63	76
13	99	141	99	142	172		
14	71	141	68				
15	137	137	135	130	135	156	
Mean (S.D.)	81.8 (26.6)	80.9 (34.5)	77.9 (24.8)	78.4 (31.5)	85.6 (37.2)	78.9 (32.6)	62.6 (18.2)

NC-G = Not Calculable - Grip Strength Missing

NC-E = Not Calculable - ESR Missing