INVITED REVIEW

CLINICAL PERSPECTIVES IN RHEUMATOLOGY: A REVIEW OF THREE COMMON FORMS OF ARTHRITIS AND RESULTS OF UNITED STATES TRIALS WITH ISOXICAM

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SYNOPSIS

This review deals with three common rheumatic disorders: rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis. The salient clinical features of each of these rheumatic entities are outlined, placing particular emphasis on those aspects that are central to early diagnosis and an understanding of drug therapy.

Results of United States trials with isoxicam in each of these disorders are reported. Isoxicam proved to be more effective and better tolerated than aspirin in rheumatoid arthritis, as effective but better tolerated than high-dose indomethacin in osteoarthritis, and more effective but comparable in tolerance to indomethacin in ankylosing spondylitis.

Unlike most nonsteroidal antiinflammatory drugs, isoxicam can be administered once daily, thereby promoting patient compliance and convenience.

INTRODUCTION:

The rheumatic diseases comprise at least 100 distinct disorders affecting as many as 36 million Americans (1). Of these, the most common are osteoarthritis, affecting 16 million Americans, rheumatoid arthritis (7.5 million), and ankylosing spondylitis (3 million).

The purpose of this report is to review the clinical aspects and therapy of these common disorders. We shall also cite studies conducted in the United States with the new nonsteroidal antiinflammatory drug, Isoxicam. In each of the studies to be reported, the daily dose of isoxicam was 200 mg, usually given as a single daily dose.

RHEUMATOID ARTHRITIS

The cause of rheumatoid arthritis (RA) is unknown, despite world-wide research into etiologic factors as varied as bacterial and viral infections, metabolic and endocrine abnormalities, heredity, and autoimmunity (2). Currently, it is postulated that RA is triggered by an infectious agent, perhaps a virus or a bacterium—or perhaps a whole host of such microorganisms—that then sets off an autoimmune reaction. The disclosure of immune complexes, rheumatoid factors, and elevated serum immunoglobulin levels in patients substantiates this concept but also helps to explain the chronicity of RA. Genetic factors also play a role; the higher than expected frequency of the HLA-DR4 tissue antigen among patients supports this view (3).

RA begins most often in the prime of life, between the ages of 20 and 50. About 5% of all patients are children (juvenile RA) and approximately 15% have disease onset after the age of 50. RA is primarily an affliction of women, whom the disease affects 3 times as often as it does men.

Early Diagnosis

Early recognition of RA is easier in adults because the vast majority of patients have a polyarticular onset (Table 1). It is not so easy in children, however, since 50% begin with a pauciarticular onset, or swelling of only one to four joints.

In polyarticular RA, had involvement is distinguished by a characteristic pattern of joint swelling (4). Initially, the distal interphalangeal joints are not affected. If they become affected at all, it is usually later in the course of RA, unlike patients with osteoarthritis or psoriatic arthritis. What you will find, instead, is swelling of the proximal interphalangeal (PIP), metacarpophalangeal (MCP), and wrist joints (Figure 1). The involvement is not only bilateral but also strikingly symmetrical so that the findings in one hand are often the mirror image of the other. Remember, however, that symmetry is primarily an early feature so that much of it may be lost after the first few months of disease. Nevertheless, this characteristic hand pattern can help you make an early diagnosis of polyarticular RA right in your office or at the patient's bedside.

Pauciarticular (oligoarticular) onset begins with swelling of four joints or less, including swelling of a single joint (monarticular onset). When only one joint is involved, joint aspiration and synovial fluid analysis are mandatory. This is especially critical in ruling out treatable infectious arthritis that may otherwise rapidly destroy a joint.

TABLE 1.
MODES OF ONSET IN RHEUMATOID ARTHRITIS

Onset	Adults	Children
Systemic (High Fever, Rash)	1%	20%
Polyarticular (Multiple Joints)	93%	30%
Pauciarticular (1 to 4 Joints)	6%	50%*

*Chronic iridocyclitis occurs at the alarming rate of 20 to 40% in children with pauciarticular onset but not at all in adults with rheumatoid arthritis.

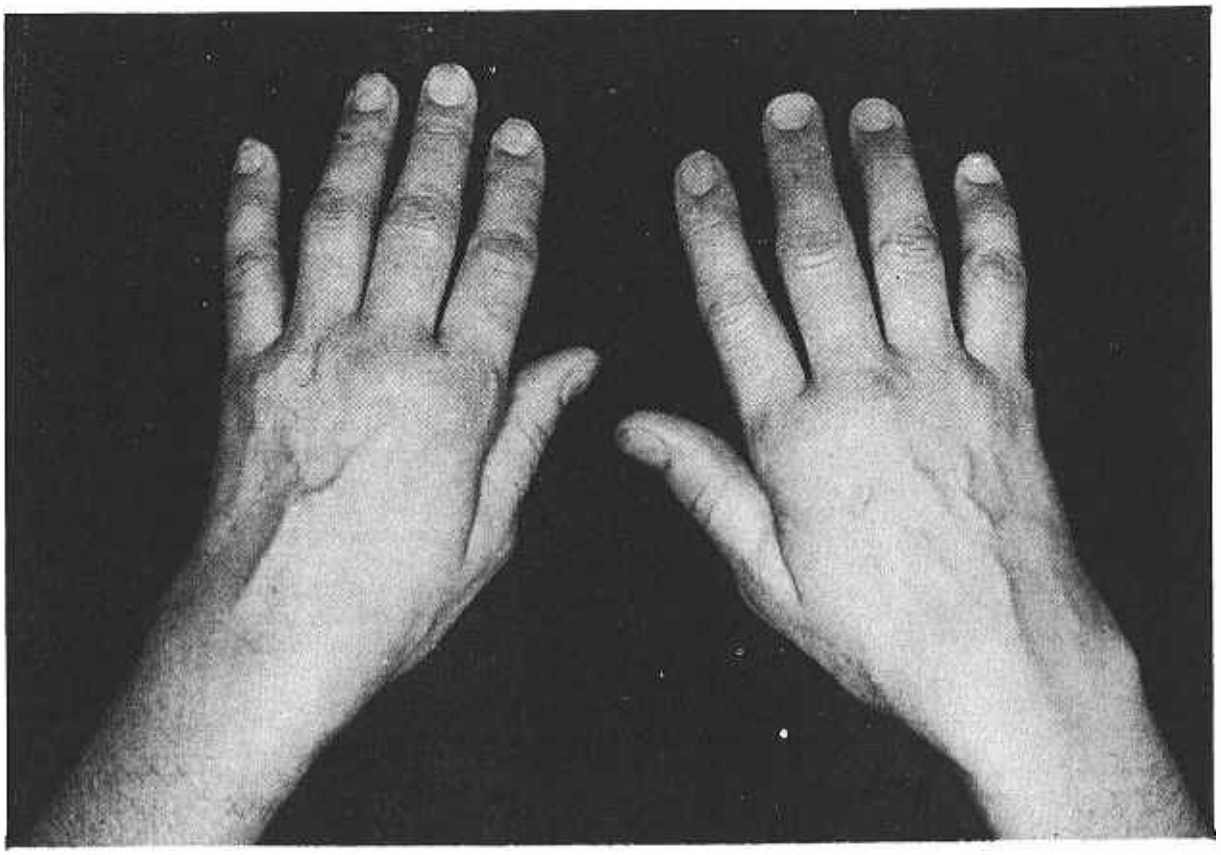

Figure 1. Early hand involvement in polyarticular onset reveals a characteristic pattern of symmetrical swelling of the proximal interphalangeal, metacarpophalangeal, and wrist joints, along with sparing of the distal interphalangeal joints.

Chronic Iridocyclitis

The major hazard of pauciarticular onset is blindness from chronic iridocyclitis that occurs only in children and not in adults with this otherwise benign form of RA (5,6). While the ocular inflammation may be found in 5 to 10% of children with RA, it occurs at the alarming rate of 20 to 40% in those with pauciarticular onset (7,8,9,10). Initially, ocular pain, redness, and tearing are usually absent, while iridocyclitis smolders quietly until vision is impaired, at first by synechiae or glaucoma and later by cataract and band keratopathy (Figure 2).

The recognition and management of iridocyclitis are difficult and should be entrusted only to an ophthalmologist (11). None of the usual eye examinations, including ophthalmoscopy, can detect early iridocyclitis. Only slit-lamp examination will reveal the inflammatory cells and protein exudates in the anterior chamber that signal early disease.

Children with pauciarticular RA, the most susceptible group, should receive slit-lamp examinations every three or four months (12). All other children with RA should be examined regularly at six-month intervals. Routine screening for silent iridocyclitis should be continued until children reach late adolescence. At this time, the ocular inflammation tends to become symptomatic with redness, tearing, and photophobia so that routine screening for silent iridocyclitis is no longer necessary.

The therapy of chronic iridocyclitis includes the topical application of corticosteroids and cycloplegics but refractory cases may require oral corticosteroids (11) or immunosuppressive drugs (13). Surgery for cataract and chelating agents for band keratopathy may also improve the outlook even for these more serious ocular manifestations (12).

Course of Disease

RA follows one of three patterns of disease course: monocyclic, intermittent, and unremitting (4). About 20% of patients have a monocyclic course in which all signs and symptoms of RA resolve within two years of onset and never recur. Between 60 and 70% of patients pursue an intermittent course, with unpredictable flares and remissions as well as variable joint involvement. In the remaining 10 to 20% of patients, the course of disease is unremitting and progressive. These refractory cases form the most challenging group and can be recognized by any or all of the following signs: continuous inflammation in all the major joints affected, despite a succession of nonsteroidal antiinflammatory drugs (NSAIDs); many hours of early morning stiffness, just as bad as before the start of drug therapy; early afternoon fatigue; frequent extra-articular or systemic manifestations; a constantly elevated erythrocyte sedimentation rate (ESR); high titers of IgM rheumatoid factor (i.e. latex fixation titers in the thousands); early erosions on serial x-rays of affected joints; and subcutaneous (rheumatoid) nodules. You must look for nodules carefully, however, because they are painless and patients are not aware of their importance. They occur primarily over bony prominences such as the tip of the elbow or other sites subjected to repeated pressure (Figure 3).

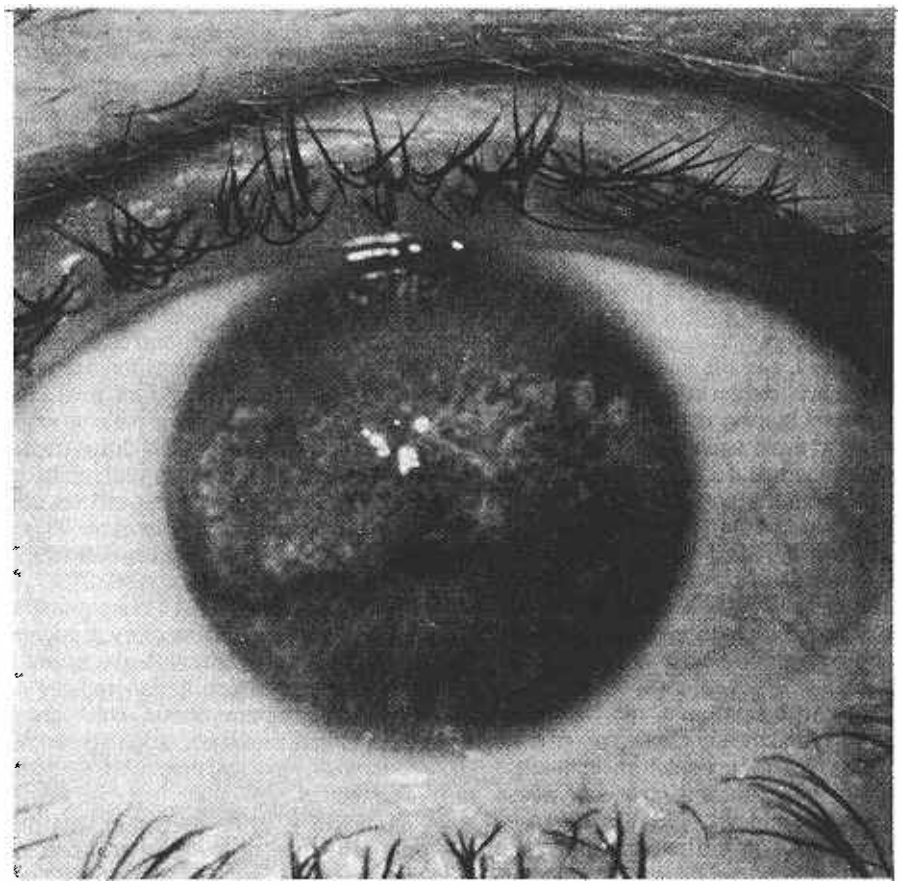

Figure 2. Undetected chronic iridocyclitis may lead to band keratopathy with calcific deposits in Bowman's membrane extending horizontally as a band across the cornea.

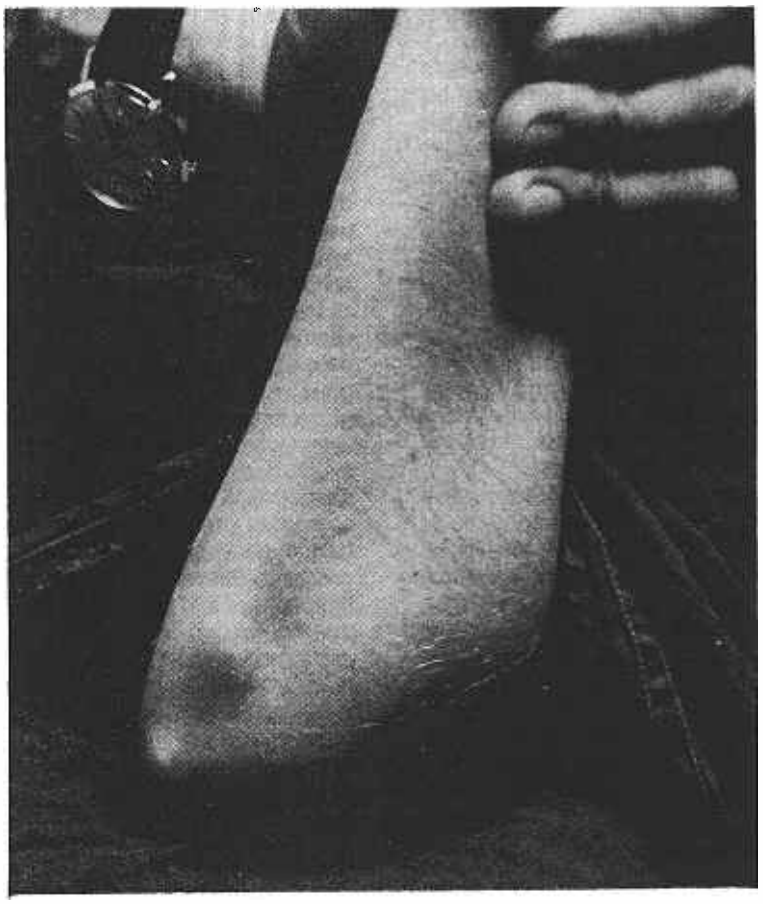

Figure 3. Suboutaneous (rheumatoid) nodules commonly appear at the olecranon process of the elbow and the proximal ulnar aspect of the forearm.

Management

Patients with a monocyclic or intermittent disease course need only the immediate acting drugs for affective care. On the other hand, patients in the unremitting group need a slow acting or remittive drug as well, and the sooner initiated the better. No drug can reverse subluxation of the wrists or ulnar drift from chronic or persistent bulging of the MCP joints, so you must use drugs to try to avoid such outcomes. Clearly, this requires a well-defined therapeutic approach. First, you have to educate patients about the nature of their disease, what they can reasonably expect from treatment, and those modalities they should best avoid. Such counseling is important, considering that Americans spend close to a billion dollars yearly on arthritis quackery, seeking quick and unproven cures. Traditional and comprehensive care, by contrast, stresses physical therapy, appropriate rest, and compliance with proven drugs.

All drugs used in RA can be grouped into two major classes: the immediate acting and the slow acting or remittive agents (4,14). Drugs in the first group exert an immediate antiinflammatory effect that is evident within days or weeks (Table 2). These include aspirin and other NSAIDs as well as the adrenocorticosteroids. Drugs in the second group are those whose antirheumatic effects are delayed for months. Consequently, they are always used in conjunction with one of the immediate acting drugs. Agents whose mode of action is delayed are intramuscular gold, auranofin (oral gold), the antimalarial drugs (chloroquine and hydroxyohloroquine), d-penicillamine, azathioprine, and other immunosuppressive agents.

Nonsteroidal Antiinflammatory Drugs

The choice of a NSAID is often a matter of trial and error. If one or another of these drugs is ineffective, you may opt for one from a different chemical class (Table 2). A patient doing poorly on ibuprofen, for example, might respond to tolmetin sodium or meclofenamate. This is only a rough guide, however, since some patients respond only to drugs of the same class, others to all drugs (regardless of class), and a few—particularly patients with refractory RA—to none. The choice of drug will also depend on other factors, such as compliance, cost, and tolerance. To avoid gastrointestinal intolerance, advise patients to take each of these drugs after meals or with a snack or milk.

It appears that all NSAIDs are primarily analgesic at lower dosages and antiinflammatory at higher dosages (4,15,16). Consequently, it is critical to give antiinflammatory quantities of these drugs. In fact, this is precisely why drugs like acetaminophen or propoxyphene, which are pure analgesics, are inappropriate as basic drugs for *active* RA. These latter drugs, while providing pain relief, do nothing to suppress joint inflammation.

Until 1974, when ibuprofen was marketed, there were only a handful of NSAIDs available in the United States. These included aspirin, phenylbutazone, oxyphenbutazone, and indomethacin (Table 2). Since then, there has been a steady proliferation of NSAIDs.

Trial of Isoxicam, Aspirin, And Placebo

In the United States, the drug of choice for RA continues

TABLE 2.
NONSTEROIDAL ANTIINFLAMMATORY DRUGS BY CHEMICAL GROUPINGS: UNITED STATES MARKETING YEAR AND HALF-LIFE

Chemical Class Generic Name	Marketing Year	Half-Life (Hours)
Salicylates		
Aspirin, Other Salicylates	1915	9–16*
Pyrazoles		
Phenylbutazone	1952	84
Oxyphenbutazone	1961	72
Indole Acetic Acids		
Indomethacin	1965	4–5
Tolmetin sodium	1976	6
Sulindac	1978	16
Propionic Acids		
Ibuprofen	1974	2
Fenoprofen calcium	1976	4
Naproxen	1976	13
Fenamic Acids		
Meclofenamate sodium	1980	4
Oxicams		
Piroxicam	1982	38
Isoxicam	1985+	31

*Only when administered in antiinflammatory quantities.
+Estimated marketing in the United States.

to be aspirin at doses of 3.6 g or more daily. In the current double blind study, isoxicam, 200 mg administered once daily, was compared to buffered aspirin, 900 mg given four times daily, as well as to placebo (17). Of 317 patients entering the six-week trial, 105 received isoxicam, 106 buffered aspirin, and 106 placebo.

The results of the clinical measurements are outlined in Table 3. Both isoxicam and aspirin were significantly superior to placebo in all variables tested. In fact, isoxicam was superior to aspirin at the 5 percent level in all clinical variables with the exception of grip strength and duration of morning stiffness. However, even in these two assessments, the trend favored isoxicam.

After six weeks, the placebo-treated group was dropped, while the isoxicam-aspirin comparison continued for an additional 20 weeks. At the six-month assessment, isoxicam was clearly superior to aspirin in all variables except for duration of morning stiffness (Table 4). When the side effects of isoxicam and aspirin were compared, most were related to the gastrointestinal tract (17). The total number of adverse reactions as well as the number of patients affected (19% for isoxicam compared to 37% for aspirin) was significantly lower for isoxicam.

Clearly, the results of this trial demonstrate that a single daily dose of 200 mg of isoxicam is not only superior to placebo but also to 3.6 g daily of aspirin. Moreover, isoxicam was also better tolerated than aspirin. This is the first study in which a NSAID has been shown to be significantly more effective rather than simply comparable to aspirin in patients with RA.

TABLE 3.
ASPIRIN- AND PLACEBO-CONTROLLED TRIAL OF ISOXICAM IN RHEUMATOID ARTHRITIS: MEAN PERCENTAGE CHANGE OF CLINICAL MEASUREMENTS FROM BASELINE TO FINAL EVALUATION AT SIX WEEKS

Clinical Measurement	Treatment		
	Isoxicam %	Aspirin %	Placebo %
Reduction in:			
Number of Tender Joints	41.5	28.8	11.0
Sum of Tenderness Scores	49.1	33.9	8.6
Number of Swollen Joints	33.4	22.1	9.2
Sum of Swelling Scores	45.7	25.0	1.6
Number of Joints Involved	34.5	20.3	8.1
Duration of Morning Stiffness	56.9	45.0	5.4
Time to Walk 50 Feet	19.1	10.9	-5.2
Increase in:			
Mean Grip Strength	23.0	14.9	-2.7

TABLE 4.
ISOXICAM (200 MG) VERSUS ASPIRIN (3.6 G) IN RHEUMATOID ARTHRITIS: PERCENT CHANGE IN CLINICAL MEASUREMENTS AT SIX MONTHS.

Clinical Measurement	Treatment	
	Isoxicam %	Aspirin %
Reduction in:		
Number of Tender Joints	46.1[a]	26.9
Sum of Tenderness Scores	57.2[b]	31.2
Number of Swollen Joints	45.6[b]	22.1
Sum of Swelling Scores	53.8[b]	25.6
Number of Joints Involved	38.0[b]	19.1
Duration of Morning Stiffness	59.7	46.7
Time to Walk 50 Feet	21.6[c]	10.6
Increase In:		
Mean Grip Strength	28.1[d]	13.9

[a]Significantly superior to aspirin ($p = 0.0010$).
[b]Significantly superior to aspirin ($p < 0.0001$).
[c]Significantly superior to aspirin ($p = 0.0020$).
[d]Significantly superior to aspirin ($p = 0.0034$).

OSTEOARTHRITIS (OSTEOARTHROSIS)

Articular cartilage and subchondral bone are the sites of major abnormalities in osteoarthritis, the most common rheumatic disorder seen in clinical practice. Two primary pathologic processes are operative: breakdown of cartilage; and proliferative osteophyte formation at joint margins. Unfortunately, we do not know yet how or why these abnormalities are set in motion or how to prevent or reverse them.

Sites of Involvement

Primary osteoarthritis of the DIP joints occurs primarily in women as young as 30 years of age and frequently runs in families. In some women, Heberden's nodes evolve painlessly, while in others, there is swelling, redness, and tenderness from small cysts that arise dorsolaterally at the DIP joints. Comparable soft tissue and osseous proliferations may also occur at the PIP joints, where they are known as Bouchard's nodes. Osteoarthritis may also affect the first carpometacarpophalangeal joint at the base of the thumb. However, unlike RA, it does not affect the MCP or wrist joints. Weight-bearing joints are also involved, including the cervical and lumbar spine, hips, knees, and the first metatarsophalangeal joints. Typical findings on x-ray examination include joint space narrowing and osteophyte formation at the margins of affected joints.

While multiple joints may be affected by primary osteoarthritis, the pattern of joint involvement is clearly different from that seen in RA. Moreover, osteoarthritis is not a systemic disorder but one that is localized to the joints and adjacent structures. Consequently, rheumatoid factor is absent and laboratory studies, including the ESR, are normal. Nevertheless, inflammation or synovitis is a common secondary event, particularly when hands, hips and knees are involved. This may explain why some patients prefer and respond better to NSAIDs than to pure analgesics. Two trials of isoxicam have been conducted in osteoarthritis; the first compares the drug to placebo, and the second to indomethacin.

Isoxicam Versus Placebo

In the initial study, isoxicam, 200 mg given once daily, was compared to placebo in a six-week trial of 214 patients, 169 with osteoarthritis of the knee and 45 with hip involvement. In osteoarthritis of the knee, isoxicam was superior to placebo in all clinical variables tested, including a number of separate pain and functional assessments (Table 5). In osteoarthritis of the hip, isoxicam was superior to placebo in 3 of 6 variables tested: pain on walking; degree of starting pain; and the intermalleolar straddle to the point of onset of pain (Table 6). In the remaining 3 parameters, while the trend consistently favored isoxicam, these failed to reach the conventional 5 percent level of significance, perhaps due to the relatively small numbers of patients studied. Nevertheless, we can conclude from this study that a single 200 mg daily dose of isoxicam is superior to placebo.

Isoxicam Versus Indomethacin

Indomethacin is frequently used at high doses in severe osteoarthritis of the knee or hip. We therefore undertook to compare the efficacy and safety of isoxicam to that of indomethacin in a multicenter study of 12 weeks in 345 patients with osteoarthritis of the knee or hip. In this particular study, 100 mg of isoxicam was given twice daily and 50 mg of indomethacin was given three times daily.

The clinical assessments for both the hip and knee have been combined and are shown in Table 7. Although the trend for each variable consistently favored isoxicam, there were no significant differences between the two treatment groups. It does document, nevertheless, that isoxicam is as efficacious as high dose indomethacin in the treatment of osteoarthritis of the hip or knee.

While the efficacy of isoxicam and indomethacin proved to be comparable, isoxicam was significantly better tolerated than indomethacin. Fewer patients reported adverse reactions with isoxicam; more patients reported neurologic adverse reactions with indomethacin and fewer patients receiving isoxicam had gastrointestinal disturbances. We can conclude from this study that whil isoxicam is as efficacious as high dose indomethacin, it is better tolerated by patients.

TABLE 5.
OSTEOARTHRITIS: ISOXICAM 200 MG ONCE DAILY VERSUS PLACEBO
Changes in Knee Parameters (Baseline to Final Evaluation)

	Treatment	
Knee Parameter	**Isoxicam**	**Placebo**
Night Pain	−37.8%**	−2.0%
Pain on Walking	−42.3%**	−7.7%
Degree of Starting Pain	−40.8%**	−7.8%
Pain on Motion	−41.3%**	−4.9%
Swelling	−41.5%**	−4.5%
Tenderness	−46.2%**	−6.6%
Limitation of Range of Motion	−39.6%**	−2.4%
Maximum Extension (cm)	+6.8%**	−0.9%
Maximum Flexion (cm)	−11.4%**	+1.1%

**Significantly superior to placebo ($p < 0.0001$).

TABLE 6.
OSTEOARTHRITIS: ISOXICAM 200 MG ONCE DAILY VERSUS PLACEBO
Changes in Hip Parameters (Baseline to Final Evaluation)

	Treatment	
Hip Parameter	**Isoxicam** n = 24	**Placebo** n = 19
Night Pain	−23.5%	−10.8%
Pain on Walking	−31.5%[a]	−6.8%
Degree of Starting Pain	−27.7%[b]	−7.5%
Pain on Motion	−23.3%	−8.4%
Int. Straddle: Point Where Pain Begins	+15.8%[c]	+0.6%
Int. Straddle: Max Displacement Tolerable	+10.8%	+1.8%

[a]Significantly superior to placebo ($p = 0.0022$).
[b]Significantly superior to placebo ($p = 0.0208$).
[c]Significantly superior to placebo ($p = 0.0355$).

TABLE 7.
OSTEOARTHRITIS: ISOXICAM (200 MG ONCE DAILY) VERSUS INDOMETHACIN (150 MG DAILY)
Changes in Knee and Hip Parameters

	Treatment	
Parameter	**Isoxicam Percent Change**	**Indomethacin Percent Change**
Starting Pain	−47.01	−44.87
Pain on Motion	−51.54	−49.78
Pain on Walking	−47.28	−46.03
Night Pain	−59.38	−55.21
Maximum Extension, cm (Knee)	−32.10	−31.60
Maximum Flexion, cm (Knee)	−18.08	−14.78
Pain-free Abduction, cm (Hip)	+14.31	+11.14
Maximum Abduction, cm (Hip)	+12.02	+9.31

TABLE 8. CLINICAL TESTS FOR EARLY DETECTION OF ANKYLOSING SPONDYLITIS

Test	Method	Interpretation
Sacroiliac compression	Exert direct compression over sacroiliac joints	local tenderness suggests sacroiliac involvement which can be asymptomatic initially
Chest expansion	Measure maximum chest expansion at the nipple line	Expansion of less than 3 cm is a clue to early costovertebral involvement
Fingers to floor	Patient bends forward with knees extended; distance from fingertips to floor is measured	Inability to touch close to floor is evidence of early lumbar involvement
Schober test	Make a mark on the spine at the level of the iliac crests and then another 10 cm directly above while patient is standing upright. Patient then bends forward maximally keeping knees extended and the distance between the two marks is measured	An increase of less than 3 cm indicates loss of lumbar flexion
Occiput to wall	Patient places heels and back against wall and tries to touch the wall with the back of the head without raising his chin above carrying level	Inability to touch head to wall signifies loss of cervical extension

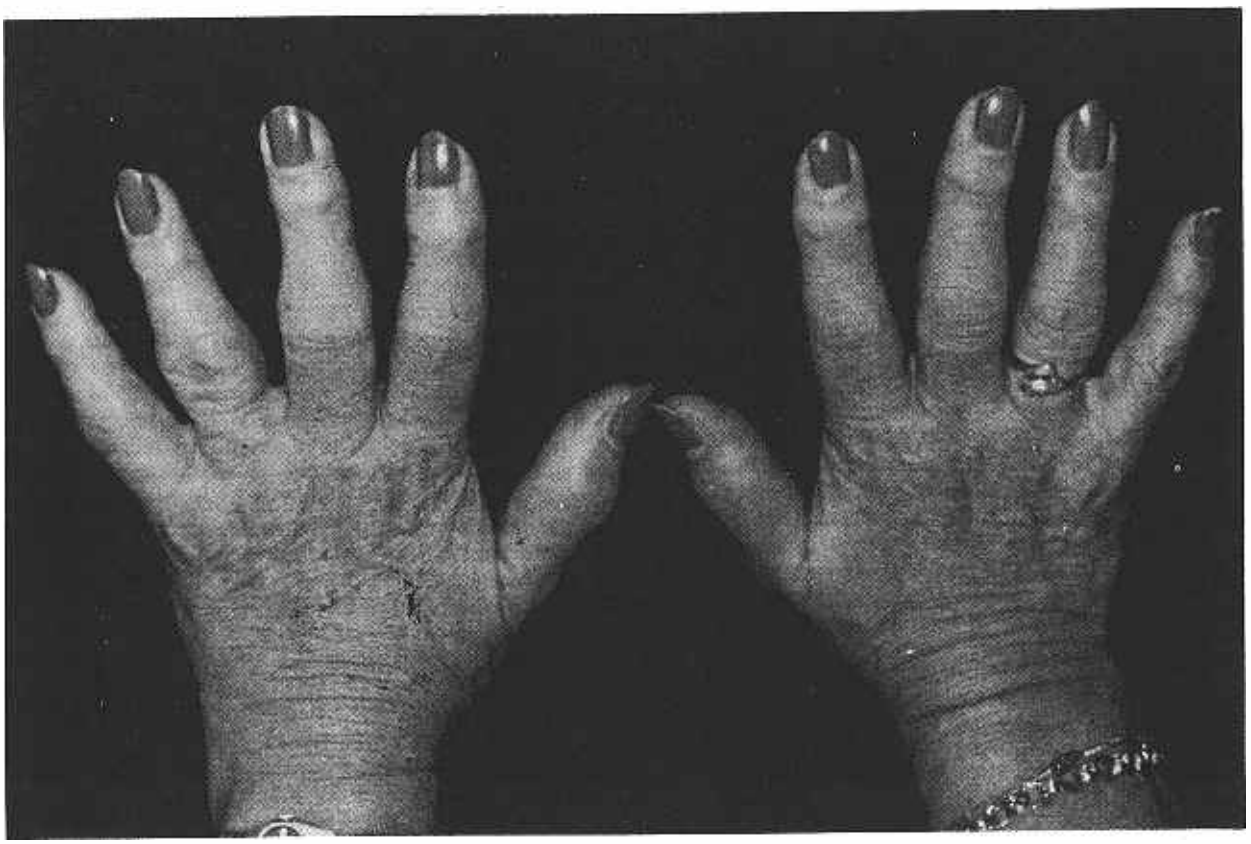

Figure 4. In osteoarthritis of the hands, Heberden's and Bouchard's nodes occur at the distal and proximal interphalangeal joints, respectively. The metacarpophalangeal and wrist joints, commonly involved in rheumatoid arthritis, are usually spared.

ANKYLOSING SPONDYLITIS

Ankylosing spondylitis (AS) is a heterogeneous and systemic rheumatic disorder that is characterized by inflammation of the axial skeleton (spine and sacroiliac joints) and large peripheral joints (18). It affects three times more men than women and usually begins between the ages of 20 and 40 years. Less than 10% of cases begin in childhood and no more than 15% after the age of 40 years. Comprehensive management is clearly enhanced by early diagnosis and patient education, each of which depend in large measure on an understanding of the epidemiology, pathogenesis, and natural history of AS.

Epidemiology And Pathogenesis

The initial 1973 disclosure and subsequent world-wide confirmation of the high frequency of the inherited tissued antigen HLA-B27 in patients and relatives when compared to healthy controls provides overwhelming evidence of a genetic predisposition in the development of AS (18). There are, however, recent reports suggesting that environmental or exogenous factors are also operative in pathogenesis (19,20). Of particular relevance in this regard are reports in which the activity or flares of AS can be closely related to the presence of *Klebsiella pneumoniae* in stool cultures (21,22,23). In fact, molecular mimicry between *Klebsiella* and the HLA-B27 antigen has been suggested, although this concept of cross-reactivity may be restricted to certain strains of *Klebsiella*.

AS is the third most common form of chronic arthritis in the United States, affecting as many as 3 million Americans (24). Estimates of the prevalence of AS vary widely throughout the world, being directly proportional to the frequency with which the B27 antigen occurs in a given population (25). Moreover, the frequency of subjects having the B27 antigen who will eventually develop AS remains unsettled. Based on two American surveys, one of B27-positive blood donors (24) and another of B27-positive tissue donors (26), it has been calculated that AS will develop in 20% of both men and women harboring the antigen.

The frequent association between spondylitis and psoriasis, Reiter's syndrome, ulcerative colitis, and regional enteritis, has until recently defied explanation. It now appears that among these disorders, the patients most apt to develop AS are those positive for the B27 antigen. In fact, it has been estimated that the risk for developing spondylitis is 40 times greater in ulcerative colitis patients carrying the B27 than in those without the antigen (25).

In addition to AS, B27-positive subjects are also prone to develop recurrent attacks of acute iritis (without arthritis or spondylitis) as well as Reiter's syndrome. They are also predisposed to psoriasis and psoriatic arthritis, although the correlation of B27 to these latter disorders is less striking (25).

Natural History

AS has three distinct modes of onset (8). The most frequent initial complaint is back pain, usually of the lumbar spine and sacroiliac joints, but occasionally of the cervical or thoracic spine. However, in as many as 30% of patients, most of whom are primarily children and women, disease begins in peripheral joints, often asymmetrically and usually of knees, hips, ankles, and heels. The time interval between the onset of peripheral arthritis and sacroiliac or back pain may be prolonged to 5, 10, or even 15 years, particularly in boys who are otherwise diagnosed as having pauciarticular JRA. Recurrent attacks of acute iritis (anterior uveitis) are the sole presenting manifestation in about 2% of cases. Early systemic manifestations may include fever, fatigue, anorexia, weight loss, anemia, and acute iritis.

Whatever the mode of onset, recurrent and intermittent back pain is an eventual complaint. Patients automatically ease back pain or paraspinal muscle spasm by adopting a flexed position. Consequently, in the untreated patient, some degree of kyphosis is common. Early diffuse costovertebral involvement is usual and soon leads to diminished chest expansion. The usual course of disease is characterized by remissions and exacerbations that may be mild in some and severe in others. Rarely is the course persistently progressive, resulting in early and severe disability.

While acute iritis is an uncommon presentation of AS, 30% of patients are eventually affected by this ocular inflammation. Attacks are usually short-lived, subsiding within a few weeks, but recurrences are common. Rarely are attacks severe or protracted so as to cause loss of vision.

Peripheral synovitis occurs frequently in the course of AS. While often transient, it becomes chronic in as many as 25% of patients. Peripheral arthritis is usually asymmetric, involving only one or a few large joints, such as hips, knees, or shoulders. Rarely are the small joints of the hand and foot involved.

Diagnostic Considerations

AS continues to remain the most commonly overlooked cause of back complaints in young people (27). Yet, all that is required for early diagnosis is the usual approach of all primary physicians—a complete history, including that of the family, and physical examination, as well as a critical interpretation of pertinent laboratory and roentgenographic findings.

History And Physical Examination. If a patient complains of back pain, there are several clues in the history that point to AS: the back pain has persisted for more than 3 months; the pain is intermittent, often worse at night; and the pain is accompanied by early morning stiffness that is readily relived by activity.

On examination, certain simple tests will disclose typical abnormalities at an early stage (Table 8). For example, to unmask local tenderness from sacroiliitis, compress the sacroiliac joints bilaterally. In a surprising number of cases, the patient will not previously have reported pain specifically in the sacroiliac joints. To explore for early costovertebral involvement, that is frequently asymptomatic, check the patient's chest expansion. If the maximum expansion is less than 3 cm, your suspicions should be aroused since normal chest expansion is 6 cm or greater. To check for lumbar involvement, ask the patient to touch to the floor keeping the knees straight. Most spondylitic patients are unable to reach with their fingertips much below knee level. Moreover, on examination of the lumbar spine, the normal lumbar lordosis may be lost becuse of paraspinal muscle spasm. One final check of early lumber involvement is the Schober test. If the skin stretches less than 3 cm, the lumbar spine is affected. The occiput-to-wall test will disclose early involvement of the cervical spine, as will loss of cervical extension and lateral bending. With appropriate management, most abnormal measurements will improve or revert to normal. Consequently, in long-term management, these simply tests should become a routine part of the patient's examination at each followup visit.

Laboratory And Roentgenographic Clues. When AS is active, the ESR is elevated in most patients, as are other acute phase reactants such as serum IgA levels. IgM rheumatoid factor is not present. Consequently, a negative test for rheumatoid factor in a young patient who has only peripheral arthritis should in fact alert you to the possibility of AS, or for that matter still another of the seronegative spondyloarthropathies. Presence of the HLA B27 is perhaps the best single laboratory clue. Its absence, however, does not preclude a diagnosis of AS.

The diagnosis of AS must be confirmed by roentgenographic examination. In the majority of patients, the earliest changes occur in the sacroiliac joints (Figure 5). It is

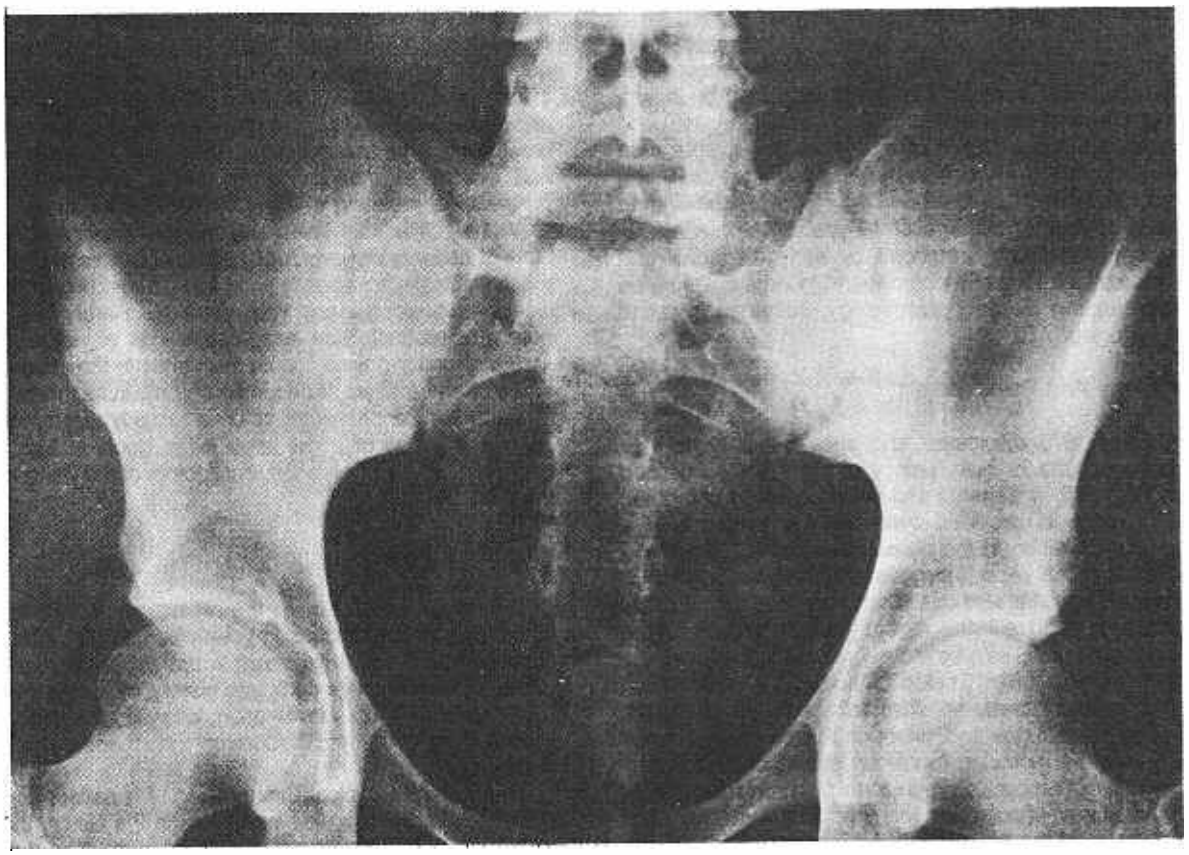

Figure 5. X-ray of the pelvis discloses pseudowidening of the sacroiliac joints from subchondral erosions and sclerosis that are more prominent on the iliac side.

customary to include frontal and oblique projections in the preliminary examination. Additional views or techniques may include antero-posterior erect, stereophotogrammetry, cranio-caudal axial projection, tomography, computerized tomography, and scintigraphy. While each of these latter techniques may be beneficial in cases where routine radiographs appear to be normal or equivocal, they are seldom needed. Moreover, with these additional approaches, the interpretation will depend largely on the skill and expertise of the radiologist.

Early changes of the lumber spine include diffuse vertebral squaring and demineralization (Figure 6). Minimal ligamentous calcification and one or two evolving syndesmophytes may be noted. The classic "bamboo spine" with its prominent syndesmophytes and diffuse paraspinal ligamentous calcification of the entire spine, the usual textbook illustration, is not useful in early diagnosis. In fact, it takes an average of 10 years to develop and is seen in patients with progressive disease, a group that comprises less than 15% of all patients.

Trial of Isoxicam Versus Indomethacin

The primary aim of drug therapy in AS is to suppress articular pain and inflammation, thereby promoting compliance with extension exercises that in turn facilitate maintenance of an upright posture. While the drugs most frequently used are indomethacin and phenylbutazone, the latter carries a small but definite risk of potentially fatal aplastic anemia.

The current double-blind trial compares isoxicam, 200 mg given once daily, to indomethacin, 25 mg administered three times daily. The trial lasted 12 weeks involving 97 patients (71 males & 26 females), with each treatment group being comparable in composition, mean age, and duration of AS.

The percentage improvementss for both treatment groups are depicted in Table 9. In 11 of the 13 variables measured, isoxicam was statistically superior to indomethacin. Further data to support the superiority of isoxicam may be derived from the trial completion rates. Only 4 patients receiving isoxicam were withdrawn compared to 23 on indomethacin. This difference is highly significant. Moreover, only one patient on isoxicam was withdrawn because of lack of efficacy compared to 15 receiving indomethacin. Adverse reactions, while more frequent with indomethacin, did not achieve statistical significance.

CONCLUSIONS

We have presented results from our clinical program of isoxicam involving a total of 973 patients. The results confirm that isoxicam is both effective and well tolerated in the treatment of RA, osteoarthritis, and AS.

In support of these conclusions, we have provided data to show: that isoxicam is more effective and better tolerated than aspirin in RA; that isoxicam is as effective but better tolerated than high-dose indomethacin in osteoarthritis; and that isoxicam is more effective but as well tolerated as indomethacin in AS.

The excellence of this therapeutic profile is further enhanced by the advantage of a convenient once daily dosing schedule as compared to multiple daily dosing required of many of the currently available NSAIDs. Isoxicam should therefore prove to be a welcome addition to our present spectrum of antirheumatic agents.

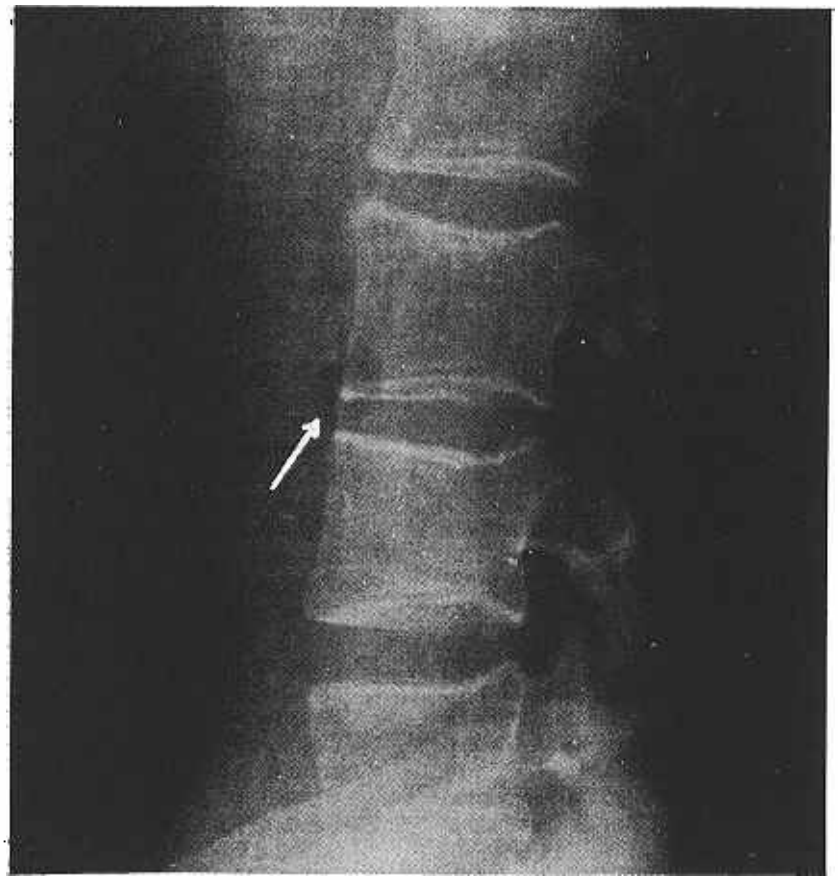

Figure 6. Lateral x-ray of the lumbar spine reveals typical early changes including demineralization and squaring of vertebral bodies as well as ligamentous calcification from L_3 to L_4 (arrow).

TABLE 9.
ISOXICAM (200 MG DAILY) VERSUS INDOMETHACIN (25 MG THREE TIMES DAILY) IN ANKYLOSING SPONDYLITES: PERCENTAGE IMPROVEMENT IN CLINICAL VARIABLES TESTED FROM BASELINE TO FINAL EVALUATION

	Isoxicam	Indomethacin	p
Chest expansion	35.9	0.4	<0.01
Time to fatigue	60.7	15.0	<0.001
Schober test	5.5	4.5	NS
Finger-to-floor test	27.9	4.8	<0.001
Spinal pain (objective)	71.1	22.0	<0.001
Spinal pain (subjective)	69.7	21.1	<0.001
Duration of morning stiffness	60.2	26.2	<0.01
Occiput to wall distance	18.6	11.5	NS
Night pain	73.6	27.2	<0.001
Overall assessment (physician)	53.3	18.6	<0.001
Overall assessment (patient)	51.0	19.0	<0.001
Global assessment (physician)	85.7	34.8	<0.001
Global assessment (patient)	83.7	34.8	<0.001

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