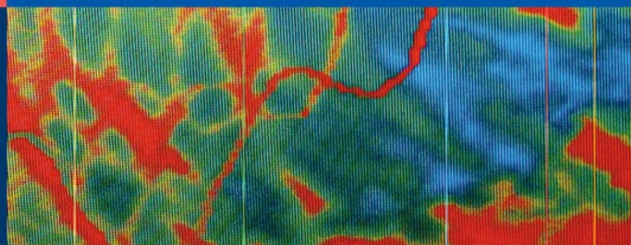


David L. Scott  
Gabrielle H. Kingsley



# Inflammatory Arthritis in Clinical Practice

 Springer

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## Abbreviations

ACR	American College of Rheumatology
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
CLASS	Celecoxib Long-term Arthritis Safety Study
COX	cyclooxygenase
CRP	C-reactive protein
CT	computed tomography
DAS	Disease Activity Score
DEXA	dual-energy X-ray absorptiometry
DISH	diffuse idiopathic skeletal hyperostosis
DMARD	disease-modifying anti-rheumatic drug
ELISA	enzyme-linked immunosorbent assays
ESR	erythrocyte sedimentation rate
FBC	full blood count
HAQ	Health Assessment Questionnaire
HIV	human immunodeficiency virus
HLA	human leucocyte antigen
ICAM	intercellular adhesion molecule
IgA	immunoglobulin A
IgG	immunoglobulin G
IL-1	interleukin-1
MHC	major histocompatibility complex
MRI	magnetic resonance imaging
NSAIDs	non-steroidal anti-inflammatory drugs
OSRA	Overall Status in RA
PEG	polyethylene glycol
PCR	polymerase chain reaction
RA	rheumatoid arthritis
SAA	serum amyloid A
SMR	standardized mortality ratio
SpA	spondyloarthropathies
TENS	transcutaneous electrical nerve stimulation
TNF- $\alpha$	tumour necrosis factor alpha
VAS	visual analogue scale



# Rheumatoid arthritis

## Introduction

Rheumatoid arthritis (RA) is an immune-mediated, chronic, inflammatory polyarthritis. Typically, it affects peripheral synovial joints in a symmetrical fashion. The prolonged clinical course of RA is characterized by exacerbations and remissions, with associated features of systemic disease.

The term 'rheumatoid arthritis' dates from Victorian times; it was introduced by Sir Archibald Garrod to distinguish the disease from gout and rheumatic fever. In 1876, Garrod wrote, "rheumatoid arthritis is a name which does not imply any error, but assumes the disease to be an arthritic or joint disease having some of the external characteristics of rheumatism". The presentation of RA in Garrod's time was much the same as it is today, as shown in an illustration from 1876 (*see* Figure 1.1).

### Illustration of rheumatoid arthritis



**Figure 1.1.** Engraving of the hand of a patient with rheumatoid arthritis after Sir Archibald Garrod.

It was many years before the term was accepted; being adopted by the Empire Rheumatism Council in 1922 and by the American Rheumatism Association in 1941.

## Diagnosis

Although the diagnosis of RA is usually straightforward, non-specific presenting features can make identification problematic. The lack of definitive laboratory tests or confirmatory physical findings in early disease also poses difficulties. The 'gold standard' for the diagnosis of RA is the opinion of a specialist rheumatologist.

The current internationally accepted diagnostic criteria, from the American College of Rheumatology (ACR), are shown in Table 1.1. RA is considered to be present when four of the seven qualifying criteria are met.

Although these criteria have high overall sensitivity and specificity, they are not particularly accurate at diagnosing RA in its early stage, nor are they helpful in predicting the severity of the disease course. Furthermore, the ACR criteria are unable to differentiate whether recent-onset synovitis is due to RA or undifferentiated, self-limiting disease.

### Summary of 1987 ACR criteria for the classification of RA

1. Morning stiffness in and around joints lasting >1 hour before improvement
2. Arthritis involving three or more joint areas
3. Arthritis of the hand joints
4. Symmetrical arthritis
5. Rheumatoid nodules
6. Positive serum rheumatoid factor
7. Radiographic evidence of RA

**Table 1.1.** ACR, American College of Rheumatology. To diagnose rheumatoid arthritis (RA), criteria 1–4 must have been present for at least six weeks; and four or more criteria must be present. The diagnosis of RA should not be made by the above criteria alone if another systemic disease associated with arthritis is present.

## Epidemiology

### Prevalence and incidence

RA occurs worldwide, with a prevalence rate in adults in the region of 1%. This frequency varies widely between different ethnic groups, however, with the highest prevalence seen in certain native-American populations and lowest rates in Asian and African ethnic groups (*see* Table 1.2). There has been much debate over whether the prevalence of RA in European and North American populations has changed in recent decades. Higher estimates suggest a prevalence of just over 1%, while other studies suggest a prevalence of 0.5%. These conflicting rates reflect both the technical problems encountered in large-scale population-based epidemiological studies and the changing classification of RA, with earlier epidemiological studies using different, less specific criteria. It is likely that the lower frequency reflects the numbers of cases of severe disease requiring specialist care.

#### Variations in rheumatoid arthritis prevalence

Population	Geographic area	Prevalence
Nigeria	Rural	Not found
Afro-Caribbean	Manchester	0.25%
Indonesia	Rural	0.3%
Taiwan	Urban	0.9%
Maoris	New Zealand	3.0%
Pima Indians	USA	5.0%

**Table 1.2.**

The age distribution of RA is unimodal and there is a peak in incidence between the fourth and sixth decade. Women are more likely than men to develop RA, and there is an increasing prevalence with age (*see* Table 1.3).

The incidence of RA is low. Research suggests that in a population of 100,000 adults there will be approximately 36 new cases of RA in women and 14 in men per year. The incidence rate rises steeply with age, especially in men. There is some evidence that the incidence of RA has fallen by one-third over the last 50 years.

Prevalence of rheumatoid arthritis by age and sex		
Age (years)	Males	Females
<35	–	–
35–44	–	0.9%
45–54	0.2%	1.1%
55–64	1.9%	2.9%
≥65	1.0%	4.9%
Overall	0.7%	1.6%

**Table 1.3.****Genetic risk factors**

Genes play a significant role in RA. Monozygotic twins have higher disease concordance than dizygotic twins (approximately 12% versus 4%, respectively). Heritability studies suggest that 60% of predisposition to RA is explained by genetic factors. RA is strongly related to the presence of histocompatibility leucocyte antigen (HLA) DR4 and a shared epitope on small regions of the DRB1\*0401 and \*0404 alleles. Although many other genetic risk factors have been studied, no further strong associations have been found. Debate continues as to whether genetic factors contribute mainly to disease susceptibility or to its severity. The evidence favours the main link being to disease severity.

**Other risk factors**

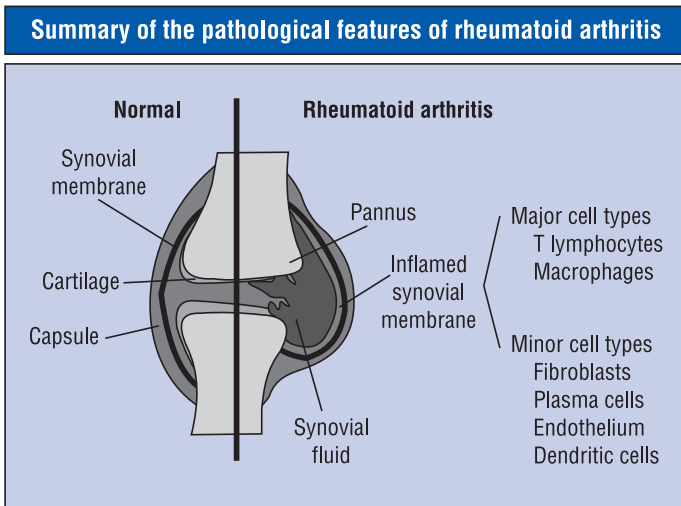
- Gender (women comprise up to three-quarters of RA patients);
- Age (although RA can occur at any age from childhood to old age, traditionally it was viewed as a disease starting in young adulthood, with a peak age of onset between 20 and 45 years. This situation is changing and the average age of onset has now increased to 60 years; the reasons for this are unknown)
- Heavy smoking;
- Obesity;
- History of blood transfusions;
- Shorter fertile period in women associated with low levels of reproductive hormones and potential effects of oral contraceptive pills;
- Coffee consumption (thought by some to be a predisposing risk factor, although evidence suggests its effect is either minimal or non-existent).
- Trauma may be a factor, although the evidence is inconclusive.

## Pathogenesis

The cause or causes of RA remain unknown. There are suggestions that infection due to viruses or bacterial can cause immune changes leading to autoimmunity, but no definite conclusions have been reached after more than 100 years intensive research.

Inflammatory synovitis is the key pathological feature in RA (*see* Figure 1.2). Its characteristics are synovial hyperplasia, inflammatory cell infiltration and vascularity. Initially, oedema and fibrin deposition predominate. Subsequently, there is synovial lining layer hyperplasia involving macrophage-like and fibroblast-like synoviocytes. This hyperplasia is accompanied by infiltration of T cells, B cells, macrophages and plasma cells in the sublining layer. Endothelial cells in the blood vessels transform to form high endothelial venules, which facilitate leucocyte transfer into the synovium.

Pannus formation, with the generation of locally invasive synovial tissue, is the other characteristic feature of RA. The RA pannus is composed of mononuclear cells and fibroblasts. It expresses high levels of proteolytic enzymes, which allow penetration of the cartilage, leading to cartilage damage and joint erosion. In late-stage RA, the pannus becomes fibrotic, with minimally vascularized pannus and collagen fibres overlying articular cartilage.



**Figure 1.2.** Summary of the pathological features of rheumatoid arthritis.

## **Lymphocytes and other inflammatory cells**

Many of the inflammatory cells in the synovial sublining layer are lymphocytes, especially T cells. These are mainly CD4 (helper) T cells, though some are CD8 (cytotoxic-regulatory). In a minority of cases these lymphocytes form aggregates, in a similar manner to those of the lymph nodes. A number of B cells and mature plasma cells secreting rheumatoid factor can also be found, though these cells are usually diffusely scattered throughout the synovium. Other white cells, including classical antigen-presenting cells and phagocytes (monocytes, macrophages and dendritic cells) can also be found.

## **Cytokines**

Cytokines are small soluble proteins involved in communication between cells participating in immune responses. They mediate cell division, differentiation and chemotaxis. Certain cytokines are pro-inflammatory while others are anti-inflammatory. In RA, two cytokines – tumour necrosis factor alpha (TNF- $\alpha$ ) and interleukin-1 (IL-1) – are present in large quantities in synovial fluid and tissue. Agents targeting these cytokines are current used in clinical practice. Additional cytokines such as IL-6 and IL-15 are also involved and are currently being investigated as potential therapeutic targets; there is currently insufficient evidence to know if this will be translated into effective therapies.

## **Chemokines**

These small chemoattractant proteins have prominent roles in leucocyte recruitment and activation at inflammatory sites. Numerous chemokines are present and active in RA synovia.

## **Metalloproteinases and other enzymes**

High levels of these destructive enzymes are produced by RA synovial lining cells. A large family of matrix metalloproteinases exists. The enzymes are involved in remodelling and destruction of the extracellular matrix and articular cartilage. Their activities are modulated by tissue inhibitors of metalloproteinases, serine proteinase inhibitors and  $\alpha_2$ -macroglobulin.

RA synovitis is mediated by many other enzymes, including cyclooxygenases (COX), nitric oxide synthase and neutral proteases.

## **Adhesion molecules, angiogenesis and other mediators**

Adhesion molecules are involved in recruitment of inflammatory cells in RA. They enable cells to adhere both to each other and to the extracellular

matrix. Expression of adhesion molecules in synovial tissue contributes to the recruitment and retention of inflammatory cells.

Angiogenesis is active in RA, particularly in the early stages, as newly formed blood vessels are needed to sustain the hypertrophied synovium. Angiogenesis is regulated by a multitude of inducers and inhibitors, including cytokines, growth factors and soluble adhesion molecules.

### **Clinical features of synovitis**

The main symptoms of RA result from inflammation of the joints. They include:

- pain;
- swelling;
- tenderness;
- difficulty moving.

There is a diurnal variation in symptoms as patients suffer most problems early in the morning, with prolonged morning stiffness lasting several hours. This mirrors the natural circadian rhythm for cortisol secretion by the hypothalamus.

### **Joint swelling and tenderness**

Soft tissue swelling due to synovitis is detectable along the joint margins. The presence of synovial effusions invariably indicates that the joint is swollen. Neither bony swelling nor deformity of the joints indicates synovitis. The range of joint movement can be useful in determining the presence of swelling; for example, decreased dorsiflexion of the wrist in RA.

Fluctuation is a characteristic feature of swollen joints.

Diagnosis of joint tenderness can be made by eliciting pain by applying pressure at rest or by moving the joint, or questioning the patient about joint pain (eg, during movement of the hip joints). To elicit tenderness, pressure should be exerted by the examiner's thumb and index finger sufficient to cause 'whitening' of the examiner's nail bed.

### **Hands and wrists**

Hands are characteristically affected in RA.

- The metacarpophalangeal, proximal interphalangeal, thumb interphalangeal and wrist joints are typically involved. Distal

interphalangeal joints is much less common and only occurs if there is co-existing disease in other hand joints.

- Tenosynovitis of flexor tendons can reduce finger flexion and strength.
- Tenosynovitis of extensor tendons can lead to swelling of the dorsum of the hand and wrist
- Nodular thickenings in flexor tendon sheaths can lead to 'trigger finger'.

Figures 1.3 and 1.4 show examples of RA involving the hands and wrists.

Damage to the wrists causes compaction of bone at the small wrist joints. In late disease this damage may progress to bony ankylosis and the distinctive deformities of RA develop.

Hand deformity in RA typically comprises:

- ulnar deviation of the fingers;
- subluxation of the metacarpophalangeal joints;
- hyperextension of the proximal interphalangeal with flexion of the distal joints (swan-neck deformity);

**Rheumatoid arthritis involving the metacarpophalangeal, proximal interphalangeal and wrist joints**



**Figure 1.3.**



### The hands of Auguste Renoir, showing late-stage rheumatoid arthritis



**Figure 1.4.**

- flexion of the proximal interphalangeal with hyperextension of the distal joints (boutonnière deformity);
- z-shaped deformity of the thumb.

#### Feet and ankles

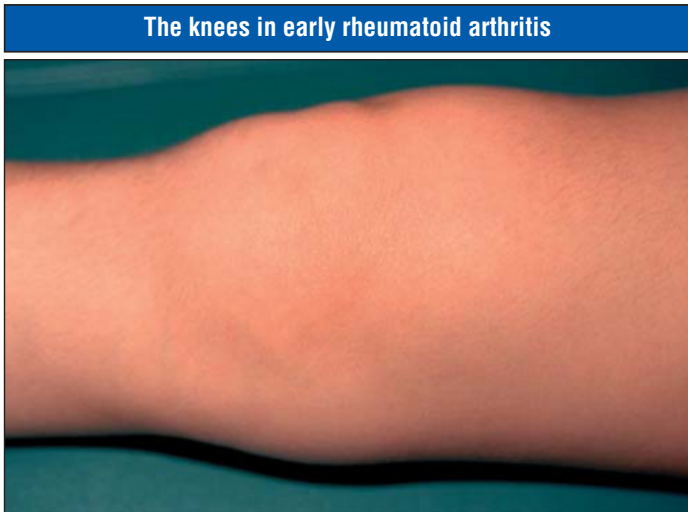
The small joints of the feet are involved at an early stage, causing considerable difficulty in walking. As the disease progresses, a complex series of changes occurs in the feet including spreading of the forefoot, dorsal subluxation of the toes and subluxation of metatarsal heads to a subcutaneous site on the plantar surface. In some cases, additional hallux valgus leads to 'stacking' of the second and third toes on top of the great toe.

The ankle joint itself is rarely involved in early RA, although it is sometimes damaged in late disease. By contrast, the subtalar joint is often involved, resulting in pronation deformities and eversion of the foot.

#### Knees

Knee involvement is common in early RA (*see* Figure 1.5). Quadriceps wasting and loss of full extension are both seen in the first stages of the dis-

ease. There is often a large effusion, which can produce a popliteal or Baker's cyst. As fluid entering these popliteal cysts does not readily return, high pressures are generated and the cyst can rupture into the calf, resulting in considerable pain and discomfort. This problem can be confused with a deep venous thrombosis.



**Figure 1.5.**

### **Shoulders**

RA affects the synovium of glenohumeral joint and also the associated bursae and rotator cuff, together with the relevant muscle groups of the chest wall. Weakness of the rotator cuff leads to shoulder subluxation.

### **Hips**

Although the hips are rarely involved in early RA, about half of patients with established disease have some evidence of hip damage. About 20% of patients develop significant hip pain and resulting joint failure. In a small number of cases the femoral head collapses and the acetabulum is remodelled and pushed medially, which results in protrusio acetabuli. This deformity usually progresses until the femoral neck impinges on to the side of the pelvis.

## Cervical spine

In early disease, many patients have cervical pain, which may be due to muscle spasm. During the course of their disease up to 90% of RA patients have some cervical spine involvement, and it is particularly common in long-standing disease and multiple joint involvement. Significant subluxations occur in about one-third of cases.

As neurological deterioration can be irreversible, it is important to look for subtle signs of early neurological involvement. In addition to painful limitation of neck motion, warning signs of cervical involvement in RA include:

- suboccipital pain;
- paresthesiae in the hands and feet;
- urinary retention or incontinence;
- involuntary leg spasms;
- evidence of upper motor neuron lesions in the legs or arms.

Common radiological presentations include atlanto-axial subluxation (the most common sign) and atlanto-axial impaction (also called basilar invagination). Such patients should have an MRI of the cervical spine to highlight other features, such as pannus of the odontoid peg and cord compression

## Other joints

Any synovial joint can be involved in RA, from the largest joints (such as the knee and hip) to the smallest (such as those in the ear or larynx). This diversity of joint involvement and the variable onset of symptoms from specific joints result in marked variation in the clinical features among patients with RA.

## Systemic features

In addition to synovitis, RA causes general ill health. Patients lack energy and often have systemic features of a 'flu-like' illness. These include loss of appetite, inability to sleep, weight loss and, in some case, a mild fever. The systemic features are most noticeable at the beginning of the disease, especially in cases with an 'explosive' onset. Generally, these features are seen in all chronic inflammatory diseases and it is likely that they represent the non-specific inflammatory response of innate immunity. A minority of

patients, especially those who are rheumatoid factor positive may have extra-articular disease (see below), which can cause systemic disease.

## Natural history

### Onset

In most patients, RA has an insidious onset with features developing over weeks or months. Their initial symptoms may be systemic, articular or both. Some patients describe fatigue, malaise, puffy hands and diffuse joint pain in the early stages, with joints becoming involved later. In 5–10% of those affected, the onset is acute, with symptoms appearing in an explosive manner over a few days. Patients in this group may pinpoint the onset of symptoms to a specific time or activity. Symptoms rapidly progress over several days or weeks and there may be marked systemic symptoms. Between these extremes, about 20% of patients experience an 'intermediate onset' that occurs over several days and weeks.

Occasionally, a patient may show an atypical pattern of onset. Examples include polymyalgic, palindromic and monoarticular onsets. Individuals with a polymyalgic onset present with shoulder girdle pain and prolonged morning stiffness. Palindromic rheumatism is characterized by pain, which usually begins in one joint or in peri-articular tissues. Symptoms worsen for several hours or days and are associated with swelling. Then, symptoms resolve without any residual damage. In some cases this pattern gradually transforms into typical RA or more rarely into other forms of inflammatory arthritis. In about 10–20% of RA cases, the onset is monoarticular or has an asymmetric pattern of disease involving the knee joints. In these individuals, the disease usually progresses into the more typical polyarticular pattern of RA.

### Clinical course

As shown in Table 1.4, the clinical course of RA may be progressive, intermittent with brief or prolonged remissions or, in a minority of cases, severe and often life-threatening with extra-articular involvement.

## Extra-articular disease

Between 20 and 40% of patients show extra-articular features of RA, especially seropositive individuals with high titres of rheumatoid factor. The extra-articular features vary in severity and duration, and only cause major problems in a few cases. However, much of the morbidity and excess mor-

Clinical course of rheumatoid arthritis		
Disease type	Frequency	Description
Progressive	70%	Chronic disease with progression and fluctuations in severity
Intermittent	25%	Intermittent attacks of arthritis, often lasting <1 year with remissions that are either: Brief (lasting <1 year in 10% cases); or Long (lasting >1 year in 10% cases)
'Malignant disease'	<5%	Severe extra-articular disease, especially vasculitis; often fatal

**Table 1.4.**

tality of RA is concentrated in patients with extra-articular disease. The main extra-articular complications are summarized in Table 1.5.

### Nodules

Nodules affect about one-quarter of patients. Most are subcutaneous on extensor surfaces such as the olecranon process (*see* Figure 1.6). They vary in consistency from soft mobile masses to hard, rubbery masses attached to underlying periosteum. Atypical nodules can be difficult to identify; for example sacral nodules may be confused with bedsores if the overlying skin breaks down. Occasionally, nodules cause local problems; for example, nodules in heart valves can precipitate valvular heart disease.

### Vasculitis and other vascular disease

Many forms of RA vasculitis exist. Isolated digital vasculitis, with characteristic splinter-lesions around the nails, is a marker of severe disease although it rarely causes problems itself. By contrast, systemic RA vasculitis can be a devastating complication involving internal organs such as the bowel. Vasculitis classically occurs in 'burned-out' RA (ie, cases with nodular and rheumatoid factor-positive destructive disease that is no longer active). Occasionally, however, vasculitis can complicate early RA.

In addition to the classical vasculitis associated with seropositive disease, patients with RA are more likely to have cardiovascular disease due to arteroma. This is partially attributable to classical risk factors such as smoking and hypertension. It is an area of active ongoing research.

Extra-articular complications of rheumatoid arthritis	
Category	Main features
Nodules	Classically at extensor surfaces
Vasculitis	Nailfold Systemic
Neurological	Nerve entrapment Cervical myelopathy Peripheral neuropathy Mononeuritis multiplex
Ocular	Keratoconjunctivitis sicca (Sjögren's syndrome) Episcleritis Scleritis
Pulmonary	Pulmonary nodules Pleural disease and effusion Fibrosing alveolitis Interstitial fibrosis Bronchiolitis Arteritis with pulmonary hypertension Small airways disease
Cardiac	Pericarditis / pericardial effusion Valvular heart disease Conduction defects
Cutaneous	Palmar erythema Pyoderma gangrenosum Vasculitic rashes Leg ulceration Felty's syndrome (low white cell counts with splenomegaly) Amyloid deposits

**Table 1.5.**

Screening of RA patients for cardiovascular risk factors is likely to be of increasing clinical interest in future years.

### Neurological features

There are several neurological features of RA. The most common is nerve entrapment, the best example of which is carpal tunnel syndrome. Cervical myelopathy is a further example, which develops due to synovitis involving the cervical spine. These types of nerve entrapment occur due to local factors and are not limited to those with sero-positive disease. Other neurological features, occur as 'classical' extra-articular features in seropositive

### Nodules at the elbow



**Figure 1.6.**

cases, and are often associated with vasculitis of the blood vessels supplying nerves. This vasculitis results in neurovascular disease, which can range from mild sensory neuropathy to severe sensorimotor neuropathy. Cases at the severe end of the spectrum are often termed 'mononeuritis multiplex', as multiple peripheral nerves are involved. Marked vascular damage can be seen in nerve biopsies in this condition.

## Infection and malignancy

The immunosuppression of RA results in an increased risk of infections, including tuberculosis and other chronic infectious diseases. There is also an increased incidence of infective arthritis due to the changed vascular supply to the joints. Finally occasional patients, especially those with severe seropositive disease or on immunosuppressive drugs, develop lymphomas. The reason for this is uncertain.

## Clinical assessment

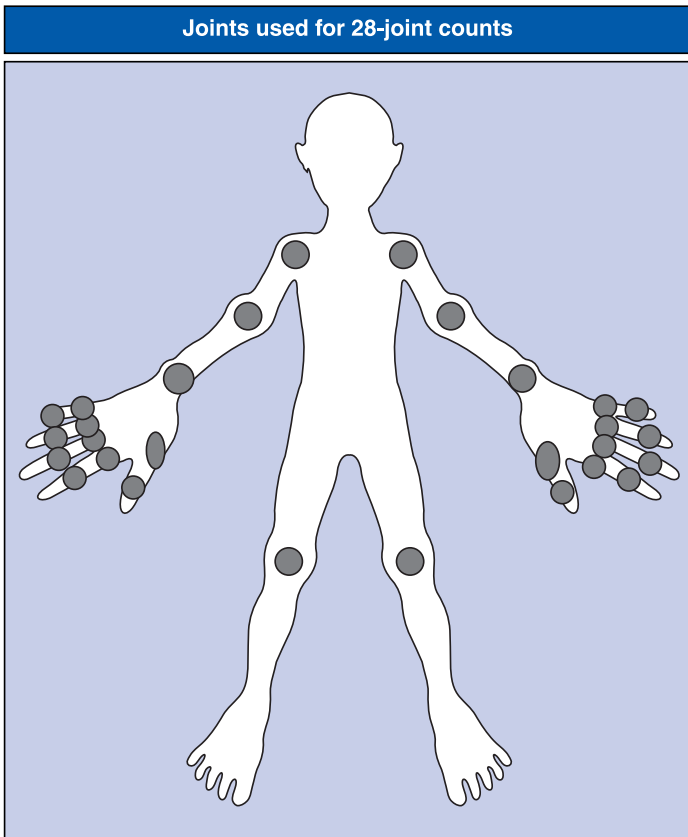
### Joint counts

Joint counts are used to assess disease activity. Traditionally this was within a research setting. However, they are now increasingly undertaken in routine clinical practice. There are a number of different methods for under-

taking joint counts, which record the number of swollen joints or the number of tender joints. The main systems involve counting 66 or 28 joints. The 28-joint index is preferable because of its simplicity. This index focuses on the joints of the upper limbs but also includes the knees (*see* Figure 1.7).

### **Pain scores and global assessments**

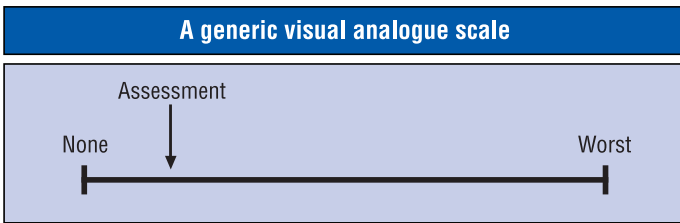
Pain is often considered 'subjective' as it is based on data obtained from the patient, which contrasts with 'objective' information from physical examination and laboratory tests. Yet it is the single most important part of the



**Figure 1.7.**



disease as far as patients are concerned. Over the last few decades, clinical methods of pain assessment have been developed using patient self-report questionnaires. The simplest approach, which is suitable for both research and routine practice, uses visual analogue scales (VAS). The standard VAS for pain is a 10-cm scale bordered on each side with the end corresponding to a zero score labelled 'No pain at all', with the other end (with the maximum score of 10) labelled 'Pain as bad as it could be'. VAS are also often used to assess overall health status and disease activity in RA. An example of a generic scale is shown in Figure 1.8.



**Figure 1.8.**

### Health status and function

Health status spans impairment, disability and handicap.

- Impairment means loss of psychological or anatomical structure or function.
- Disability implies a restriction or lack of ability to perform an activity in the manner considered normal, as the consequence of an impairment.
- Handicap, which is specific for an individual, indicates limitations in fulfilling normal roles for that individual due to impairment or disability.

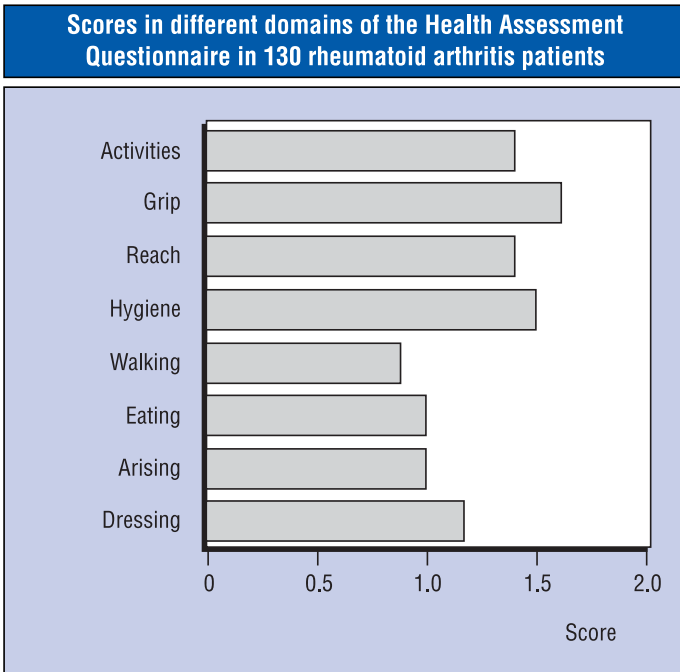
Consequently, impairments and disabilities interact with the physical and social environment to cause handicaps.

Historically, assessments of health status in RA concentrated on measures of function. More recently they have extended to include measures of quality of life. Although function can be measured using 'objective' measures of observed performance, self-completed or interviewer-administered questionnaires of the patient's perception of function are preferred.

The Health Assessment Questionnaire (HAQ) is the most widely used self-completed questionnaire to assess disability. It was developed 25 years ago at Stanford University as a comprehensive measure of outcome in patients with a variety of rheumatic diseases, including RA. It focuses on self-reported, patient-oriented outcome measures, rather than process measures. HAQ scores usually focus on the physical disability scale. This assesses upper and lower limb function related to the degree of difficulty encountered in performing a range of specified daily living tasks. HAQ scores range from 0 (without any difficulty) to 3 (unable to do). Scores for each section are transformed to give an overall disability score of 0–3 where 0 represents no disability and 3 denotes severe disability and high dependency. The HAQ is illustrated in Figure 1.9 and an example of scores from the different domains is shown in Figure 1.10.

<b>Part of the Health Assessment Questionnaire</b>				
<b>Please tick the one response that best describes your usual abilities over the past week</b>				
	<b>Without any difficulty</b>	<b>With some difficulty</b>	<b>With much difficulty</b>	<b>Unable to do</b>
<b>1. Dressing and grooming</b>				
Are you able to:				
Dress yourself, ie tying shoelaces and doing buttons?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Shampoo your hair?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>2. Rising</b>				
Are you able to:				
Stand up from an armless straight chair?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Get in and out of bed?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>3. Eating</b>				
Are you able to:				
Cut your meat?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Lift a full cup or glass to your mouth?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Open a new carton of milk (or soap powder)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

**Table 1.9.**



**Figure 1.10.**

Many other functional assessments have been used in RA, including the Arthritis Impact Score and the Lee functional index. None of these has achieved the wide usage of the HAQ scores.

In addition to the arthritis-specific measures, it is possible to assess RA patients using generic health status questionnaires such as the 36-item short form (SF-36), the Nottingham Health Profile and the EuroQoL, although these are rarely used in clinical practice. These are useful in research studies as they can be applied to all disease areas and can therefore compare the impact of different types of disease on the quality of life.

## Laboratory assessments

- Quantitative laboratory markers such as the erythrocyte sedimentation rate (ESR) are useful for monitoring because they indicate systemic disease.

- Qualitative markers such as rheumatoid factor indicate prognosis and may have pathogenic relevance.

### **Acute phase response**

The acute phase response can be measured indirectly using the ESR or directly using C-reactive protein (CRP) or serum amyloid A (SAA). ESR or CRP levels correlate with clinical measures of disease activity. In early RA they correlate mainly with joint swelling. A persistently elevated acute phase response is associated with a high rate of progressive joint damage.

Although an elevated acute phase response is an excellent marker for disease activity, in a substantial minority of patients both the ESR and the CRP are normal. In patients in whom it is elevated, however, the acute phase response provides an excellent 'flag' for the catabolic processes of RA. The aim of treatment is therefore to return the elevated acute phase proteins to normal levels.

### **Rheumatoid factor and other tests**

An estimated 65–80% of RA patients have rheumatoid factors in their blood. These factors are antibodies that bind specifically to the Fc fragment of immunoglobulin G (IgG), forming immune complexes. Patients with clinically significant levels of rheumatoid factors are termed 'seropositive'. Measuring rheumatoid factor is an essential part of diagnosing RA. Rheumatoid factor, especially in high titre in early RA, also identifies patients with a poor prognosis. It can be found in many other diseases, such as chronic infections and connective tissue diseases, especially Sjögren's syndrome.

Rheumatoid factor is the best predictor of RA outcome.

The first rheumatoid factor tests to be made available used agglutination methods. Examples of these tests include the Rose-Waaler tests based on sheep red cells and latex tests. These early methods detect mainly IgM rheumatoid factors. Newer solid-phase techniques, particularly enzyme-linked immunosorbent assays (ELISA), can measure IgG and immunoglobulin A (IgA) rheumatoid factor isotypes. IgA rheumatoid factor, which is elevated in over half of RA patients, may be a good marker of disease severity and potential joint damage. However, research in this area has generated conflicting results. Consequently, measuring rheumatoid factor isotypes has not become routine.

Some centres are using a new antibody test – anticyclic citrullinated peptide antibody (anti-CCP), which is more specific and equally sensitive as

rheumatoid factor. The place of these new antibodies in routine clinical practice is currently being established.

## Radiological assessments

### Patterns of change

X-rays can reveal many changes in RA, including:

- soft-tissue swelling;
- peri-articular osteoporosis;
- loss of joint space;
- juxta-articular bony erosions;
- subchondral cysts;
- subluxation;
- ankylosis.

Most changes are not specific and expert observers often disagree about their presence and extent. Erosions are diagnostic, however.

Figure 1.11 shows a typical X-ray presentation of RA. The relationship between the changes observed by X-ray and RA pathology is shown in Table 1.6.



**Figure 1.11.**

<b>X-ray observations and joint pathology</b>	
<b>Observation</b>	<b>Synovial pathology</b>
Soft tissue swelling and joint space widening	Synovial inflammation and effusions
Osteoporosis	Hyperaemia
Narrowing of joint space	Destruction of cartilage
Juxta-articular bony erosions	Pannus damaging bone at margin of joint
Large bony erosions and subchondral cysts	Extension of pannus
Deformity, subluxation and sclerosis	Laxity of capsule and ligaments
Bony ankylosis	Ankylosis

**Table 1.6.**

### **Disease progression**

The progression of changes observed on X-rays provides an objective measure that is useful for both following the course of RA and assessing the long-term effects of treatment. Once the cascade of damage starts, rapid progression is seen in the early years, with tapering later on. Rapid disease progression indicates the need for more aggressive treatment especially at an early stage where it may be possible to avoid or abort subsequent major joint damage. The progression and increase of radiographic scores correlates with disease duration. The curve of radiographic progression changes from linear in the early stages, S-shaped mid-course and flattened in a plateau at later stages.

### **Scoring X-rays**

There are many methods to quantify the amount and progression of X-ray-observed damage. The two widely used approaches are:

- the Sharp method, which scores most of the joints in the hand and wrist on a graded scale for erosions and narrowing;
- the Larsen method, which scores radiological appearances compared with a set of reference X-rays.

### **Limitations of plain X-rays**

X-rays have several limitations as outcome measures and their place as one of the gold standards of predicting RA outcome has been challenged.

- There are floor and ceiling effects of the scoring system used (ie, even though the highest score has been reached, further deterioration can occur).
- It can be difficult to determine whether erosions have increased in size or whether the position of the joint is slightly different from a previous radiograph.
- The score may not directly reflect the patient's functional disability.

New imaging methods, such a ultrasound and MRI are the focus on much research interest, though their place in clinical practice has not yet been determined.

## Outcome measures

### Core data set

In RA, no single measure is universally appropriate to judge the success or failure of treatment. The benefits of treatment are usually derived from a reduction in symptoms or slowing of the disease progression rather than achieving a cure. Until recently the outcome measures in both clinical trials and routine practice were chosen more by chance than design and there was no agreement on which, if any, measure was best. In the last few years, a limited 'core' set of preferred outcome measures has been defined by international consensus (*see* Table 1.7).

The core data set should be used in every clinical trial of RA and is suitable for use in routine practice.

### Core data set for rheumatoid arthritis

Number of swollen joints  
 Number of tender joints  
 Pain assessed by the patient  
 Patient's global assessment of disease activity  
 Assessor's global assessment of disease activity  
 Laboratory evaluation (ESR, CRP or equivalent)  
 Self-administered functional assessment (eg, HAQ)  
 X-ray assessment for joint damage

**Table 1.7.** CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire.

### Composite disease activity indices

Table 1.8 summarizes the current composite disease activity indices. The leading European index is the Disease Activity Score (DAS). This score has been modified for use with 28-joint counts for tenderness and swelling. It combines changes in joint counts, global responses and the ESR (or CRP) using fairly complex mathematical formulae. The scores fit a continuous scale that ranges from 1 to 9. The higher the score, the more active the arthritis. DAS can also be used to define the response to treatment. Increases or treatment-related decreases in score of 0.6 are meaningful and changes of 1.2 are highly significant.

The DAS:

- can be used to measure the absolute level of disease activity and response to treatment in both clinical trials and routine practice;
- is simple to use but is as valid as more comprehensive articular indices that are more time consuming to use.

### ACR response criteria

These criteria were developed in 1995 to simplify the assessment of response in clinical trials. They use components of the core data set and

Composite disease activity scores		
Year	Authors	Main features
1958	Lansbury	Morning stiffness, fatigue, aspirin consumption, grip strength, ESR, haemoglobin
1956	Lansbury and Haut	As above plus area weighted articular index
1977	Smyth	A pooled index
1981	Mallya and Mace	An index of disease activity
1990	Davis	Stoke index
1990	Van der Heijde	DAS
1990	Stewart	An index of disease activity
1993	Jones	Modified Stoke index
1995	Symmons	Overall Status in RA (OSRA) - activity and damage score
1995	Prevo	Modified DAS (for 28-joint counts)

**Table 1.8.**



involve improvements both in swollen and tender joint counts and in three of the following:

- patient global assessment;
- physician global assessment;
- pain
- ESR;
- a functional measure, such as HAQ.

Improvements can be at 20%, 50% or 70% levels (termed ACR-20 to ACR-70 responses). In simple terms, ACR-20 to ACR-70 responders show 20% or 70% improvements in most of the core data set measures. For a drug to be considered effective, it must be associated with a minimum of an ACR-20 response. This simplification of a complex situation results in a considerable loss of information; for example a 19% ACR response is negative whilst 20% ACR response is positive. In addition the ACR response criteria cannot be used to define the absolute level of disease activity, they are only able to identify responses to treatment.

The ACR response:

- has been developed purely for use in clinical trials;
- the index is not immediately relevant to clinical practice;
- ACR responder indices place patients into simple categories: 'responders' and 'non-responders'.

## Outcomes of rheumatoid arthritis

In addition to the clinical outcome measures described above, assessments of joint damage, disability, mortality and treatment costs can be used to assess treatment outcome in RA. Each of these measures has a different implication for patients, healthcare providers and clinicians treating the disease. The assessments are interrelated at a global level in that, on average, patients who show significant radiological damage also have the most disability, higher mortality and greater associated treatment costs. However, there are marked individual variations and many patients have considerable radiological damage, but little disability, or *vice versa*.

### Progression of joint damage

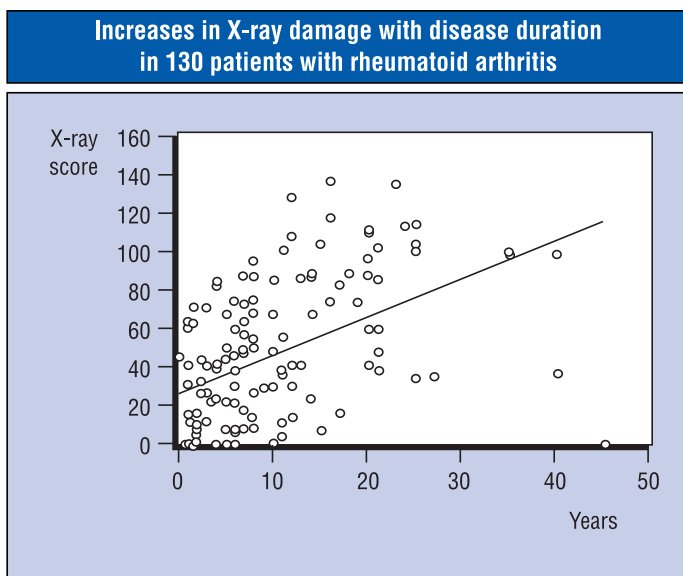
In early RA, the key change is the development of juxta-articular erosions. In the first few years of RA, 50–75% of RA patients will develop one or more erosions in their hands and wrists. Patients with no erosions after three years are unlikely to develop them later in the disease.

In late disease, end-stage joint damage is the primary concern. After 20 years of RA, about 20% of joints will be damaged, and many of these will need surgical replacement. In comparison, in early disease <5% of joints are totally damaged.

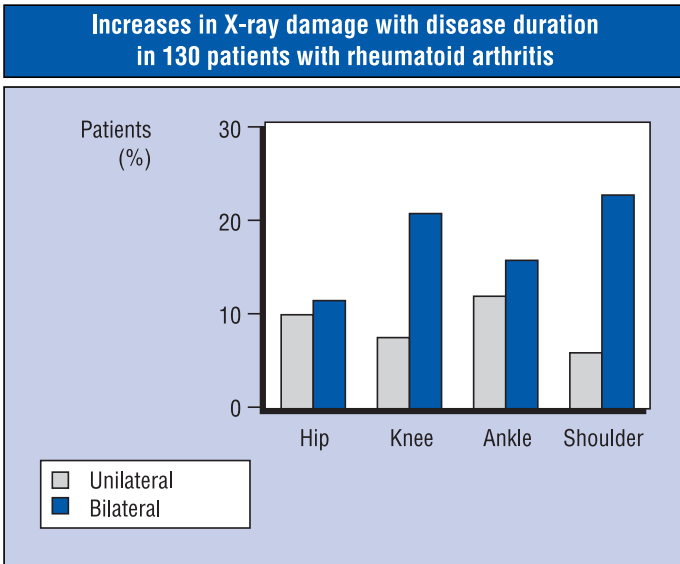
During the course of RA, there is a steady progression of joint damage. This is shown in Figure 1.12 for a single group of 130 patients treated at one UK centre. Longitudinal studies have shown that in early disease patients show, on average, less than 20% of the maximum possible damage. By 20 years this has increased to about 50% of maximum possible damage; an increase of 1–3% per year. Damage to large joints is a major cause of disability and by 12 years many large joints will start to show problems, as shown in Figure 1.13.

### Progression of disability

Average HAQ scores in groups of patients increase with disease duration. After five to seven years of RA the average HAQ score is about 0.8 (corresponding to 27% maximum possible disability). The average HAQ score increases in a linear manner by 1–3% per year so that after 18–20 years it is in the region of 1.11 (37% maximum possible disability). However, in the



**Figure 1.12.**



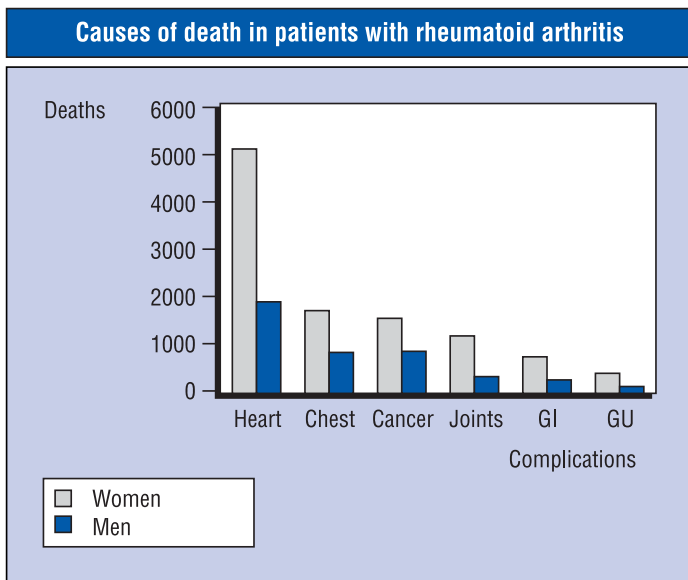
**Figure 1.13.** Prevalence of damage to large joints after 12 years of rheumatoid arthritis.

first five years of RA, the HAQ scores follow a 'J-shaped' curve. The scores fall in the initial stages because disability is due to active disease, and this responds to treatment. Thereafter, other causes of disability come into play, such as joint damage, and disability then increase in a stepwise manner.

## Mortality

The mortality rate from all causes is higher in RA patients than in people of similar age and sex without RA. Standardized mortality ratios (SMR), which allow comparisons across different populations, show RA patients have SMRs for all cause of death between 1.1 and 3.0 relative to the general population. In keeping with the general causes of death in Europe and North America, heart disease is the most common cause of death in RA patients (*see* Figure 1.14). Hospital-based RA patients have higher SMRs than community cases, suggesting RA disease severity is an important indicator of premature death.

Cardiovascular diseases, such as myocardial infarction and stroke, cause 40–50% of mortality in the general population and in patients with RA.

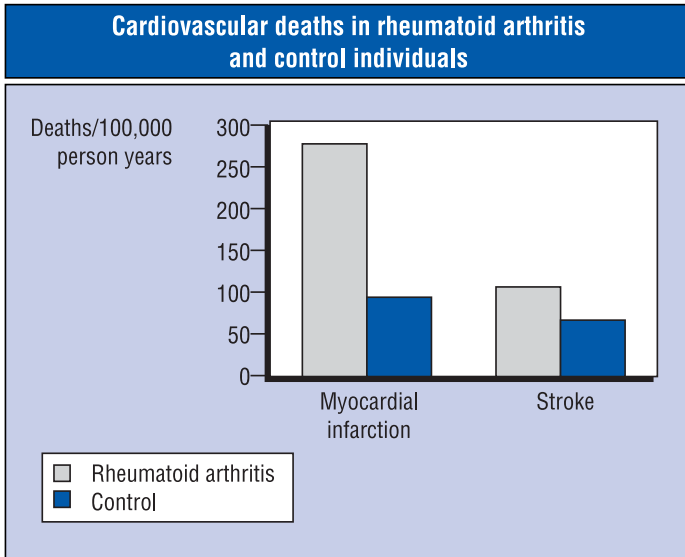


**Figure 1.14.** GI: gastrointestinal; GU, genitourinary.

Both of these events are more common in RA compared with control individuals (*see* Figure 1.15). Not only are cardiovascular diseases common causes of morbidity and mortality in RA as the overall death rate is raised in RA, but RA patients also have a specific increased risk of developing these disorders. Cardiac deaths are most likely in patients who are seropositive for rheumatoid factor, who have a specific predisposition of cardiovascular diseases. Other factors may also be involved, including steroid treatment, diabetes mellitus and hypertension.

Overall, cancer deaths are not increased in RA; with one exception. As previously explained, RA patients have a marked, and possibly time-limited, increased risk for malignant lymphomas. There is little to suggest this excess results from inherited or environmental risk factors. Instead, lymphomas complicating RA appear to be a direct consequence of the inflammation or its treatment. However, the number of RA patients who develop lymphomas is small.

In addition there are more deaths from infections in RA. However, as the likelihood of death from infection in the general population is low, a sub-



**Figure 1.15.** MI, myocardial infarction. Cardiovascular deaths in rheumatoid arthritis and control individuals.

stantial rise in risk, as occurs in RA, only results in a small additional number of deaths.

## Predicting outcomes

### Potential predictors

Rheumatoid factor is the dominant predictor of erosive damage. However, another auto-antibody exists which is also highly specific for RA. It is detected using anticyclic citrullinated peptide ELISA tests, and is related to antikeratin antibodies. Combined with rheumatoid factor this anticyclic citrullinated peptide antibody (anti-CCP) is highly predictive of erosive disease.

CRP has been known for many years to predict erosive damage. A time lag exists between synovial inflammation and joint damage. Time-integrated CRP values correlate closely with radiological progression in each patient with marked variations between individuals with similar radiographic scores.

The role of genetic markers is unclear, even in patients with early aggressive RA. Some experts believe that the presence or absence of the RA-associated shared epitope modulates progression but others disagree and the situation remains clouded in uncertainty.

Other factors predictive of outcome in RA are the initial level of disability, pain, depression, rheumatoid factor status and the extent of X-ray damage. RA-associated disability, indicated by HAQ scores, is greatest in the elderly and in women. Low socioeconomic status is also associated with higher HAQ scores. The overall predictors of severe disease and poor general health are shown in Table 1.9.

Factors predicting rheumatoid arthritis outcome	
Indicators of severe disease	Indicators of poor general health
Many joints involved	RF positivity
High ESR/CRP levels	Rheumatoid nodules
Slow onset	Late presentation
Older age	Female
	Many co-morbidities
	Poverty

**Table 1.9.** CRP: C-reactive protein; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor.

### Limitations of predicting outcomes

Although one aspiration of clinicians is to focus aggressive treatment on patients who will develop the most severe disease, prediction is too inaccurate to allow this aim to be achieved reliably. Even the most sensitive evaluation of risk factors provides a maximum of 75% prediction of the likely outcome in any given patient. This is no more reliable than clinical intuition. The era of focused treatment has not yet arrived, though it must remain a hope for the future.

## **Costs of rheumatoid arthritis**

The direct medical costs of treating RA are in the region of £3575 per person per year, ranging from £1189 to £7189. Some of the direct medical costs can be attributed to RA itself, and these have been calculated to be in the region of £4546 annually. Non-RA direct medical costs are estimated to be an average of £1198 annually; these costs are due to other disorders in patients with RA, such as associated cardiovascular and hypertensive disease. Indirect costs, including the cost of patients becoming unemployed or requiring care in the community, are in the region of £3060 per person per year and range from £676 to £11,514. Much of the medical cost of treating RA is focussed on the small number of cases who require hospital admission. Patients who are significantly disabled with high HAQ scores are also likely to incur high medical costs.

## Spondyloarthropathies

### Introduction

Spondyloarthropathies (SpA), also known as seronegative arthropathies, are a group of inflammatory arthritides characterized by spinal involvement and enthesitis. Table 2.1 shows the forms included in this group. In undifferentiated SpA, features characteristic of SpA are present but the full diagnostic criteria required to diagnose one of the specific disorders included in the group are not met. SpA are associated with class I histocompatibility molecules HLA-B27 and are rheumatoid-factor negative. The European Spondyloarthropathy Study Group has published criteria for use in the diagnosis of SpA (*see* Table 2.2).

Examples of spondyloarthropathies
Ankylosing spondylitis
Psoriatic arthritis
Reactive arthritis
Enteropathic arthritis
Undifferentiated spondyloarthropathies

**Table 2.1.**

The 1991 European Spondyloarthropathy Study Group criteria
Inflammatory spinal pain or synovitis (asymmetric or predominantly lower limb) <b>and</b> one of the following:
Alternating buttock pain
Enthesopathy
Sacroiliitis
Family history
Psoriasis
Inflammatory bowel disease

**Table 2.2.**



## Epidemiology

SpA are most frequently seen in young adults but can present at any age and have a male predominance (*see* Table 2.3). As a group, they represent the second most common inflammatory rheumatic disease after rheumatoid arthritis (RA). Their overall prevalence is 0.5–1%; there are racial and geographical variations largely correlating with the local prevalence of HLA-B27. For example, ankylosing spondylitis is common in Caucasians and American Indians (where prevalence of HLA-B27 is high) but rare in Africans and Japanese (where HLA-B27 is low). Approximately 1–2% of individuals who are positive for HLA-B27 develop ankylosing spondylitis and this increases to 15–20% if they have a first-degree relative with the disease.

## Pathogenic mechanisms

### Genetics

Genetic and environmental factors play a role in the pathogenesis of SpA. There is a strong association with HLA-B27 though some subtypes of

Male : female ratio of spondyloarthropathies			
Ankylosing spondylitis			4 : 1
Psoriatic arthritis			M=F
Reactive arthritis			3 : 1
Enteropathic arthritis	Peripheral		M<F
	Spinal		M>F

**Table 2.3.** F, female; m, male.

Prevalence of HLA-B27 positivity			
Ankylosing spondylitis			90%
Psoriatic arthritis	Peripheral		20%
	Spinal		50%
Reactive arthritis			60–75%
Enteropathic arthritis	Peripheral		no increase
	Spinal		50%
Undifferentiated SpA			50–70%

**Table 2.4.** SpA, spondyloarthropathies.

HLA-B27 may be protective. The occurrence of HLA-B27 varies among the different types of SpA. It is found most frequently in SpA patients who have spinal involvement, such as those with ankylosing spondylitis (AS) and some of those with psoriatic arthritis and other SpAs (*see* Table 2.4). The association between HLA-B27 and ankylosing spondylitis is less marked in non-Caucasians (50%) compared with Caucasians (95%).

Although the genetic association between HLA-B27 and SpA is one of the earliest described and strongest, the role of HLA-B27 in disease pathogenesis remains unknown. Current hypotheses include:

1. 'genetic linkage theory' – this proposes that HLA-B27 is in genetic linkage with the true disease associated gene, for example, tumour necrosis factor (TNF) genes.
2. 'thymic selection theory' – this proposes that the T-cell repertoire selected in the thymus of HLA-B27 positive patients B27 predisposes them to SpA
3. 'arthritogenic peptide theory' – this proposes that HLA-B27 specific bacteria-derived peptides are presented to pathogenic CD8+ T cells which induce arthritis
4. 'molecular mimicry theory' – this proposes that the initial immune response is stimulated by a bacterial moiety cross-reactive with HLA-B27. The cross-reactive HLA-B27 sequence then perpetuates an autoimmune response. Though first suggested at the antibody level (antibodies which cross-react with HLA-B27 and bacteria), cross-reactivity at the T-cell level is now considered more relevant.
5. 'HLA-B27 homodimer theory' – this builds on the unusual structure and cell biology of HLA-B27. Due to its unpaired cysteine at position 67, HLA-B27 can form heavy chain homodimers; unlike all other mature MHC Class I molecules, these lack  $\beta_2$ -microglobulin. Furthermore, significant numbers of SpA T cells express a ligand for these homodimers. Though the details remain unclear, it is proposed that such HLA B27 heavy chain dimerization may be involved in SpA pathogenesis.
6. 'HLA-B27 as self-antigen theory' – this hypothesis proposes that HLA-B27 derived peptides are presented by MHC Class II molecules to CD4+ T cells as has been shown in some animal models.
7. 'Altered self theory' – this variant of the above proposes that the unpaired cysteine at position 67 of HLA-B27 is chemically modified *in vivo*; this altered form of HLA-B27 would be more likely to act as a self antigen and stimulate an immune response.
8. 'Altered bacterial response theories' – there are two versions of this.

The first proposes a defective response whereby HLA-B27 positive CD8+ T cells respond suboptimally to bacteria and fail to eliminate them; such persistent bacteria then induce arthritis. The second suggests that there is a super-normal response to bacteria by HLA-B27 positive cells either because HLA-B27 acts as a receptor for a bacterial ligand or because it interacts with a bacterial superantigen.

Other genes must be involved in SpA because disease concordance in twin studies is between 24% and 60%. HLA-B60 is associated with a threefold risk of disease and HLA-DR1 has also been associated with SpA, as have abnormalities in the TNF gene.

## Infection

Infection is a major aetiological factor for SpA. Whipple's disease has long been known to be triggered by infection; recently the causative bacteria has been shown to be *Tropheryma whippelii* using polymerase chain reaction (PCR)-based methods. Evidence for infection can be found in up to 60% patients with reactive arthritis and undifferentiated SpA. Though triggering bacteria cannot be cultured from the joint, bacterial antigens may be detected by immunofluorescence and bacterial DNA by PCR. Further evidence for the role of infection includes the finding of activated T cells responding to triggering organisms in affected joints. Bacterial DNA (consistent with the presence of live bacteria) is more commonly found in patients with *Chlamydia*-induced reactive arthritis than in those with enteric disease, suggesting differences in bacterial biology between the two diseases. The involvement of bacteria in SpA is also supported by research using animal models. For example, SpA can be triggered by infection in HLA-B27 transgenic rodents.

Further evidence concerning the role of infection in pathogenesis comes from therapeutic studies with antibiotics. In animals, *Yersinia*-triggered reactive arthritis in rats can be cured with early antibiotic treatment. In humans, a short course of appropriate antibiotics to clear *Chlamydia* from the genital tract definitely reduces subsequent episodes of reactive arthritis. In contrast, studies of prolonged antibiotic therapy (aimed at clearing bacteria from the joint or other reservoirs) have produced conflicting results. An early analysis in *Chlamydia*-triggered reactive arthritis showed three months of lymecycline decreased arthritis duration though it did not alter long-term outcome. A large randomized controlled trial of three months ciprofloxacin showed no overall benefit at one year in reactive arthritis or undifferentiated SpA; there was a trend towards benefit in the small subset with *Chlamydia*-induced disease consistent with the PCR findings that bacterial DNA is more commonly found in sexually-acquired than in enteric disease. Another smaller trial also found three months of ciprofloxacin offered no overall benefit at one year; interestingly however,

a follow-up study undertaken four to seven years after recruitment suggested antibiotic-treated patients showed a reduced rate of chronic reactive arthritis and ankylosing spondylitis (although numbers were small). Finally, a pan-European study of prolonged azithromycin in early inflammatory oligoarthritis failed to demonstrate any benefit for antibiotic treatment at one year.

### **Gastrointestinal tract inflammation**

Ileocolonoscopy studies have shown subclinical gut inflammation in two-thirds of patients with SpA even in the absence of gut symptoms; bowel inflammation is more common in those with active arthritis. Other work has demonstrated increased gut permeability in SpA patients. These findings, along with the work in transgenic rodents alluded to above, suggest a role for bowel inflammation in the pathogenesis of SpA.

One hypothesis is that the inflamed bowel, being more permeable, allows the passage of bacteria or bacterial components across the gut wall where they can be presented to intestinal lymphocytes. This notion is supported by reports of identical T-cell clones in colon mucosa and synovium and by humans and animal studies demonstrating the presence of gut flora derived components such as peptidoglycan in the synovium of patients with chronic arthritis.

### **Clinical features**

The clinical features and differential diagnosis of SpA are shown in Tables 2.5 and 2.6.

### **Laboratory investigations**

- **Full blood count (FBC)** should be undertaken to exclude anaemia
- **Acute phase markers** (erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP]) may be raised
- **Rheumatoid factor** should be evaluated if peripheral arthritis is present
- **Urethral** and **cervical** swabs should be evaluated in suspected reactive arthritis (irrespective of the presence of genitourinary symptoms) since asymptomatic carriage of *Chlamydia* is common and antibiotic therapy is required if it is found
- **Stool cultures** should be evaluated only in patients with gastrointestinal symptoms
- **Joint aspiration** to exclude septic or crystal arthritis is mandatory where these are appropriate differential diagnoses (notably patients with monoarthritis or fever)

Clinical features of spondyloarthropathies		
Location	Feature	Comment
Musculoskeletal	Spondylitis	Present with bilateral or unilateral buttock and sacroiliitis pain, which is worse with inactivity. Associated with early morning stiffness. Symptoms may be confused with sciatica
	Peripheral arthritis	Usually asymmetrical and affecting the lower limbs
	Enthesitis	Entheses are the sites of insertion of ligaments and tendons into bone. Common sites involved include the plantar fascia, Achilles tendon, iliac crest, greater trochanter, ischial tuberosity, costochondral junctions and lateral epicondyles
	Dactylitis	Inflammation of the whole finger or toe involving the joints and tendons ('sausage digit'). Dactylitis is a characteristic feature of both psoriatic and reactive arthritis
Skin	Psoriasis and keratoderma blenorrhagica	Seen in reactive arthritis
Eye	Conjunctivitis	
	Iritis (anterior uveitis)	Occurs in 4–5% patients with SpA. Patients need to be warned about possible eye involvement and urgent ophthalmologic review is required
Gastrointestinal	Inflammatory bowel disease	Common
Genitourinary	Urethritis and cervicitis	Seen in reactive arthritis
Cardiovascular	Carditis and aortitis	Both are rare features

**Table 2.5.** SpA, spondyloarthropathies.

### Differential diagnosis of spondyloarthropathies

Spondylitis/sacroiliitis	Mechanical back pain and sciatica Diffuse idiopathic skeletal hyperostosis (DISH) Septic sacroiliitis (staphylococcal or tuberculosis)
Monoarthritis	Septic arthritis Crystal arthritis Trauma
Polyarthritis	Rheumatoid arthritis Sarcoidosis

**Table 2.6.**

Routine HLA-B27 testing is not helpful, even for ankylosing spondylitis where the association is strongest. Although the test is very sensitive (>95% of ankylosing spondylitis patients are HLA-B27 positive) it is not specific (>10% of the normal population are HLA-B27 positive). Since ankylosing spondylitis is rare (<1% of population) and the main differential diagnosis, mechanical low back pain, is common (30% of population), the positive predictive value of such a sensitive but non-specific test is low. It should therefore be reserved for specialist use in difficult cases.

Antibacterial serology is not as useful as might be anticipated for two reasons. The first is that adequate serological tests do not exist for some relevant bacteria such as *Shigella* and *Salmonella*. The second is the relative lack of specificity of serology. Though there are good serological tests for *Chlamydia*, *Yersinia*, and *Borrelia*, positive serology is frequently found in the relevant background population such as sexually active young adults (for *Chlamydia*) or people from the same geographical location (*Yersinia*, and *Borrelia*).

## Imaging

### Radiography

Radiographs of sacroiliac joints may show sacroiliitis but changes may not be present in the very early stages of disease. The earliest changes include loss of the subchondral sclerotic line and focal osteoporosis. Later erosions develop on the iliac side with apparent widening of the joint; finally this is followed by sclerosis and ankylosis. Sacroiliitis can be graded using the New York index.

## Investigations

Laboratory	FBC, ESR and CRP HLA-B27 not useful Urethral or cervical swabs Stool cultures Joint aspirate
Radiology	Radiography Radionuclide scan CT scan MRI scan

**Table 2.7.** CRP, C-reactive protein; CT, computed tomography; ESR, erythrocyte sedimentation rate; FBC, full blood count; HLA, human leucocyte antigen; MRI, magnetic resonance imaging..

The New York index for sacroiliitis:

0 = normal;

I = suspicious;

II = minimal disease;

III = moderate disease;

IV = ankylosis.

In the spine, early changes include squaring of the vertebrae, usually in the lower thoracic and upper lumbar spine, followed by ossification of the annulus fibrosus leading to formation of bony bridges between the vertebrae (known as syndesmophytes). After several years of severe disease, complete fusion of the spine (often called 'bamboo spine') may develop.

Proliferative new bone formation may be seen at the entheses in all SpA.

Radiographic changes seen in peripheral psoriatic arthritis include osteolysis, periostitis, ankylosis of the joint and pencil-in-cup erosions, with lack of peri-articular osteoporosis compared with RA. Radiographs are usually unhelpful in acute reactive arthritis but erosions may be seen in chronic cases.

### Radionuclide scanning

Quantified bone scintigraphy can be used to detect early sacroiliitis when plain radiographs are unhelpful or equivocal. However, increased uptake

can be seen in normal patients and other imaging techniques are now often used in preference.

### **Computed tomography and magnetic resonance imaging**

Computed tomography (CT) and magnetic resonance imaging (MRI) scanning are highly sensitive in detecting different aspects of sacroiliitis and are gradually superseding radionuclide scanning. CT scans detect bony changes including loss of subchondral bone, erosions and irregular joint margin and show abnormalities earlier than plain X-rays. MRI demonstrates the earliest sacroiliac changes of all, such as oedema in the subchondral bone marrow. MRI can also be used to detect early spinal inflammation.

### **Ankylosing spondylitis**

Ankylosing spondylitis mainly affects the axial skeleton (sacroiliitis and spondylitis) although peripheral arthritis occurs in about 20% of patients, affecting primarily the lower limbs. It is most common in young males aged 20–40 years but the sex ratio changes with age from a male : female ratio of 6:1 at the age of 16 years to 2:1 at the age of 30 years. Ankylosing spondylitis occurs more frequently in Caucasians than in other ethnic groups and has a prevalence of 150 per 100,000 population in the UK.

#### **Clinical features**

The typical presentation is of insidious low back pain radiating into the buttocks with early morning stiffness; the buttock pain is often alternating unlike that due, for example, to disc disease. The symptoms are normally worse with inactivity and improve with exercise. Diagnosis is often delayed because back pain is so common in the population. Enthesitis, such as Achilles tendonitis, is frequently present. Table 2.8 shows the Modified New York criteria used in diagnosis. Apart from imaging, laboratory tests are usually unhelpful but ESR and CRP are raised in 30–35% of patients.

Possible extra-articular features are described in Table 2.9. The most important of these is iritis, which occurs in 25–30% patients, is usually unilateral and tends to recur. Patients should be specifically warned about this complication as, untreated, it can result in visual loss. Common respiratory features include chest pains due to intercostal tendonitis and reduced chest expansion. By contrast cardiovascular involvement, such as aortic valve disease, and pulmonary fibrosis are rare. Lung fibrosis can be complicated by cavitation and subsequent *Aspergillus* infection, although these problems are extremely rare and other causes of cavitating lung disease, notably tuberculosis, should be excluded.



## Modified New York criteria for diagnosing ankylosing spondylitis

### Clinical criteria

- Low back pain and stiffness for >6 months that improves with exercise and is not relieved by rest
- Limitation of motion of the lumbar spine in both sagittal and frontal planes
- Limitation of chest expansion relative to normal values for age and sex

### Radiological criteria

- Sacroiliitis of grade II or higher
- Grade III or IV sacroiliitis unilaterally

### Combined diagnostic criteria

- Definite ankylosing spondylitis is present if the radiological criterion is associated with at least one clinical criterion
- Probable ankylosing spondylitis is diagnosed if:
  - There are three clinical criteria
  - The radiological criterion is present without any signs or symptoms satisfying the clinical criteria

**Table 2.8.**

## Extra-articular features and complications of ankylosing spondylitis

### Extra-articular features

Iritis

Cardiovascular

- Aortic regurgitation
- Aortitis
- Conduction defects

Respiratory

- Apical pulmonary fibrosis
- Reduced chest wall expansion

### Complications

Spinal fractures

Cauda equina syndrome

Amyloidosis

**Table 2.9.**

Patients with an ankylosed spine are at increased risk of fracture even with minor trauma; fractures in the cervical spine are the most common. Amyloidosis is now a very rare complication and occurs primarily in patients with severe, active, long-standing disease with a persistently raised acute phase response. Urinalysis should be carried out in these patients to identify proteinuria.

### **Clinical assessment**

Initially, spinal movement is restricted; as the disease progresses, there is loss of the normal lumbar lordosis with increased thoracic and cervical kyphosis. Full spinal ankylosis can develop in a minority of patients after at least ten years.

Restriction of spinal movements is most commonly evaluated by the modified Schober's test of anterior lumbar flexion. Spinal flexion is measured as the increase in distance between a point 5cm below and another 10 cm above the dimples of Venus; in a person of normal height, the value should be greater than 5cm. Serial measurements can be used to assess progression. Other tests of spinal movement include 'occiput to wall' and 'finger to floor' distances..

General examination should be also undertaken to identify extra-articular features; in particular, examination of the eyes, heart and chest. Chest expansion should be serially to assess progression; normal chest expansion is greater than 3 cm.

### **Disease outcome measures**

Disease outcome measures are currently primarily used in clinical research to assess disease activity and response to treatment. They include:

- Bath Ankylosing Spondylitis Disease Activity Index (BASDAI);
- Bath Ankylosing Spondylitis Functional Index (BASFI).
- Ankylosing Spondylitis Assessment Score (ASAS)

The use of these measures in routine practice will become more common now that TNF inhibitors have been licensed for SpA since they are a required part of assessing patient eligibility for treatment in many countries.

### **Natural history**

The natural history of ankylosing spondylitis is very variable but factors predicting worse outcome include male sex, young age at onset (<16 years), early loss of lumbar spinal mobility, raised acute phase response, poor response to non-steroidal anti-inflammatory drugs (NSAIDs), hip involve-

ment (which is associated with younger age of onset) and low socioeconomic class. There is no increase in mortality associated with this form of SpA but there may be significant morbidity and disability.

## Psoriatic arthritis

Psoriatic arthritis is an inflammatory arthritis associated with psoriasis; it is usually rheumatoid-factor negative. 5–30% of patients with psoriasis will develop arthritis and the psoriatic form has a prevalence of 100 per 100,000 population. The severity of disease in the skin and in joints is not correlated suggesting that the presence of psoriasis alone (or even a predisposition to the condition) is the relevant risk factor. The severity of psoriasis and arthritis is enhanced in individuals infected with human immunodeficiency virus (HIV).

Skin lesions in certain sites including the scalp, natal cleft, genitalia and feet are often overlooked and should be sought carefully. Though skin changes usually precede the development of arthritis, they may follow it in about 15% of cases. Nail changes are present in 80% of patients with arthritis (compared to only 20–30% of patients with skin psoriasis alone) hence providing a useful clue. In patients where arthritis precedes psoriasis (psoriatic arthritis sine psoriasis), other hints to aid diagnosis include a positive family history and a typical asymmetric or lower limb predominant pattern of arthritis. Systemic features are rare in psoriatic arthritis and their presence should lead to a re-evaluation of the diagnosis; however, iritis is found in 7% and conjunctivitis in 20% of patients.

Differential diagnoses include rheumatoid arthritis and other SpAs but, since it is an entirely treatable condition, the diagnosis of chronic gout must be definitively excluded in patients with asymmetric arthritis.

Five subsets of psoriatic arthritis have been described (*see* Table 2.10). Except for arthritis mutilans, these subsets are not fixed so patients move between them over time; in particular mono- or oligoarthritis often evolves to polyarthritis. Spinal disease can occur in with any peripheral subtype of psoriatic arthritis except arthritis mutilans.

Psoriatic arthritis usually follows a milder course than RA and is often non-erosive. However, about one-third of patients will have significant disability and there is an increase in mortality due to co-morbid disease.

## Reactive arthritis

Classical reactive arthritis (previously known as Reiter's syndrome) is an arthritis occurring one to four weeks after urethritis, cervicitis or gastro-

### Moll and Wright classification of psoriatic arthritis

Mono/oligoarthritis	Usually associated with dactylitis in the large joints of the lower limbs
Rheumatoid-like polyarthritis	Symmetrical polyarthritis that is indistinguishable from RA involving the small joints of the hands and feet without nodules. Rheumatoid-factor negative. Can be confused with seronegative RA
Distal interphalangeal joints	Usually associated with nail changes and dactylitis
Spondylitis	Similar to ankylosing spondylitis but usually unilateral or asymmetrical sacroiliitis and syndesmophytes are horizontal and thicker. Often associated with enthesitis
Arthritis mutilans	Rare, deforming arthritis with shortening of digits due to dissolution of bone resulting in telescoping of the fingers

**Table 2.10.** RA, rheumatoid arthritis.

enteritis. It is most common in young adults aged 20–40 years with a prevalence of 30 per 100,000 population. *Chlamydia trachomatis* is found in up to 50% of cases with clinical urethritis but many patients have asymptomatic infection.

Reactive arthritis usually presents with mono- or oligoarthritis affecting the knees or ankles; upper limb involvement is uncommon. Enthesitis is typical and dactylitis and acute sacroiliitis may occur. Spondylitis may develop in up to 20% patients with severe relapsing disease. Skin and mucous membrane involvement (oral ulcers and circinate balanitis) occur in 20% and conjunctivitis in about one-third of patients. Iritis is less common and usually occurs in recurrent or chronic disease. Keratoderma blennorrhagica can affect the palms and soles and may be confused clinically and histologically with pustular-palmar psoriasis. Carditis is a rare feature. The majority of first attacks resolve completely within 20 weeks, but attacks can recur. Rarely, there may be progression to chronic reactive arthritis or ankylosing spondylitis.

Similar to other arthritides, the treatment of reactive arthritis is largely symptomatic and is discussed in the ensuing chapters. However, the use of antibiotics is largely specific to this condition and undifferentiated SpA and is therefore discussed here. As a result of the high incidence of asymptomatic carriage of *Chlamydia*, all reactive arthritis patients who

do not have a clear enteric cause for their disease should be screened for chlamydial infection. If this is present, a short course of an appropriate antibiotic to eradicate *Chlamydia* from the genital tract has been shown to reduce the subsequent frequency and duration of arthritis. Patients with enteric disease should not receive antibiotics as this enhances enteric carriage of the organisms. As discussed earlier, there is currently no clear evidence that prolonged antibiotic treatment alters the duration or outcome of the arthritis itself, whatever its bacterial aetiology, though more trials are needed.

Other forms of reactive arthritis, like streptococcal reactive arthritis and Lyme disease are not considered part of the SpA group and, hence, have not been discussed in this chapter.

### Infections causing reactive arthritis

*Chlamydia pneumoniae and trachomatis*  
*Salmonella*  
*Shigella*  
*Yersinia*  
*Campylobacter*

**Table 2.11.**

### Clinical features of reactive arthritis

Musculoskeletal	Lower limb mono/oligoarthritis Enthesitis Lower back pain/sacroiliitis
Genital	Circinate balanitis Urethritis
Skin	Keratoderma blenorrhagica
Eye	Conjunctivitis Iritis
Cardiac	Carditis

**Table 2.12.**

## Enteropathic arthritis

Arthritis occurs in 2–20% of patients with ulcerative colitis and 10–20% of those with Crohn's disease. Three patterns of arthritis have been described:

- spinal arthritis similar to ankylosing spondylitis in 5–10% of patients with Crohn's disease;
- lower limb oligoarticular peripheral arthritis with associated enthesitis and tendonitis;
- polyarticular peripheral arthritis affecting the upper and lower limbs.

Spinal disease activity is unrelated to bowel disease but there is a relationship between peripheral arthritis and bowel activity.

Polyarthritis and SpA also occur in Whipple's disease. Polyarthritis is seen in coeliac disease and has been reported in 5–50% of patients following intestinal bypass surgery. As described previously, subclinical bowel inflammation has been found on ileocolonoscopy of patients with SpA; about 6% of these progress to overt Crohn's disease.

Enteropathic arthropathies
Inflammatory bowel disease
Crohn's disease
Ulcerative colitis
Reactive gastroenteritis
Whipple's disease
Coeliac disease
Intestinal bypass surgery
Subclinical bowel disease

**Table 2.13.**

## Undifferentiated spondyloarthropathies

The term 'undifferentiated SpA' was introduced and defined by the European Spondyloarthropathy Study Group in 1991. It refers to patients with typical features of SpA such as sacroiliitis, enthesitis, dactylitis and iritis but who do not fulfil the diagnostic criteria for any of the specific dis-

eases within the group. Diagnosis requires the presence of inflammatory back pain and/or peripheral arthritis with one other characteristic feature such as enthesitis, a positive family history for SpA, psoriasis or inflammatory bowel disease. Dactylitis, iritis and HLA-B27 do not form part of the European Spondyloarthropathy Study Group criteria but their presence may help to indicate the diagnosis in individual patients. Prevalence data for undifferentiated SpA are scarce, but it appears to be at least as common as ankylosing spondylitis. Undifferentiated SpA may represent an early phase or incomplete form of another SpA. As would be expected for a relatively undefined entity, prognosis is variable; 30–50% of cases develop into ankylosing spondylitis after several years.

## *Symptomatic drug treatment*

### **Pain and other symptoms**

Chronic pain is a major medical problem, reported by nearly half the adult population. It is particularly prevalent in the elderly and has been linked to poverty, being retired and being unable to work.

Arthritis is the most common cause of pain in the community.

Pain is the dominant symptom in arthritis. It is present from the earliest stages of synovitis and persists throughout the course of the disease. In early inflammatory arthritis, pain is predominantly related to synovitis. In late disease, pain is influenced by the development of joint damage and failure.

There are several ways to control pain:

- giving symptomatic drug treatment with analgesics or anti-inflammatory drugs (most important approach);
- controlling the underlying inflammatory disease process;
- replacing damaged joints (only relevant in late disease);
- instigating non-specific measures such as exercise therapy or treating co-existent depression (the effects of antidepressants may extend beyond merely treating depression to having a direct effect on pain itself).

Other important symptoms in arthritis stem from joint inflammation. Pain is accompanied by joint tenderness, swelling and stiffness, together with morning stiffness. Symptomatic treatment with anti-inflammatory drugs improves stiffness and tenderness and to some extent will reduce joint swelling. The effect of symptomatic treatment on joint tenderness and swelling is less than that of disease-modifying treatments.

### **Historical perspective**

The development of aspirin, the classic anti-inflammatory and analgesic drug, can be traced back to Hippocrates' time, when willow extracts were used to treat fevers. During the 1700s the Reverend Edward Stone publicized the beneficial effects of willow bark. By the 1800s its active component had been identified as salicin. Subsequently, salicylic acid was synthesized. Although it showed antirheumatic properties, it caused excessive



dyspepsia and tasted bitter. These problems prompted a search for palatable alternatives. As a result, Felix Hoffman developed acetylsalicylic acid for the Bayer Company. The name 'aspirin' was introduced in the 1890s: 'a' referred to the acetyl group and 'spirin' recalled the botanical genus *Spiraea* from which salicylates could be extracted. In the early years of the twentieth century, aspirin was the best selling drug worldwide. Later, phenylbutazone, indomethacin and other anti-inflammatory drugs were developed; the role of aspirin for treating arthritis has now ceased.

Historical development of anti-inflammatory drugs	
Period	Advance
Ancient Greeks	Used salicylate extracts from myrtle leaves and willow leaves
Middle Ages	Medicinal herb gardens featured salicylate in wintergreen and meadowsweet
1760s	Rev Stone reported on use of willow bark powder as an anti-pyretic
1850s	Von Gerhardt synthesized acetylsalicylic acid
1860s	Hoffman synthesized acetylsalicylic acid
1949	Phenylbutazone introduced
1963	Indomethacin introduced
1971	Vane demonstrated that NSAIDs inhibit prostaglandin production
1974	Ibuprofen introduced
1976	Miyamoto purified the COX enzyme
1982	Piroxicam introduced
1989	Simmons identified the COX-2 enzyme
1999	Celecoxib introduced

**Table 3.1.** COX, cyclooxygenase; NSAID, non-steroidal anti-inflammatory drug.

A somewhat separate path in history was the development of paracetamol, which is the classic simple analgesic. Its development can also be traced back to the search in the late nineteenth century for drugs to reduce fever. Common antipyretics at that time came from natural compounds like cinchona bark. Cheaper synthetic substitutes were sought when cinchona bark became in short supply. This led to the development of acetanilide and phenacetin in the 1880s. Both compounds combined antipyretic with analgesic properties. In the 1890s, another compound was identified with rapid

analgesic and antipyretic effects. It is now known as paracetamol (acetaminophen in the USA). The research field fell static until the 1940s when paracetamol was shown to be a key metabolite of phenacetin and acetanilide, and was also less toxic than either of them. Subsequently, paracetamol was introduced as a prescription drug in the 1950s, later becoming an over-the-counter analgesic. It has also become an ingredient of compound analgesics with centrally acting compounds such as codeine, dihydrocodeine and dextropropoxyphene.

## Simple analgesics

Simple analgesics should be used in all patients with inflammatory arthritis, as an adjunct to non-steroidal anti-inflammatory drug (NSAID) and disease-modifying antirheumatic drug (DMARD) therapy. Table 3.2 shows the range of commonly used analgesics. Although there is some evidence from clinical trials that analgesics reduce pain in rheumatoid arthritis (RA), the data are limited. Most trials of these drugs were carried out >20 years ago and by current standards were too small and of insufficient duration. However, almost all rheumatologists still recommend this form of treatment, although only a small proportion of patients with RA and other inflammatory arthropathies will achieve successful disease control through analgesics alone.

Commonly used analgesics	
Simple	Compound
Paracetamol	Co-proxamol (paracetamol/dextropropoxyphene)
Codeine	Co-codamol (paracetamol/codeine)
Dihydrocodeine	Co-dydramol (paracetamol/dihydrocodeine)
Tramadol	

**Table 3.2.**

### Paracetamol

Paracetamol is the most commonly used analgesic. A single 1000-mg dose of paracetamol provides >50% pain relief over four to six hours in moderate or severe pain compared with placebo. Its analgesic effects are comparable to those of conventional NSAIDs. There are virtually no contraindications,

significant drug–drug interactions or side effects at the recommended dosage. Furthermore, it is well tolerated by patients with peptic ulcers.

Interestingly, despite being used for many years, the mechanism of action of paracetamol is not well understood. It may be centrally active, producing analgesia by elevating the pain threshold through prostaglandin synthetase inhibition in the hypothalamus. At therapeutic dosages it does not inhibit prostaglandin synthetase in peripheral tissues, so has no anti-inflammatory activity.

The drawback of paracetamol is that it is relatively ineffective; patients need to take six to eight tablets daily in three to four divided doses to achieve any analgesic benefit so most prefer to take NSAIDs. Figure 3.1 shows the outcome of a survey of patients' perspectives of paracetamol efficacy; only a minority found it effective and the majority found NSAIDs more effective.

Paracetamol is a relatively weak analgesic which has to be taken several times daily. Patients prefer to take NSAIDs as they find them more convenient and effective.

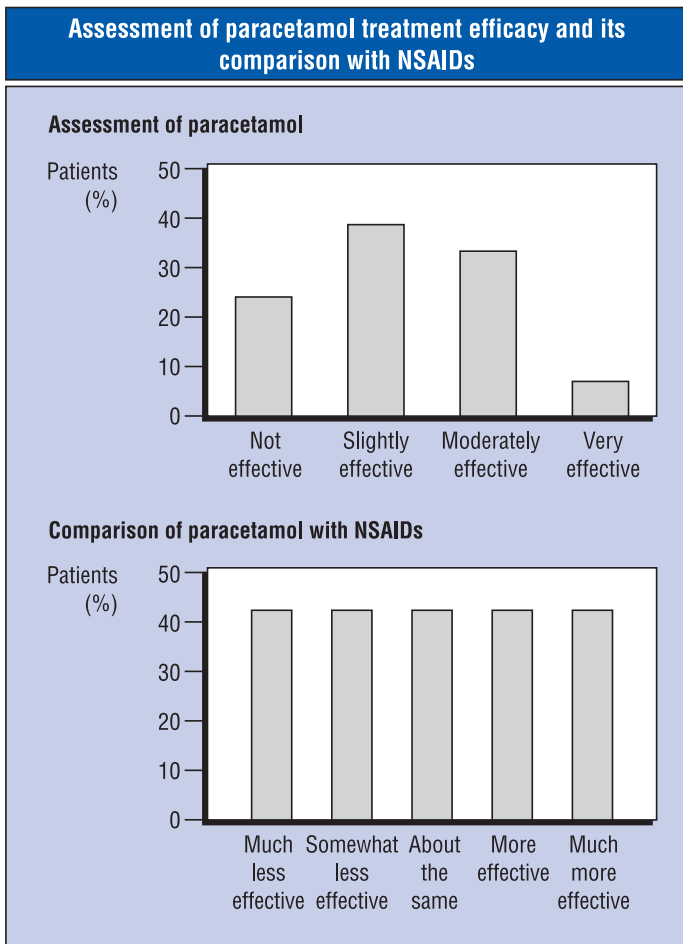
## **Tramadol**

Tramadol is effective in relieving moderate to moderately severe pain, and may be useful in a small proportion of patients with inflammatory arthritis. It is a synthetic, centrally acting analgesic, with some opioid properties. Tramadol causes less constipation than opiates and dependence is not a clinically relevant problem.

To be fully effective, tramadol needs to be given at a dose of 50–100 mg every four to six hours. A slow-release formulation can be useful if pain during the night is a particular problem. Common adverse effects of tramadol include headache, dizziness and somnolence, which often preclude its use in patients who need to be mentally alert during the day.

## **Codeine and dihydrocodeine**

These weak opioids have centrally mediated effects. Their effect is evident 20–30 minutes after administration and lasts for about four hours. Dihydrocodeine has about twice the potency of codeine. Both agents show a ceiling effect for analgesia and higher doses give progressively more adverse effects, particularly nausea and vomiting. These side effects outweigh any additional analgesic effect. They also cause constipation and central side effects such as drowsiness.



**Figure 3.1.** Assessment of paracetamol treatment efficacy and its comparison with non-steroidal anti-inflammatory drugs (NSAIDs). From a survey of 1799 patients with rheumatoid arthritis.

Strong opiates, such as morphine, are almost never used in inflammatory arthritis. This is probably because their addictive nature is perceived to overshadow their therapeutic benefit. However, this view is based on custom and practice rather than rigorous scientific testing.

This question has recently been reopened by an observational trial using transdermal fentanyl (a newer strong opiate in patch form) in RA patients whose pain was not adequately controlled by nonopioid analgesics and/or weak opioids. Though concomitant antiemetics were sometimes needed especially initially, the number of patients with adequate pain control increased from only one third to almost 90% by day 28 and there were similar improvements in other pain measures, function (assessed by the Health Assessment Questionnaire [HAQ]) and quality of life (assessed by the 36-item short form [SF-36]). Almost 80% of patients said they would recommend it suggesting that transdermal fentanyl should be further considered in treatment programs for patients with RA.

## Compound analgesics

Paracetamol can be taken concomitantly with a weak opiate, either as two single agents or in combined form. Co-proxamol, which is the combination of paracetamol with dextropropoxyphene (an agent that is rarely used alone), is historically popular with clinicians though there is no obvious reason for this preference. However, it is now undergoing a phased withdrawal in the UK at the behest of the Medicines and Healthcare products Regulatory Agency who believe that its benefits are outweighed by the risk of intentional or accidental fatal overdoses. Alternatives are combinations of paracetamol with codeine (co-codamol) or dihydrocodeine (co-dydramol). The efficacy and tolerability of the compound drugs is the same as the individual drugs taken together.

## Non-steroidal anti-inflammatory drug

NSAIDs are a diverse group of drugs. Their name distinguishes them from anti-inflammatory steroids (glucocorticoids) and non-narcotic analgesics. NSAIDs are one of the most frequently used group of drugs overall, although their benefits must be set against significant, sometimes fatal, gastrointestinal and renal toxicity and also the recently described cardiovascular risks with cyclooxygenase (COX)-2 inhibitors.

### Mechanism of action and COX-1/COX-2 effects

Inflammation involves many locally produced chemical mediators, including prostaglandins, leukotrienes, complement-derived products, products of activated leucocytes, platelets and mast cells.

The central and most important effect of NSAIDs is inhibiting COX.

COX was originally purified in the 1970s. By 1990 it was realised that the enzyme had two isoforms.

- The COX-1 isoform is responsible for the production of 'housekeeping' prostaglandins critical for normal renal function, gastric mucosal integrity and vascular haemostasis.
- By contrast, COX-2 is an inducible enzyme. It is upregulated in macrophages, monocytes and other inflammatory cells by various stimuli including IL-1 and other cytokines.

NSAIDs can be classified according to their relative effect on COX-1 and COX-2. Generally, the risk of gastrointestinal adverse effects is reduced with increasing COX-2 selectivity. However, other factors are involved in the causation of gastrointestinal toxicity because, paradoxically, certain NSAIDs that are relatively COX-2 selective have been associated with a higher incidence of gastrointestinal adverse events.

NSAIDs have many actions other than their effect on COX. These include:

- uncoupling oxidative phosphorylation;
- inhibiting lysosomal enzyme release;
- inhibiting complement activation;
- antagonising the generation of activity in kinins;
- inhibiting free radicals.

Further work is required to elucidate the complex mechanism(s) of action of NSAIDs.

### **Features**

NSAIDs can be classified not only by their relative COX-1/COX-2 inhibition but also by their chemical class and plasma half-life. Most of the drugs within the NSAID class are organic acids with low pKa values, allowing penetration of inflamed tissue where the pH is often low. The more acidic NSAIDs usually have shorter half-lives in comparison.

NSAIDs are often produced in slow-release or sustained-release preparations, which allow once-daily dosing and may reduce the rate of gastrointestinal side effects.

There is marked individual variation in response to NSAIDs, although the causes of such variations are not known. Unfortunately this variability makes it difficult to predict how an individual patient will respond to treatment.

All NSAIDs exhibit anti-inflammatory properties and are often used as first-line treatment in inflammatory arthritis. Their efficacy relative to placebo is evident within 2 weeks in patients with active RA. Virtually all NSAIDs relieve pain when used in doses substantially lower than those required to demonstrate suppression of inflammation. The analgesic action of NSAIDs is generally considered to be peripheral, as opposed to the central effect of narcotics. However, some recent evidence suggests that selective COX-2-inhibiting NSAIDs may also have a central action by blocking pain transmission or altering pain perception in the central nervous system and spinal cord.

### Conventional NSAIDs

Although several NSAIDs have been developed, only a few are routinely used in clinical practice. The earliest agents have either been withdrawn, in the case of phenylbutazone, or are used infrequently, as in the case of indomethacin. Table 3.3 shows a small range of conventional NSAIDs.

Range of conventional NSAIDs suitable for most patients with arthritis			
Drug	Suggested dose	Advantages	Limitations
Diclofenac	75 mg slow release bid	Rapid onset of action and relatively good efficacy	Risk of unusual toxicity, especially liver damage
Ibuprofen	600 mg tid	Well known and widely used with short half-life giving great flexibility of use	Requires frequent dosing
Naproxen	500 mg bid	Effective when used twice daily	Standard NSAID with no major benefits or drawbacks
Piroxicam	20 mg daily	Effective once daily	Greater risk of side effects, especially gastrointestinal ulceration
Indomethacin	75 mg slow release bid	Useful in acute gout or severe ankylosing spondylitis	Greater risk of side effects and frequent central nervous system adverse reactions

**Table 3.3.** *bid, twice daily; NSAID, non-steroidal anti-inflammatory drug; tid, three times daily.*

NSAID dosage schedules range from once to three times daily. Administering NSAIDs frequently provides greater flexibility in achieving the best dose for an individual patient. A once-daily NSAID is often more convenient for the patient, but this is offset by greater relative toxicity. Giving the lowest dose compatible with symptom relief, and reducing or stopping treatment when patients have achieved a good response to disease-modifying drugs, can minimize the risks of toxicity with conventional NSAIDs.

When choosing an agent, it is important to realise that systematic reviews have found no major differences in efficacy between the currently available NSAIDs over a range of doses. However, they have found differences in the adverse event profiles.

### **Side-effect profile**

Adverse events are the major problem limiting use of NSAIDs. The risk of NSAID-related adverse effects increases markedly with the patient's age so these drugs must be used carefully in the elderly. The most clinically significant adverse reactions are summarized in Table 3.4. Central nervous system effects, such as drowsiness and confusion, are often underestimated. Haematological side effects are rare. Furthermore, minor adverse effects such as dyspepsia and headache are commonplace. NSAIDs can also exacerbate asthma and cause rashes, though these both are usually mild.

The main risks of standard (non-COX-2 NSAIDs) are discussed below.

### ***Renal adverse events***

Prostaglandins regulate kidney function, especially intrarenal perfusion. As a consequence, NSAIDs inevitably carry a risk of adversely affecting renal function. These renal side effects are dose-dependent and occur in a small but consistent proportion of patients. Common problems comprise peripheral oedema, hypertension, and reduced effects of diuretics and antihypertensive drugs. When renal blood flow is reduced, for example by cardiac failure or diuretic use, the added inhibition of prostaglandin synthesis by NSAIDs further impairs blood flow, which can cause overt renal failure. This problem affects the elderly in particular. Other renal problems seen occasionally include acute renal failure, hyperkalaemia, interstitial nephritis and papillary necrosis.

### ***Gastrointestinal toxicity***

Adverse events affecting the gastrointestinal system are the main problem with NSAIDs and again are most common in the elderly. The range of adverse effects includes:

- dyspepsia;



Adverse reactions to non-steroidal anti-inflammatory drugs	
System affected	Type of adverse reaction
Renal	Acute and chronic renal failure Interstitial nephritis
Gastrointestinal	Dyspepsia Peptic ulceration Small bowel ulcers and enteropathy
Cardiovascular	Cardiac infarction and sudden death Exacerbation of cardiac failure Exacerbation of hypertension
Hepatic	Elevated transaminases Hepatic failure (rare)
Central nervous system	Headache Drowsiness Confusion
Haematological	Thrombocytopenia Haemolytic anaemia

**Table 3.4.**

- gastric erosions;
- peptic ulceration;
- bleeding;
- perforation;
- haematemesis or melaena;
- small bowel inflammation;
- occult blood loss;
- anaemia.

The most serious problems are perforations, ulcers and bleeds (*see* Table 3.5). Between 1% and 2% of RA patients taking NSAIDs for one year will suffer serious gastrointestinal complications.

**Risk factors for NSAID-associated upper gastrointestinal ulcers**

Aged >65 years
History of ulcer
Higher doses of NSAIDs
Concomitant use of corticosteroids
Co-morbidity

**Table 3.5.** NSAID, non-steroidal anti-inflammatory drug.

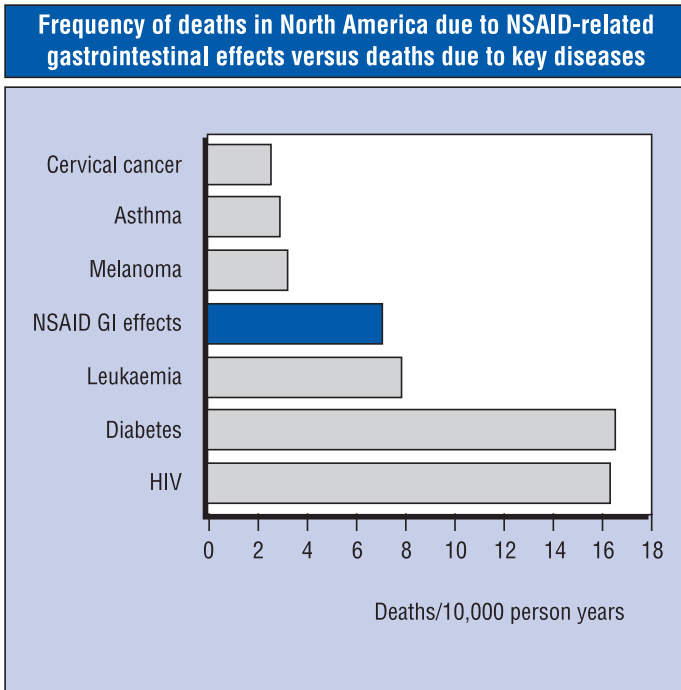
The mortality risks attributable to gastrointestinal adverse effects that can be attributable to NSAID use is four times greater in NSAID-treated individuals than the mortality from similar causes in those not using NSAIDs. There is some evidence that mortality rate from NSAID-related gastrointestinal events is similar to that of leukaemia and greater than that of melanoma (*see* Figure 3.2).

In many patients who experience serious gastrointestinal complications, there may not be a history of prior dyspepsia. In the absence of warning signs there is no way to ascertain whether the complications are imminent. When NSAID use is unavoidable, a protective strategy is needed, particularly in those at greatest risk. This could comprise:

- co-prescribing a proton pump inhibitor, such as omeprazole (these drugs are effective and tolerable);
- co-prescribing an histamine H<sub>2</sub>-receptor antagonists (comparably less effective than proton pump inhibitors);
- co-prescribing a prostaglandin analogue, such as misoprostol (although effective, side effects such as diarrhoea make the drug less well tolerated than proton pump inhibitors);
- switch to an NSAID with an improved side-effect profile (ie, one of the newer COX-2 drugs though these should not be used in patients with cardiovascular risks).

## Cyclooxygenase-2 drugs

The discovery of the two COX isoenzymes was thought to be a significant advance for the treatment of RA. COX-2 was considered to provide anti-inflammatory action and pain relief, as seen with conventional NSAIDs, but without the gastrointestinal toxicity associated with COX-1 inhibition (*see*

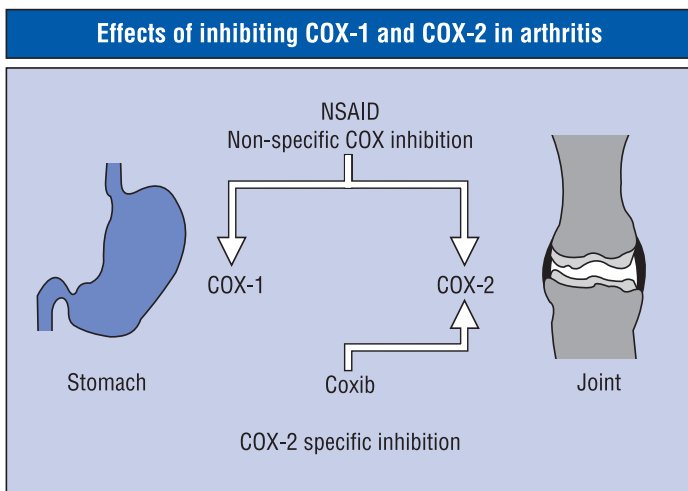


**Figure 3.2.** Frequency of deaths in North America due to NSAID-related gastrointestinal effects versus deaths due to key diseases.

Figure 3.3). This concept led to the development of a new class of drugs that specifically inhibit COX-2. Four drugs in this class have been licensed for RA: rofecoxib, celecoxib, valdecoxib and etoricoxib. However, rofecoxib and valdecoxib have been subsequently withdrawn because concerns about cardiovascular toxicity in the former and skin problems (Stevens-Johnson syndrome) in the latter; something of a shadow hangs over the whole group as a result.

### Assessing COX-2 selectivity

*In-vitro* human whole blood assay is an accepted and reproducible standard to assess COX-2 selectivity. However, it may not truly reflect the COX inhibition in target tissues such as the gastric mucosa. Recently developed assays use human target cells such as gastric mucosal cells and synovio-cytes which are thought to be more accurate.



**Figure 3.3.** COX, cyclooxygenase; NSAID, non-steroidal anti-inflammatory drug.

There are wide variations in ratios reported by using different assay techniques. Furthermore, results from *in-vitro* testing are no more than a general guide to the relative *in-vivo* selectivity of different drugs.

### Clinical efficacy

There is a substantial body of evidence from large trials, some of which are of long duration, to support the efficacy of COX-2 drugs in RA. These trials show that coxibs are more effective than placebo and equally effective as maximum daily doses of standard NSAIDs (such as diclofenac and naproxen). The essential data for celecoxib are summarized in Table 3.6. Examples of improvements in clinical measures – the American College of Rheumatology (ACR) responder index and the number of swollen joints – are shown in Figures 3.4 and 3.5.

### Side-effect profile

#### **Gastrointestinal effects**

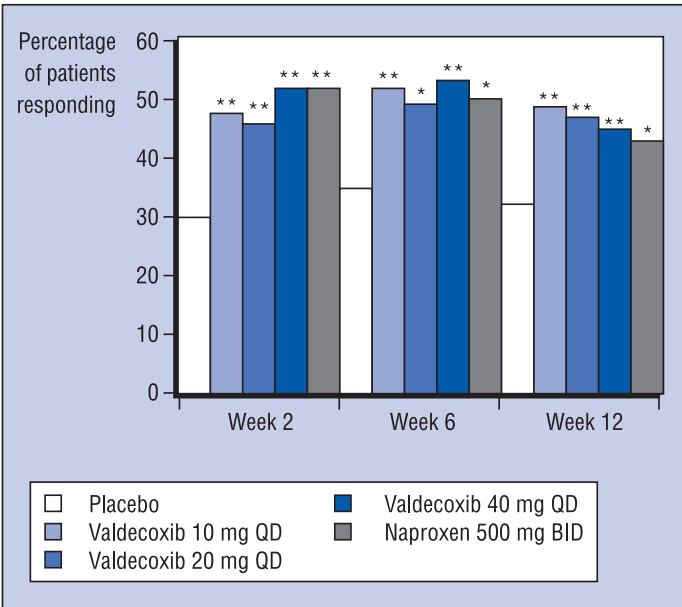
Although COX-2 inhibitors increase the incidence of gastrointestinal adverse events compared with placebo, the magnitude is substantially less than with standard NSAID therapy. Celecoxib, valdecoxib and etoricoxib have a lower

### Summary of key trials for registration of celecoxib in RA

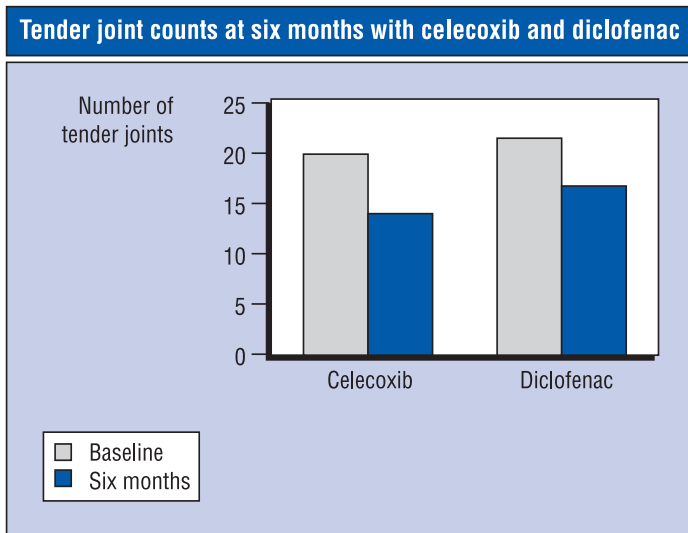
Trial reference	Duration	N	Treatment arms	Results
Simon 1998	4 weeks	328	Celecoxib 80 mg and 400 mg or placebo	Higher doses of celecoxib better than placebo
Emery 1999	6 months	655	Celecoxib 400 mg or diclofenac 150 mg	Efficacy similar in most outcomes
Simon 1999	3 months	1149	Celecoxib 200–800 mg, naproxen 1000 mg or placebo	All active treatments similar and superior to placebo

**Table 3.6.** RA, rheumatoid arthritis.

### ACR response rates in a trial of valdecoxib, naproxen and placebo



**Figure 3.4** ACR, American College of Rheumatology; bid, twice daily; qd, once daily.



**Figure 3.5.** An example of the clinical efficacy of coxibs.

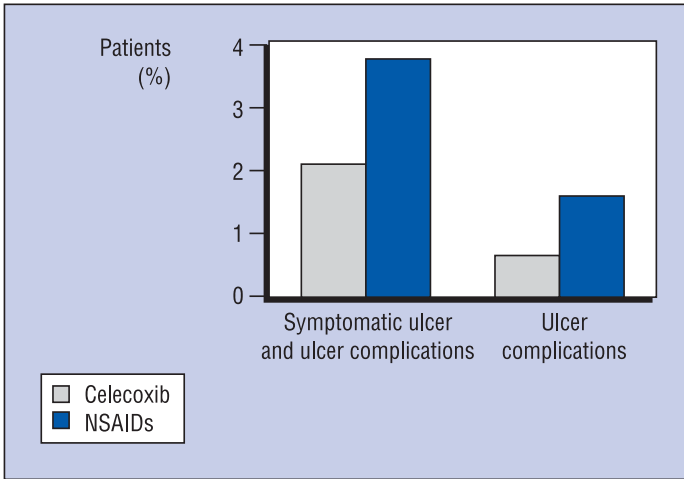
incidence of gastric erosions on endoscopy compared with standard NSAIDs. However, the value of this finding as a surrogate for peptic ulceration and other major gastrointestinal adverse effects in clinical practice is uncertain.

The key evidence focuses on the effect of coxibs on peptic ulcerations, perforations and bleeds. The balance of evidence, from large trials involving several thousands of patients, is that the rate of serious upper gastrointestinal adverse events with coxibs is similar to that of placebo and substantially below that of conventional NSAIDs. For example, in the Celecoxib Long-term Arthritis Safety Study (CLASS) celecoxib was compared with conventional NSAIDs ibuprofen and diclofenac in over 8000 patients with RA. After six months of therapy, the annualized rate of serious upper gastrointestinal ulcer complications was 0.76% with celecoxib and 1.45% with conventional NSAIDs. An overview of the results is shown in Figure 3.6.

### **Cardiovascular effects**

Importantly, trials have found a relatively high incidence of myocardial infarction with rofecoxib, especially at high doses. Initially there was debate about whether this was due to a harmful effect of rofecoxib or a protective (aspirin-like) effect of naproxen, the main comparator in some of the early

### Tender joint counts at six months with celecoxib and diclofenac



**Figure 3.6.** Fewer serious upper gastrointestinal adverse events with celecoxib compared with non-steroidal anti-inflammatory drugs (NSAIDs).

trials. The balance of evidence now suggests this is a specific negative effect of coxibs; so far only rofecoxib has been withdrawn from the market by its manufacturers but the story is still unfolding. Coxibs might block potentially protective effects of COX-2 on ischaemic myocardium or on atherogenesis. Also, the effect of coxibs on blood pressure and renal function could prove more detrimental than those of conventional NSAIDs. At present, coxibs should not be used in patients with cardiovascular risk factors.

#### **Other side effects**

Additional side effects of coxibs are broadly similar to those seen with conventional NSAIDs and include renal problems, central nervous system effects and rashes.

#### **Newer coxibs**

The most recent coxib is lumiracoxib, which at the present time is licensed for treatment of osteoarthritis only. Its role, like other coxibs, will depend on the studies now being undertaken to clarify cardiovascular risks. This issue will also determine whether further coxibs will be developed.

**When to prescribe coxibs**

Although the newer coxibs bring therapeutic benefits over conventional NSAIDs, their expense and their cardiovascular risk profile has caused regulatory bodies to minimize their use. At present, coxibs are generally restricted to use in patients most at risk of serious upper gastrointestinal side effects, ie those:

- aged 65 years or over;
- using concomitant medications known to increase the likelihood of upper gastrointestinal adverse events;
- with serious co-morbidity;
- with a history of prolonged use of maximum recommended doses of standard NSAIDs; or
- those without significant other cardiovascular risk factors.

In patients with a history of gastroduodenal ulcer, gastrointestinal bleeding or gastroduodenal perforation, the risk of NSAID-induced complications is particularly increased. The use of even a COX-2-selective agent in such patients should therefore be considered carefully. There is no evidence to justify the simultaneous prescription of gastroprotective agents with COX-2-selective inhibitors as a means of further reducing potential gastrointestinal adverse events.



# *Disease-modifying antirheumatic drugs*

## **Background**

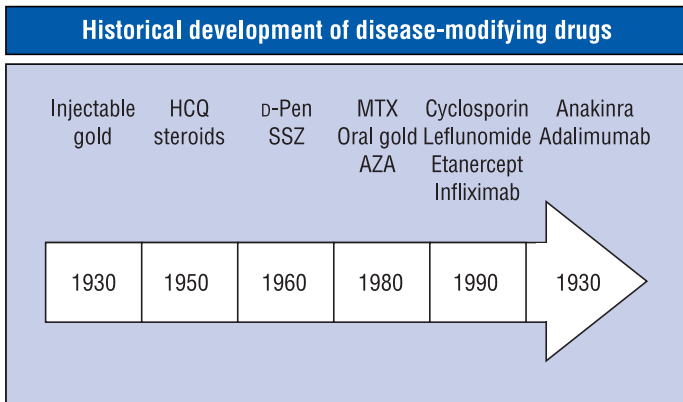
This diverse group of drugs is considered collectively because they not only improve symptoms but also modify the course of the disease (ie, they slow down or halt erosive joint damage and reduce disability). However, there is little evidence that treatment with these drugs causes remission. Although commonly known as disease-modifying antirheumatic drugs (DMARDs), other descriptors include 'second-line drugs', 'slow-acting antirheumatic drugs' and 'remission-inducing drugs'. However, these drugs should not necessarily be used as second-line, are not particularly slow-acting and usually fail to induce remissions. Therefore, these terms have been abandoned because of their misleading or inappropriate connotations.

## **Historical perspective**

The use of DMARDs can be traced back to the 1920s. The first drug was injectable gold. Since then, research and development efforts have continued, bringing forth several novel agents, particularly in recent years. The latest advance is injectable immunotherapy with adalimumab. The time sequence of DMARD development is summarized in Figure 4.1.

The initial use of injectable gold to treat rheumatoid arthritis (RA) stemmed from its role in treating tuberculosis in the 1920s. The French rheumatologist Jacques Forestier, Director of the Spa at Aix-les-Bains, believed that there was a resemblance between tuberculosis and RA. He was sufficiently convinced of the relationship to start using gold to treat RA in 1928, reporting his results in the early 1930s. Interestingly, gold failed to benefit patients with tuberculosis but was successful in RA, providing one of the first examples where the rationale for a treatment was wrong but the result positive.

Since double-blind randomized studies had not yet been devised, the first evidence supporting the use of gold in RA came from a large observational study conducted in Leeds, UK in the 1930s and published in 1937. 750 RA patients and 150 cases with miscellaneous musculoskeletal diseases were treated and benefit seen in approximately two-thirds of them. The first randomized trial of gold treatment was undertaken in the 1940s in Scotland; interestingly this was the first published double-blind study of any agent. This trial involved



**Figure 4.1.** AZA, azathioprine; HCQ, hydroxychloroquine; MTX, methotrexate; SSZ, sulfasalazine. Historical development of disease-modifying drugs.

103 patients with RA, of whom 57 were treated with 1-g gold in divided doses and 43 received placebo. After 12 months, 82% of patients receiving gold treatment showed clinical improvement compared with less than half of those in the placebo group. Further trials undertaken in the 1960s and 1970s, including the well-known Empire Rheumatism Council study from 1961, confirmed the beneficial effect of gold therapy.

Other disease-modifying drugs were developed between the 1950s and 1970s. These drugs included antimalarials (chloroquine and hydroxychloroquine), sulphasalazine, pencillamine and methotrexate. None of these drugs was introduced as a result of concerted research programmes focussing on RA. Instead, they were identified by the chance observations of individual clinical rheumatologists who adapted available pharmaceuticals for use in RA. This period of observational research, relying on serendipity, has now come to an end.

## Treatment targets

The main goal of DMARD treatment is to reduce the signs and symptoms of RA for at least six months.

When given an effective DMARD, a proportion of patients can be expected to achieve a major clinical response in which there is a marked reduction

in joint inflammation that lasts up to 12 months. Furthermore, a small minority of patients may enter a period of sustained remission.

The two other important goals for RA treatment are:

- slowing or halting the progression of erosive joint damage;
- improving or maintaining joint function.

It is likely that highly effective DMARDs, which induce remission in a substantial number of patients, will also stop erosive damage and improve joint function. However, until now, the search for drugs that reliably induce remission has not been successful.

Assessing response to treatments such as DMARDs involves evaluation of several factors (*see* Table 1.7 in Chapter 1 for the core data set for RA). The measures can be combined to give overall response indices, of which the most widely used are the Disease Activity Score (DAS) and the American College of Rheumatology (ACR) responder index (*see* Chapter 1 for discussion).

When regarding the evidence for DMARD efficacy in RA, it must be noted that clinical trials have traditionally enrolled patients with:

- $\geq 6$  swollen joints;
- $\geq 6$  tender joints;
- an erythrocyte sedimentation rate (ESR) of  $\geq 28$  mm/h;
- morning joint stiffness lasting  $\geq 30$  minutes.

The trial data supporting DMARD efficacy are exclusively for patients with such active disease. The impact of starting DMARDs in patients with less active disease, as is carried out in routine practice, has been less well studied in controlled clinical trials.

## Currently used conventional disease-modifying antirheumatic drugs

Table 4.1 classifies the available DMARDs according to the frequency of their use. At present, methotrexate is the most commonly used DMARD; accounting for over 80% of DMARD prescriptions for RA in specialist units. Leflunomide and sulphasalazine are the two remaining DMARDs to be used to any appreciable extent.

The pattern of DMARD use broadly follows the strength of evidence of their efficacy. The Cochrane database, which collects the results of all published randomized controlled trials, shows that there is good evidence that methotrexate, leflunomide and sulphasalazine are effective, while the evi-

Conventional disease-modifying antirheumatic drugs		
Commonly used	Infrequently used	Rarely used
Methotrexate	Hydroxychloroquine/chloroquine	Cyclosporin
Leflunomide	Injectable gold	Auranofin
Sulphasalazine	Azathioprine	Cyclophosphamide

**Table 4.1.**

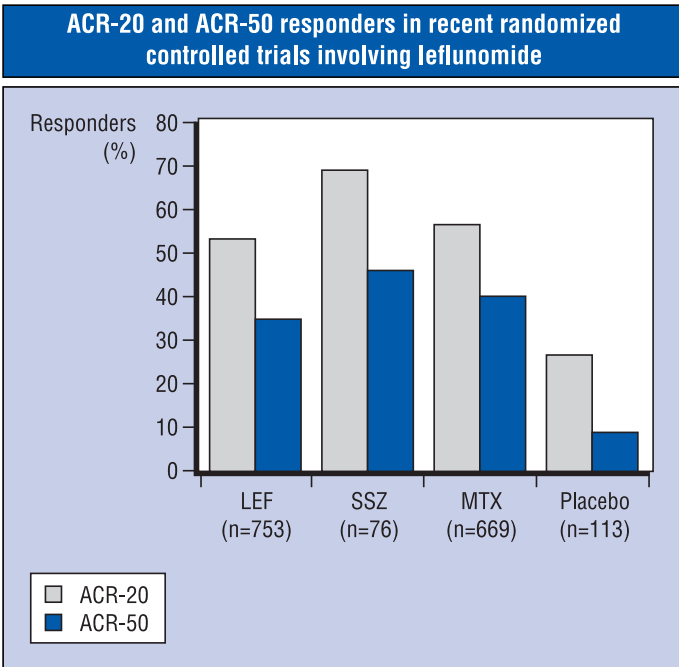
dence in favour of the other drugs is weaker. Key aspects of the Cochrane database are summarized in Table 4.2. The ACR-20 and ACR-50 responses in recent trials with leflunomide are shown in Figure 4.2.

## Methotrexate

The popularity of methotrexate in treating RA is interesting since, unlike many other drugs, it is not promoted by pharmaceutical sponsors. It is also

Summary of randomized controlled trials of disease-modifying antirheumatic drugs in rheumatoid arthritis			
DMARD	Number of trials	Number of patients receiving active therapy	Strength of evidence supporting efficacy
Methotrexate	5	300	+++
Leflunomide	6	413	+++
Sulphasalazine	6	468	+++
Injectable gold	4	195	++
Hydroxychloroquine	4	290	++
Cyclosporin	3	318	++
Auranofin	7	539	+
Azathioprine	3	81	+/-
Cyclophosphamide	2	31	+/-

**Table 4.2.** +++, strong; ++, moderate; +-, modest; +, minimal; +/-, weak. Data from Cochrane database.



**Figure 4.2.** ACR, American College of Rheumatology; LEF, leflunomide; MTX, methotrexate; SSZ, sulfasalazine. ACR-20 and ACR-50 response rates in recent randomized controlled trials involving LEF.

an 'old' drug that has been used in medicine for the last 50 years and its use in rheumatology dates back several decades. The only reasonable explanation for its current success is that the combined features of efficacy, tolerability, relative lack of toxicity, ease of administration and patient acceptability mean that methotrexate is preferred by clinicians and patients.

### Mechanism of action

Methotrexate is an antimetabolite that inhibits folate metabolism. It was first used to treat lymphatic malignancies. In RA, methotrexate is used at low doses whereby it does not kill cells in the same way as in cancer treatment, exerting its effects on synovitis through other mechanisms. These mechanisms include changes in adenosine metabolism, leucocyte accumu-

lation and angiogenesis. However, the exact mode by which methotrexate reduces synovitis is not known.

### **Administration and dosage**

Low-dose methotrexate is administered weekly either orally or parenterally by subcutaneous or intramuscular injections. Although the bioavailability of oral methotrexate is relatively high, there is individual patient variability. Absorption is not reduced by concomitant food intake. Methotrexate is strongly bound to plasma proteins. Although theoretically there could be an increase in free methotrexate because of displacement from albumin by more highly bound drugs (such as NSAIDs), in practice this is not a problem.

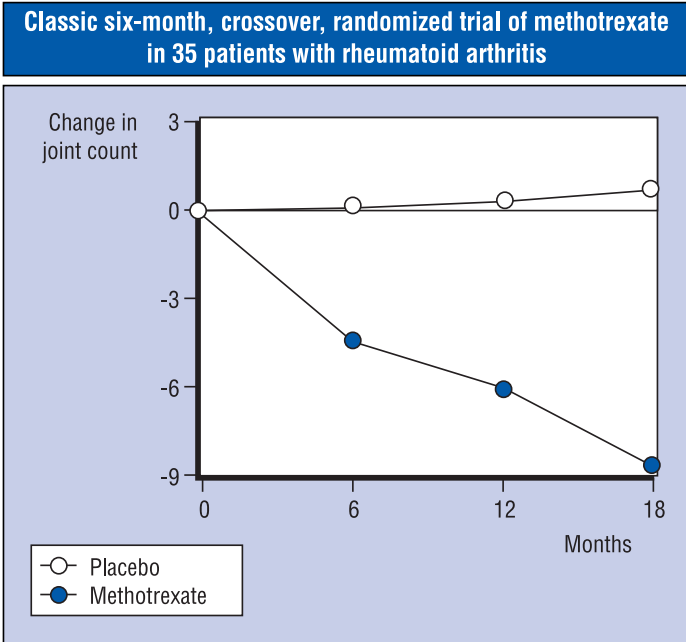
Methotrexate is usually started orally at a dose of 7.5 mg per week. This is gradually increased to a target dose of 15–20 mg per week. (The recommended upper limit of the target dose has gradually increased over the years to the current 20 mg; and some rheumatologists use a maximum of 25 or even 30 mg per week). If patients experience difficulty in tolerating high doses of methotrexate, the dose can be restricted to below 15 mg per week or, particularly if the intolerance is gastrointestinal, parenteral dosing can be tried. Low-dose folic acid is given concomitantly with methotrexate as it has been shown to reduce the risk of adverse reactions, both serious (hepatic toxicity) and less serious (nausea), without significantly impacting on efficacy.

### **Efficacy**

Methotrexate improves all clinical measures of disease activity including active joint counts, ESR and other acute phase markers.

Positive observational reports of the efficacy of low-dose methotrexate in RA date back to the early 1970s. Furthermore, its parent compound, aminopterin, had been used in RA patients 20 years previously. The results from these uncontrolled studies of methotrexate were sufficiently encouraging to initiate definitive placebo-controlled trials. These early trials involved RA patients who had failed prior therapies, including gold salts.

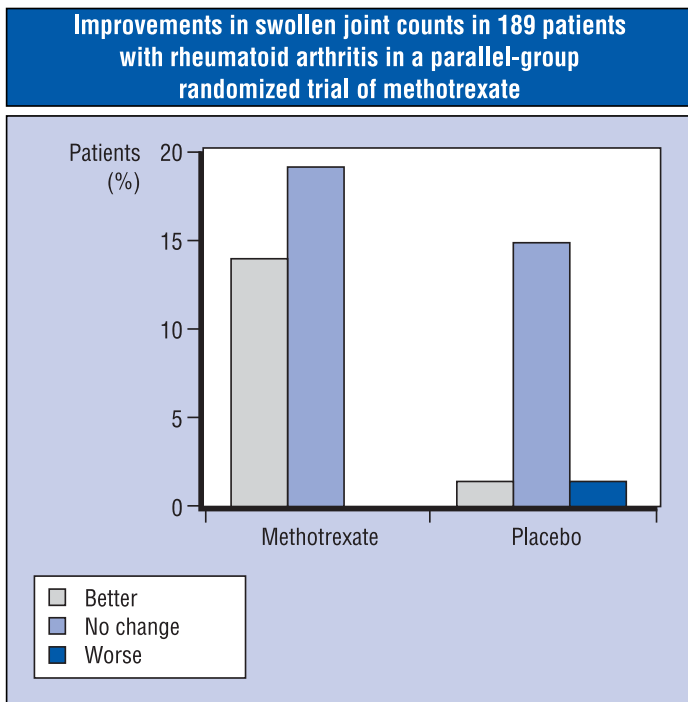
There were four trials in the 1970s and 1980s, all of which showed that methotrexate was effective in treating active RA. The results from two of the most important of these trials are shown in Figures 4.3 and 4.4. The most well-known trial, led by Michael Weinblatt, was a 35-patient double-blind, crossover trial of low-dose (7.5–15 mg weekly) methotrexate versus placebo. This trial lasted six months and improvement began within three weeks of methotrexate initiation. Another trial evaluated 189 RA patients treated for 18 weeks with low-dose methotrexate or placebo; significant treatment-related improvements were seen in all clinical variables.



**Figure 4 3.**

The short-term benefits of methotrexate shown in clinical trials lasting six months or more have been supported by findings in prospective, open, long-term studies. More than 50% of patients in the methotrexate group continued treatment beyond three years, which is longer than any other DMARD studied. Although certain early observational studies suggested that methotrexate did not slow radiographic progression in advanced RA, subsequent research has shown that methotrexate is effective in reducing the progression of joint damage in both early and late disease.

Not all patients respond to methotrexate. As with all DMARDs, about 30% of patients show a poor or inadequate response. There is, as yet, no simple way of predicting who will respond. In general terms, responses are better in early RA and worse in late disease, when patients have already tried and failed several other DMARDs. It is easier to detect a good response in patients with more active disease, although milder cases can also respond.



**Figure 4.4.**

- If there is no improvement after three months of methotrexate treatment, the chances of success are limited.
- After six months of treatment, methotrexate should be stopped if there is no evidence of benefit.

### **Side-effect profile**

Although adverse events may occur at any time, they tend to develop in the early months of treatment with methotrexate. Events are common but most are minor and usually can be managed without stopping therapy. Gastrointestinal adverse effects are the most common. These include anorexia, nausea, vomiting and diarrhoea. They often resolve or improve with dose reduction or a switch to parenteral administration. Stomatitis, including erythema, painful ulcers and erosions are also frequent.



Prophylactic folic acid supplementation can reduce the rate of gastrointestinal and oral side effects. The optimal dosage of folic acid is uncertain, although 5mg weekly appears adequate and has no more than a modest impact on efficacy. Alopecia is fairly frequent and causes particular concern to female patients. Other skin reactions include urticaria, and cutaneous vasculitis. Occasionally, methotrexate causes accelerated nodulosis, usually involving small nodules on the fingers or elbows. These nodules are indistinguishable from rheumatoid nodules except for their rapid onset and the fact that they can develop in patients negative for rheumatoid factor. Controversy surrounds their management; ie, whether to stop methotrexate treatment or add an antirheumatic drug such as hydroxychloroquine which has been shown to reduce nodules in this circumstance. Other adverse events related to methotrexate therapy include fever, fatigue or myalgia. Infections sometimes occur, including opportunistic infections with organisms like *Pneumocystis carinii*, fungal infections and localized or disseminated herpes zoster.

Serious side effects include cytopenias (seen only rarely) or, most commonly, mild-to-moderate leucopenia, which responds to withdrawal of the drug. More severe bone marrow suppression may be treated with leukovorin or recombinant colony-stimulating factors. Mild transaminase elevations are common during treatment with methotrexate, but serious hepatotoxicity that can lead to fibrosis or frank cirrhosis is rare.

A feared but rare complication of methotrexate therapy is acute pneumonitis (acute pulmonary interstitial disease) which usually occurs early in the course of therapy (within 32 weeks in 50% of instances). In a recent study of over 600 methotrexate-treated patients, 551 of whom had RA, six cases of pneumonitis were identified one of which resulted in death. Suggested risk factors include older age, rheumatoid pleuropulmonary involvement, previous DMARD use and diabetes mellitus; however, prediction is very imperfect and the most important measure is to ensure that all patients and clinicians are aware of this potential problem. Methotrexate can also be linked to other more chronic forms of respiratory involvement although it is often difficult to assess whether such problems arise from the underlying disease or from treatment.

Patients should be monitored prior to and during treatment with methotrexate. Conventionally, full blood count (FBC) and liver function tests are undertaken monthly. A chest X-ray is taken at the beginning of treatment, providing a baseline against which any subsequent lung problems can be evaluated. To avoid methotrexate-induced liver damage, it is also standard practice to advise patients to drink either no or very little alcohol. The true value of these monitoring policies, in terms of evidence-based medicine, is

open to question as considerable resources are used to detect relatively few significant events. However, in the current risk-averse climate, it seems unlikely that guidance from pharmaceutical companies, national health agencies or national rheumatology societies will change.

Teratogenicity is a potential risk of methotrexate when used to treat RA. The foetal aminopterin-methotrexate syndrome is well documented in children of women taking high-dose methotrexate for malignancies. This syndrome includes skeletal abnormalities, microcephaly and hydrocephalus. With low-dose methotrexate, the risk is less clear though many reported pregnancies have resulted in births of full-term healthy infants. Nevertheless, pregnancy is a contraindication for methotrexate treatment. Women taking methotrexate who are at risk of pregnancy should use reliable methods of birth control. After methotrexate treatment is stopped, women should wait at least three months before trying to conceive; many national teratology agencies and companies recommend a longer period of withdrawal of up to six months because of the tendency for methotrexate to be retained in tissues. Methotrexate has no effect on fertility in women, and if the drug is stopped at least 30 days prior to attempting conception, it will not affect the foetus. Breast-feeding is not recommended while taking methotrexate, because the drug may enter the mother's milk.

Methotrexate may lower sperm count, although the count should normalize once the drug is discontinued. There is limited information regarding the risk of birth defects from a father taking methotrexate at the time of conception. However, it is recommended that males discontinue methotrexate three months prior to attempting conception.

## Leflunomide

### Mechanism of action

Leflunomide is the first new DMARD to become available for many years. It was developed as an immunosuppressant and acts as a pyrimidine synthesis inhibitor with consequential antiproliferative activity. Leflunomide is a pro-drug and is rapidly converted in the gastrointestinal tract and plasma to its active metabolite, a malononitrilamide, which is responsible for its activity *in vivo*. The active metabolite of leflunomide at therapeutic doses reversibly inhibits dihydroorotate dehydrogenase, the rate-limiting step in the *de-novo* synthesis of pyrimidines. Unlike other cells, activated lymphocytes expand their pyrimidine pool by approximately eightfold during proliferation. To meet this demand, lymphocytes must use both salvage and *de-novo* synthesis pathways. Thus, the inhibition of dihydroorotate dehydrogenase prevents

lymphocytes from accumulating sufficient pyrimidines to support DNA synthesis; its immunomodulatory effect is consequent upon this.

### **Administration and dosage**

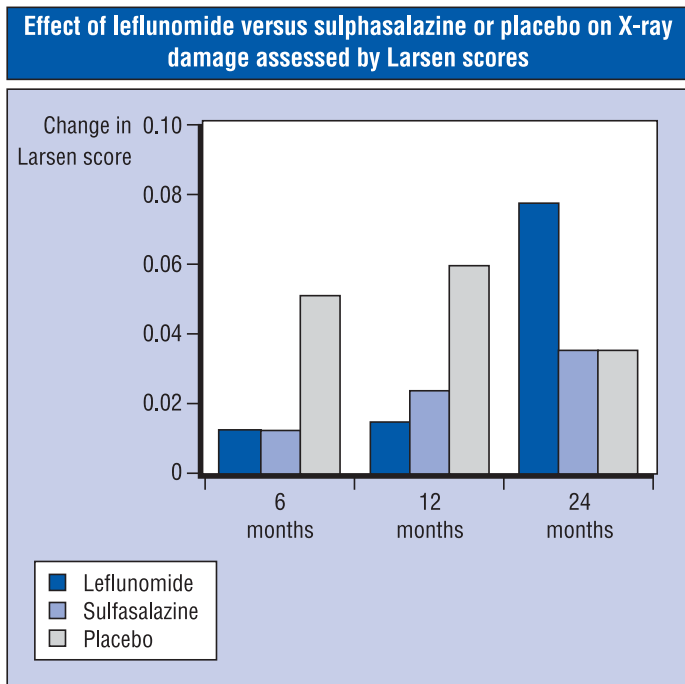
Peak levels of the active metabolite are seen 6–12 hours after oral dosing of leflunomide. As the active metabolite has a long half-life, in the region of two weeks, loading doses of 100 mg leflunomide for three days were used in the initial clinical studies to facilitate the rapid attainment of steady-state levels of the active metabolite. Without a loading dose, steady-state plasma concentrations require about two months of dosing to develop.

### **Efficacy**

The initial dose-ranging trial of leflunomide indicated that the effective dose ranged between 10 mg and 25 mg daily. A subsequent multinational trial programme comprised three large, prospective, randomized, controlled trials, each lasting between 6 and 24 months. The trials examined a dose of 20mg leflunomide per day preceded by a loading dose of 100 mg daily for three days. One of the trials compared leflunomide with placebo and sulphasalazine, a second compared it with placebo alone and a third compared leflunomide with methotrexate. These trials showed leflunomide to be superior to placebo and similar to sulphasalazine or methotrexate in improving most measures of disease activity in RA. Overall, patients showed improvements of 20% or more in all key outcome measures, including pain, number of tender and swollen joints, patient and physician global assessments, and ESR. Leflunomide also reduced disability scores by 40–60% (sustained for up to two years) and reduced the progression of erosive damage over 12 months or longer (*see* Figure 4.5). Open label extension studies subsequently confirmed that clinical improvement was maintained for up to five years.

### **Side-effect profile**

Common adverse reactions with leflunomide include diarrhoea, nausea, reversible alopecia and rashes. Diarrhoea has been reported by >15% of patients in clinical trials. This side effect is of particular concern as it often causes patients to discontinue treatment. There is some evidence that omitting the loading dose reduces the frequency and severity of diarrhoea. Hypertension is sometimes seen and regular blood pressure monitoring is recommended. However, other concomitant therapies such as NSAIDs can also raise blood pressure so it can be difficult to identify the contribution of each agent. Occasionally, patients report weight loss with leflunomide treatment, although its relationship to therapy has not been proved. There is



**Figure 4.5.**

also a small increase in risk of infections, in common with other immunosuppressive drugs. A small proportion of patients develop low white blood cell or platelet counts, and in these circumstances treatment should be stopped.

The main cause of concern with leflunomide is liver damage. Transient increases in liver enzymes are commonplace, and usually need no more than careful observation. If the levels rise to more than three times the normal level, treatment should be stopped. Only a minority of patients have developed either cirrhosis or liver failure whilst taking leflunomide, and the issue of causality is unclear. Careful consideration should be made before commencing leflunomide therapy in patients with prior liver disease or in those with significant levels of alcohol intake and there has also been concern about concomitant prescription of other hepatotoxic drugs, notably

methotrexate. Patients receiving leflunomide should have their liver function monitored and blood counts assessed regularly for early detection of liver problems. These tests should be undertaken every two weeks for the first 6 months, although the frequency can reduce thereafter.

Leflunomide, like other DMARDs, can cause foetal damage and for this reason it should not be given to women at risk of pregnancy. Given the long half-life of the drug, it needs to be stopped for many months prior to conception, and some authorities recommend a two-year period of cessation. A washout procedure can be considered in patients having severe side effects or in men or women considering conception. This involves giving cholestyramine or activated powdered charcoal for one or two weeks.

## **Injectable gold**

Gold salts are the oldest DMARDs and among the most effective. However, they are also highly toxic and may take months to show any evidence of efficacy. Gold is usually given as parenteral gold sodium thiomalate, though another preparation, gold sodium thioglucose, can be given.

### **Mechanism of action**

Although the mode of action of gold treatment has been investigated for many years, little is known. There are several reasons for this lack of knowledge:

- the use of gold was the result of serendipity rather than design. Consequently there was no prior hypothesis about the way it may work;
- its use predated the modern era and by the time its mechanisms of action could reliably be investigated there was little interest in evaluating them;
- because injectable gold is a highly complex compound, containing many different chemical constituents formed after its manufacture, it is difficult to determine which constituent should be studied.

### **Administration and dosage**

Parenteral gold is administered by intramuscular injection in a weekly schedule. Based empirically on clinical experience, the following schedule is recommended. Two initial 'test doses' of injectable gold are given (10 mg for the first week and 25 mg for the second week); if there is no reaction, these are followed by 50 mg weekly doses thereafter assuming no significant toxicity develops. If there is substantial clinical improvement, some

authors recommend a stepwise reduction in dosage to 25–50 mg every two to four weeks; ultimately, withdrawal may be considered if patients enter a prolonged remission. In the past, it was suggested that gold should be stopped after a dose of 1 g was reached; there is no clear evidence to support this recommendation and many patients have received significantly more than this without problems.

### **Efficacy and tolerability profile**

Adverse reactions include:

- **mucocutaneous:** these are by far the most common side effects, usually presenting as stomatitis or rashes; alopecia and pruritis may also occur.
- **haematological:** low white cell count, thrombocytopenia or eosinophilia are among the more significant relatively common side effects; more rarely pancytopenia from bone marrow aplasia may occur
- **renal:** proteinuria leading in some cases to nephrotic syndrome
- **respiratory:** interstitial lung disease has been described, although it is difficult to be certain whether this is a consequence of the drug or the underlying disease
- **gastrointestinal:** patients describe nausea and similar mild subjective side effects; abnormal liver function is unusual but can be serious
- **neurological:** patients describe headache and mood changes but objective events, such as peripheral neuropathies, are rare.

### **Vasomotor (nitritoid) reactions**

With the decreasing use of gold therapy, nurses and doctors are often unaware of vasomotor (nitritoid) reactions. However, it is important to distinguish them from true anaphylaxis since tolerance (tachyphylaxis) may develop to vasomotor reactions (so gold can be continued under supervision) whereas for anaphylaxis the drug must be withdrawn. Characteristically, reactions occur within minutes of drug administration with flushing, sweating, dizziness, nausea, malaise, weakness, feelings of faintness and hypotension; though often regarded as mild, patients may find them frightening and dramatic. Reactions usually occur early in the course of gold therapy but can occur in long-established patients. Reactions, which occur in 3–5% of patients, are usually self-limiting and may occur only a few times. The outcome is generally benign but there are rare reports of subsequent myocardial infarction, stroke or other more severe vascular events; in some of these, there appears to have been concomitant significant vascular disease suggesting particular care needs to be taken in such cases.

Approximately one-third of patients treated with parenteral gold discontinue therapy due to side effects, another third achieve a good clinical and radiographic response and in the remainder, neither response nor toxicity are seen.

## Other disease-modifying antirheumatic drugs

### Hydroxychloroquine

This antimalarial drug initially was used by rheumatologists to treat lupus. Subsequent placebo-controlled trials showed it to be effective in RA, especially in patients with a short duration of disease. It is usually given at a dose of 400 mg per day. However, hydroxychloroquine is not as effective as other DMARDs such as methotrexate, sulphasalazine or injectable gold in improving clinical measures (eg, joint counts and ESR) and has little effect on disease progression measured on X-ray. Hydroxychloroquine is therefore used mainly in early or mild RA because of its favourable tolerability and toxicity profiles; more recently it has become an important component of combination regimes.

Common adverse effects include rash, abdominal cramps and diarrhoea. The main concern is the possibility of retinopathy, a rare but potentially serious complication. The UK Royal College of Ophthalmologists recommends that all patients should have baseline evaluation by the rheumatologist who should ask about visual symptoms (not corrected by glasses) and should record near visual acuity using a reading chart. Such screening should be repeated yearly and ophthalmological or optometric referral undertaken if problems develop. Patients at high risk of retinopathy (ie, those aged >60 years, receiving treatment for more than five years or at a dosage >6.5 mg/kg per day) need annual ophthalmological examinations. Patients on the related drug, chloroquine, also appear to be at higher risk; this drug should be avoided where possible; if it is used, eye screening is required.

### Cyclosporin

The primary use of cyclosporin is to prevent rejection in organ transplant recipients. It was initially assessed as a treatment for RA on the basis of its systemic immunosuppressive properties, particularly its effect on T-cell function. A number of clinical trials in RA have shown cyclosporin to be superior to placebo, with comparable efficacy to methotrexate. However, its efficacy may be dose-dependent, as may its toxicity. There is evidence that cyclosporin improves joint function and reduces progression as seen on X-ray, especially in early RA. Its adverse effects, particularly nephrotoxic-

ity and hypertension, make long-term cyclosporin therapy a complex issue in RA, particularly in patients with renal dysfunction and other co-morbidities. Fortunately, the decline in renal function is largely reversed when therapy is discontinued. Cyclosporin is usually reserved for use in refractory RA when no other obvious therapeutic options are available.

### **Azathioprine**

Azathioprine is used in RA because of its systemic immunosuppressive effects. It is a pro-drug of 6-mercaptopurine, and is metabolized to its active metabolites, 6-thioguanine nucleotides. Clinical trials in RA show azathioprine to be more effective than placebo, but comparative studies with methotrexate have given inconsistent results. There is little indication that azathioprine slows disease progression. Due to these modest clinical effects, azathioprine is used only in refractory RA patients who have failed other agents.

Importantly, azathioprine can cause significant haematological toxicity, severe forms of which, such as myelosuppression, can result from abnormal azathioprine metabolism. This is linked to particular genetic polymorphisms of thiopurine methyltransferase, one of the main enzymes involved in metabolising purines such as azathioprine. The mutant thiopurine methyltransferase alleles are associated with lower enzyme activity; this leads to intracellular accumulation of the therapeutically active 6-thioguanine nucleotides and hence profound bone marrow toxicity. Thiopurine methyltransferase status can be assessed in patients pre-treatment by measuring enzyme activity or by genotyping techniques. Individualizing the dose of azathioprine on the basis of thiopurine methyltransferase status (in particular, reducing the dose substantially in patients homozygous for the two mutant alleles) has been suggested to reduce drug-induced morbidity and avoid the costs of hospitalisation and rescue therapy. However, because haematological toxicity and marrow suppression can be influenced by many other factors, it does not obviate the need for the normal ongoing haematological monitoring.

### **Auranofin**

Auranofin is an oral gold compound used to treat RA. Its use has declined in recent years, mainly due to its limited efficacy. Although trials consistently show it has clinical benefits in reducing disease activity, these are modest compared with methotrexate or parenteral gold. It has no benefit on radiological signs of progression. Furthermore, it causes severe diarrhoea and still requires the same level of monitoring as other DMARDs.



## Combining disease-modifying antirheumatic drugs

### Rationale

Despite conventional therapy with DMARDs, many RA patients continue to have aggressive disease with progressive joint destruction and marked disability developing over five to ten years or longer. In particular, deterioration is often seen when DMARDs are used sequentially. There is also some evidence that RA can be more aggressive in its early stages and that early therapy with DMARDs improves outcome. Together, these observations have led to a paradigm shift in the management of RA, with a focus on more aggressive early therapy including the possibility of combination therapy.

Many arguments justify the use of combination therapy in RA. These include the following:

- the results of sequential monotherapy are ultimately inadequate;
- low doses of combined DMARDs may improve toxicity/efficacy ratios;
- the sequential use of DMARDs may deprive the patient of any residual benefit of the previous 'failed' drug;
- sequential use of inadequate monotherapy deprives the patient of effective disease control during the critical early period of the disease.

Early studies of DMARD combination therapy were relatively disappointing so, prior to the 1990s, the consensus was that combination DMARD therapy offered little if any advantage over monotherapy, at least not without unacceptable toxicity. However, it became clear that there were significant design problems in these initial trials which often involved too few patients for inadequate lengths of time. Even though the evidence from the early trials was unconvincing, clinicians came to believe that combination therapy was likely to be effective and this view was supported by encouraging results from more recent research. Consistent with this, surveys of rheumatologists' prescribing practice over the last decade show a marked increase in the use of combination therapy in RA.

### Triple therapy with methotrexate, hydroxychloroquine and sulphasalazine

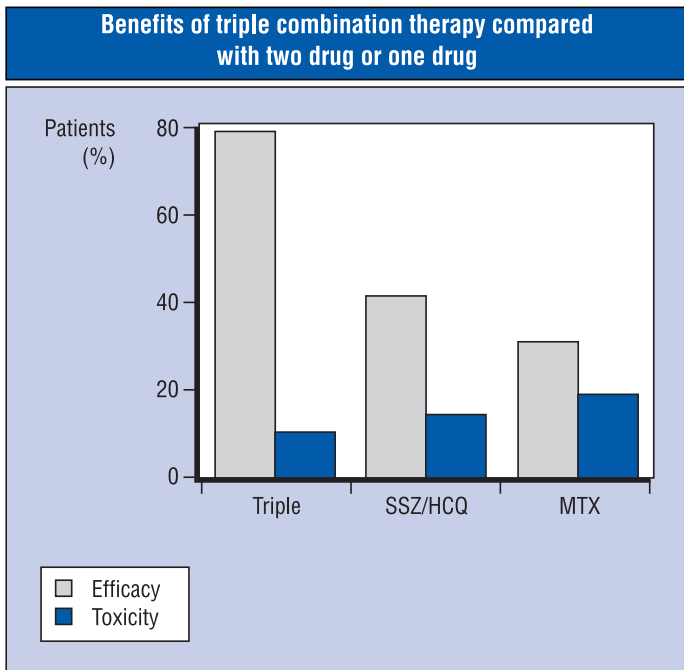
Several early trials combining methotrexate with sulphasalazine gave negative results. However James O'Dell led a landmark trial in the mid-1990s that showed this combination was more effective than methotrexate monotherapy. This trial involved 102 patients with RA of more than six months duration and who had failed at least one DMARD. The patients who received triple therapy with sulphasalazine (1 g daily),

hydroxychloroquine (400 mg daily) and methotrexate (7.5–17.5 mg weekly) had better clinical responses and fewer adverse reactions compared with those who received methotrexate alone (*see* Figure 4.6). Longer-term follow-up showed that this benefit continued for up to three years. Subsequent studies by the same group showed that all three components of the regime were required for optimal effect.

There is also evidence, from two large trials, that the combination of methotrexate, sulphasalazine and a steroid is effective in inducing remission and preventing joint damage in early RA.

### Methotrexate and cyclosporin

Although cyclosporin has been combined with a number of drugs, including gold and hydroxychloroquine, the only proven effective combination is with methotrexate. A key trial from the 1990s, led by Peter Tugwell,



**Figure 4.6.** HCQ, hydroxychloroquine; MTX, methotrexate; SSZ, sulfasalazine.

showed that in patients with an incomplete response to methotrexate adding cyclosporin improved joint counts and global assessments over six months. This benefit was also sustained for one year.

### **Methotrexate and leflunomide**

There is also evidence that administering leflunomide to patients with an incomplete response to methotrexate improves disease activity without triggering an excessive number of adverse events. This has been shown in both a small open study and a large randomized controlled trial. However, the approach remains controversial because of concerns expressed by regulatory bodies that this combination presents an unacceptable risk of liver toxicity.

### **Conclusions**

After disappointing early results, the last decade has seen significant progress in our understanding of the benefit of DMARDs in combination therapy. The most promising results have been obtained with methotrexate, particularly when combined with sulphasalazine and hydroxychloroquine, with cyclosporin or with leflunomide. It is now widely accepted that combination therapy for the treatment of RA can confer a significant advantage over traditional monotherapy. However, further work is required to clarify the optimum combination and duration of treatment and to better identify patients at significant risk of joint damage in whom such therapy is required early.

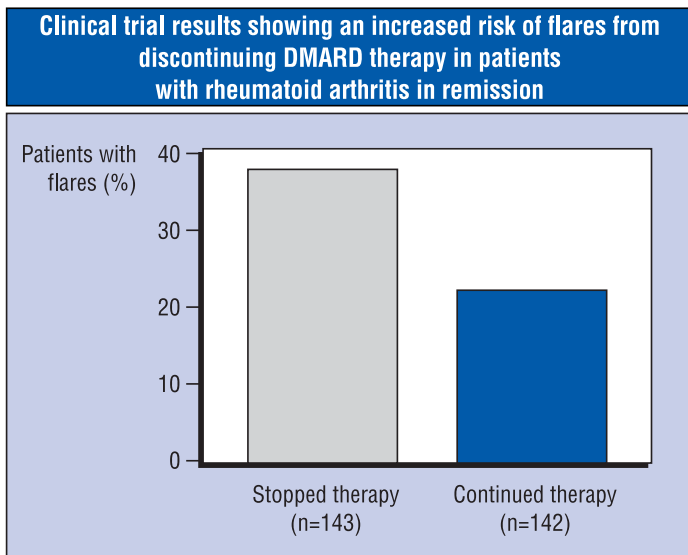
## **Current best practice with disease-modifying antirheumatic drugs**

### **Early treatment**

There is a growing consensus that DMARDs should be used as early as possible, the main problem being to establish which of a group of patients presenting with early synovitis has RA. Observational studies have shown that patients with active RA in whom DMARDs are started early have better functional and radiological outcomes after five years than when treatment is delayed. Randomized trials support these observational findings. Trials of early treatment with sulphasalazine, or weaker drugs like auranofin and hydroxychloroquine, all show that early treatment reduces disease activity. With sulphasalazine there is also evidence that early intervention reduces erosive damage.

### Withdrawing DMARDs

Discontinuation of DMARD therapy during remission increases the risk of a flare (*see* Figure 4.7). For this reason it is usually best to continue therapy throughout remission.



**Figure 4.7.** DMARD, disease-modifying antirheumatic drugs.

### Conclusions

There is no doubt that DMARDs are effective in RA. The evidence from randomized clinical trials is inevitably incomplete and best practice reflects not only that available evidence, but also the overall current consensus amongst practising clinicians. The key issues are:

- DMARDs are most effective in patients with active RA;
- DMARDs should be started early in the course of the disease;
- methotrexate is the drug of first choice; leflunomide or sulphasalazine are the best alternatives;

- if patients experience an adverse reaction to a DMARD a different DMARD should be used;
- patients who show an incomplete response should have another DMARD added;
- DMARDs should be continued in patients who have entered complete or partial remission.

## *Biologics in rheumatoid arthritis*

### **Introduction**

The introduction of biologic agents has revolutionized rheumatoid arthritis (RA) treatment in recent years. These therapies improve symptoms and modify the progression of RA. Their success has underlined the key roles of inflammatory cytokines in RA pathogenesis; particularly the roles of tumour necrosis factor alpha (TNF- $\alpha$ ) and interleukin-1 (IL-1).

The complex interactions of cytokines and the multiplicity of cytokine targets mean that it is difficult to predict the effectiveness and toxicity of cytokine-based interventions. Several treatment strategies involving cytokines have been explored, including:

- neutralizing cytokines using soluble receptors or monoclonal antibodies;
- receptor blockade;
- activating anti-inflammatory pathways with bioengineered versions of immunoregulatory cytokines.

Conventional drugs inhibit small molecules. However, as cytokines are large peptides they can only be inhibited by large molecules. Biologic drugs are proteins, based on immunoglobulins, which have been produced by new biotechnological methods. In the fullness of time it may be possible to replace these biologics with small molecules by blocking their target receptors or otherwise interfering with their mechanism of action.

### **Historical perspective**

The T cell was probably the first immunotherapeutic target in RA, reflecting the belief that T cells were the driving force behind RA. Open studies, conducted in the late 1980s and early 1990s, with antibodies to a variety of T-cell components gave positive results. However, subsequent larger randomized controlled trials showed a combination of lack of effect and excessive toxicity.

The different immunotherapeutic approaches tested during the 1990s are outlined in Table 5.1. With the exception of therapies targeting TNF- $\alpha$  or, to a lesser extent, IL-1, these immunotherapeutic approaches were ulti-

Potential targets for immunotherapy		
Target	Approach	Effect
T cells	Campath-1h	Beneficial but toxic
	Depleting anti-CD4	Relatively ineffective
	Non-depleting anti-CD4	Possibly effective but too toxic
MHC trimolecular complex	DR4/DR1 vaccine	Ineffective
Adhesion molecules	Anti-ICAM	Ineffective
Interferons	IFN- $\beta$	Ineffective
Cytokines	IL-4 and IL-10	Ineffective
	IL-1	Modest effect
	TNF- $\alpha$	Major benefit

**Table 5.1.** ICAM, intercellular adhesion molecule; IFN, interferon; IL, interleukin; MHC, major histocompatibility complex; TNF- $\alpha$ , tumour necrosis factor alpha.

mately unsuccessful. Although major benefits from targeting TNF- $\alpha$  are now obvious, the situation in the early 1990s was far from clear; indeed many experts thought inhibiting TNF- $\alpha$  would be ineffective. In one respect, TNF inhibition has not lived up to early expectations. It was initially suggested that inhibition of this 'boss' cytokine would switch off the abnormal cytokine network in RA and induce long-term remission. In fact ongoing therapy is required to maintain remission which has both health economic and toxicity implications.

After a period of consolidation, in which the main focus has been on implementation of therapies targeting TNF- $\alpha$  or, to a lesser extent, IL-1, in the clinic, further agents are being evaluated including CTLA4-Ig (T-cell co-stimulation blocker), MRA (an anti-IL-6 monoclonal antibody) and rituximab (a monoclonal antibody targeting CD20+ B cells). These are likely to be followed by further biologics aimed at novel targets until we reach the 'holy grail' of permanent or long-term remission with a single or short course of treatment.

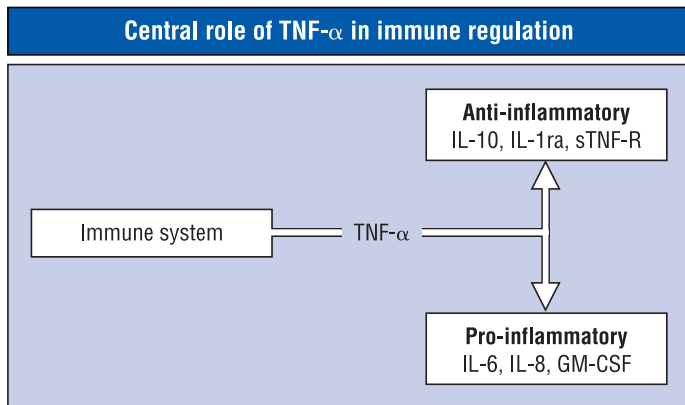
## Tumour necrosis factor alpha

### Roles in inflammatory diseases

TNF- $\alpha$  is an inflammatory cytokine. It is released by activated monocytes, macrophages and T lymphocytes and promotes inflammation. TNF- $\alpha$  binds to two receptors, the type 1 TNF receptor (p55) and the type 2 TNF recep-

tor (p<sub>xx</sub>). These receptors are found on many cell types. RA patients have high concentrations of TNF- $\alpha$  in the synovial fluid; synovial biopsy demonstrates that TNF- $\alpha$  is particularly localized to the junction of the inflammatory pannus and healthy cartilage. A high concentration of TNF- $\alpha$  is associated with the erosion of bone.

There is a widely held belief that TNF is a 'pivotal' cytokine. This role is shown in Figure 5.1. After stress, TNF is the first cytokine to be detected in the blood, and it appears to act as the 'fire alarm' that calls in the 'firefighters' (inflammatory cells) through the expression of adhesion molecules and chemokines. In a model of a 'normal' immune response, blocking TNF markedly reduced and delayed the production of IL-1 and IL-6. This finding suggests that the TNF-dependent cytokine cascade is relevant in both pathological tissues in disease and as part of the normal homeostatic physiological inflammatory response.



**Figure 5.1.** *GM-CSF, granulocyte and macrophage colony-stimulating factor; IL, interleukin; IL-1ra, IL-1 receptor antagonist; TNF, tumour necrosis factor; sTNF-R, soluble TNF receptor.*

Studies in animal models of arthritis have shown that antagonism of TNF- $\alpha$  with anti-TNF antibodies is a viable therapeutic strategy. Subsequent proof-of-concept studies in patients with RA concurred that blocking TNF improved symptoms.

Currently, there are three TNF- $\alpha$  inhibitors that can be used to treat RA (see Table 5.2). Despite the differences between them, all these TNF inhibitors



Currently available TNF- $\alpha$ inhibitors			
TNF- $\alpha$ inhibitor	Site of action	Dosage	Methotrexate co-therapy
Etanercept	Binds TNF- $\alpha$ , lymphotoxin and competitive inhibitor of TNF receptor	Subcutaneous twice weekly	Optional to co-prescribe
Infliximab	Binds soluble and transmembrane TNF- $\alpha$ and inhibits binding of TNF- $\alpha$ to TNF receptors	IV administration every 4–8 weeks	Essential to co-prescribe
Adalimumab	Binds soluble and transmembrane TNF- $\alpha$ and inhibits binding of TNF- $\alpha$ to TNF receptors	Subcutaneous fortnightly	Optional to co-prescribe

**Table 5.2.** TNF- $\alpha$ , tumour necrosis factor alpha.

have a relatively rapid onset of action with the majority of patients improving within a few weeks. Despite this prompt and continued response, drug-free remission remains rare. Many patients have increased disease activity when they discontinue therapy, and therefore the majority continue on long-term treatment.

### Indications

TNF- $\alpha$  inhibitors should be considered in those with active RA enduring after an adequate trial of other effective disease-modifying antirheumatic drugs (DMARDs; eg, methotrexate). Within the UK, current guidance is for two effective DMARDs to be given for six months; one of which must be methotrexate. TNF- $\alpha$  inhibitors can be added to pre-existing treatment with DMARDs. In some cases they may replace DMARDs. Their use as first-line therapy for the treatment of RA should, at present, be limited to research studies.

### Etanercept

Etanercept is a recombinant soluble p75 TNF-receptor–Fc fusion protein. It is comprised of two dimers; each has an extracellular, ligand-binding portion of the higher-affinity type 2 TNF receptor (p<sub>xx</sub>), which is linked to the

Fc portion of human IgG1. This fusion protein binds to both TNF- $\alpha$  and TNF- $\beta$  and prevents them from interacting with their receptors. Etanercept is administered subcutaneously at a dose of 25 mg twice a week. This dosing reflects its half-life of about four days. It can be given alone or in combination with other DMARDs such as methotrexate to enhance efficacy.

### **Infliximab**

Infliximab is a chimeric IgG1 anti-TNF- $\alpha$  antibody in which the antigen-binding region is derived from a mouse antibody and the constant region originates from a human antibody. It binds to soluble and membrane-bound TNF- $\alpha$  with high affinity, blocking the binding of TNF- $\alpha$  to its receptors. Infliximab also kills cells that express TNF- $\alpha$  through antibody-dependent and complement-dependent cytotoxicity. There is considerable inter-patient variability in the pharmacokinetics of infliximab. The standard dosage is 3 mg per kg every eight weeks. However, trough concentrations at eight weeks after a standard dose vary enormously between patients. Shortening the interval between doses may be more effective than increasing the dose in raising the trough levels, although either approach can be utilised. Unlike the other two anti-TNF agents, where concomitant DMARD therapy is optional and designed to improve efficacy, infliximab must be given with methotrexate. This is recommended to prevent the formation of human antichimeric antibodies (antibodies against the mouse part of the chimeric molecule) which are associated with a higher rate of infusion reactions. Such antibodies also reduce the half-life of infliximab but to date this has not proved to be associated with reduced efficacy in practice.

### **Adalimumab**

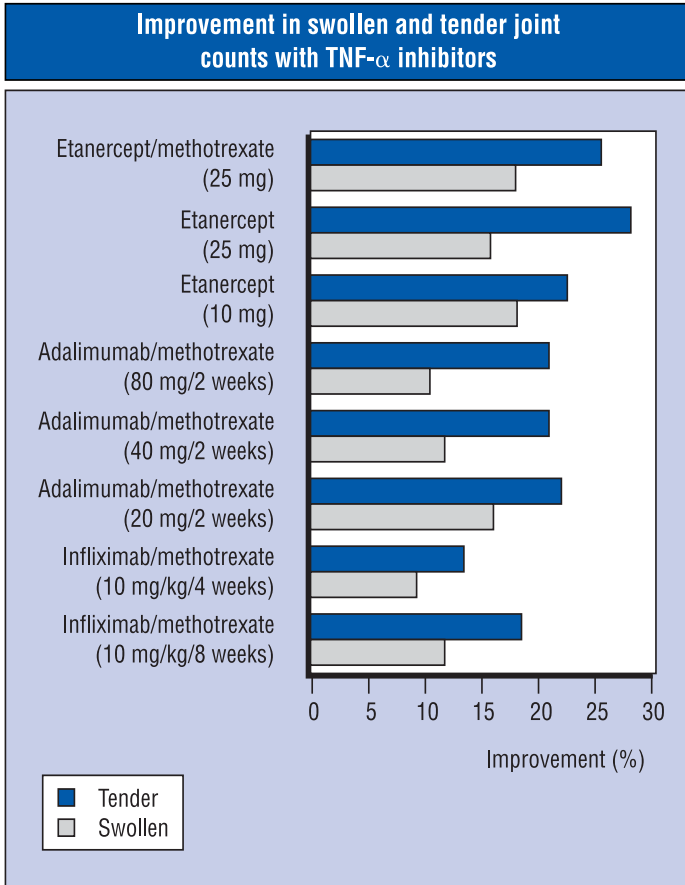
Adalimumab is a recombinant human monoclonal anti-TNF- $\alpha$  antibody. It binds to human TNF- $\alpha$  with high affinity and, as a consequence, stops the cytokine binding to its receptors. Adalimumab also lyses cells that express TNF- $\alpha$  on their surface. The drug is given by subcutaneous injection. The absorption rate is slow; peak concentrations are achieved after 120 hours. Although the absorption rate differs between patients, adalimumab is usually given fortnightly; it can be given alone or in conjunction with other DMARDs to enhance efficacy.

### **Efficacy**

TNF- $\alpha$  inhibitors, when given in adequate doses, produce major improvements in symptoms, signs and laboratory measures of RA. This improvement occurs within 12 weeks of starting treatment. There is no evidence that any particular TNF- $\alpha$  inhibitor is more effective than any other. As

such, any agent can be chosen as initial therapy. Benefit from switching to another TNF- $\alpha$  inhibitor when the first has failed is well documented, though not supported by evidence from clinical trials.

Individually important responses should occur within 8–12 weeks. Treatment should not be continued if there is no evidence of benefit. In patients with an incomplete response, increasing the dose or reducing dosing intervals may provide additional benefit, as may the addition or substitution of other DMARDs. Figure 5.2 shows the potential treatment benefit



**Figure 5.2.** TNF, tumour necrosis factor.

**Overall response rates in key trials of anti-TNF- $\alpha$  therapy**

Treatment	N	ACR-20	ACR-50	ACR-70
Placebo	80	11	5	1
Etanercept	78	59	40	15
Placebo/methotrexate	30	27	3	0
Etanercept/methotrexate	59	71	39	15
Placebo/methotrexate	84	20	5	0
Infliximab/methotrexate	83	50	27	8
Placebo	110	19	8	2
Adalimumab	113	46	22	12
Placebo/methotrexate	62	15	8	5
Adalimumab/methotrexate	67	67	55	27

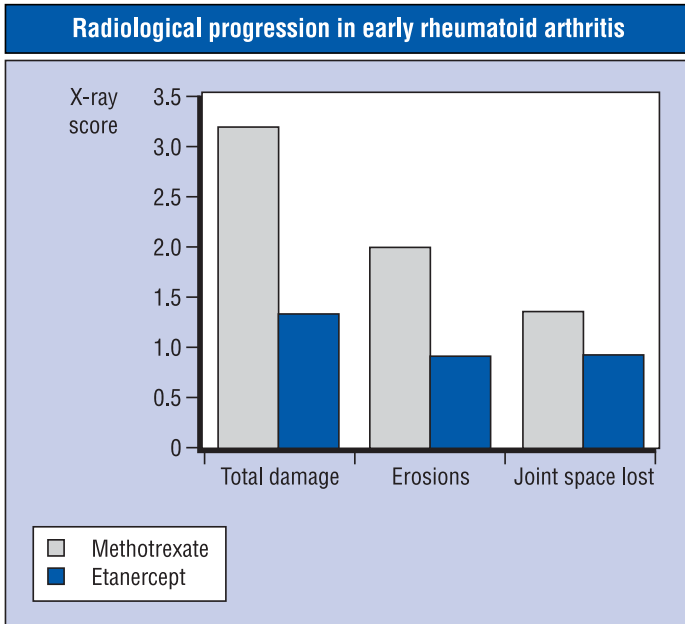
**Table 5.3.** ACR, American College of Rheumatology; TNF- $\alpha$ , tumour necrosis factor alpha.

from TNF- $\alpha$  inhibitors. Table 5.3 summarizes the effect of these treatments on American College of Rheumatology (ACR) response criteria.

There is growing evidence that TNF- $\alpha$  inhibitors slow or prevent radiographic progression in RA (*see* Figure 5.3), particularly in early RA. Combined therapy using methotrexate and a biologic is associated with an even greater reduction in the rate of progression. However, though erosive radiological damage is one of the best markers of ultimate disability levels, the long-term clinical relevance of slowing radiological damage remains uncertain in terms of the degree of disability prevented. Therefore influencing radiographic progression should not be the only factor influencing clinical decision making.

### Adverse effects

Local transient reactions such as minor redness and itching at the injection site are common with etanercept and adalimumab. Minor symptoms such as headache and nausea are common in patients during infliximab infusions. Symptoms suggesting hypersensitivity to infliximab infusions (eg, urticaria) are uncommon but well described; serious anaphylaxis is rare. Antihistamines, steroids and adrenaline should be kept available while infusions are being given, though they are seldom needed.



**Figure 5.3.**

Serious and opportunistic infections occur in patients receiving TNF- $\alpha$  treatment, but, with the exception of intracellular infections like tuberculosis, it is unclear how much higher their incidence is compared to patients with severe RA treated with DMARDs or steroids. Studies examining this using data from Biologics Registries is currently in progress. TNF- $\alpha$  inhibitors are contraindicated in the presence of serious infections (eg, septic arthritis, infected prostheses, acute abscesses and osteomyelitis) and should be avoided in patients with serious viral infections, particularly hepatitis B and C.

A notable concern with TNF- $\alpha$  inhibitor treatment is the increased susceptibility to primary tuberculosis and the propensity for prior tuberculosis to be reactivated. The risk of reactivation of latent tuberculosis is highest during the first 12 months of treatment; maximum vigilance is therefore needed during this period. All patients should be screened for latent tuberculosis through a detailed history and examination, plus screening tests such as skin tests and a chest radiograph; the nature of the screening programme depends

on the incidence of tuberculosis, and hence the likely prior exposure, in the country and area concerned so local guidelines should be followed. Anti-tuberculosis treatment or prophylaxis should be considered for patients who may be at risk and expert respiratory advice should be sought. Some experts consider TNF- $\alpha$  inhibitors may be started as soon as the antituberculosis treatment is started, although there is debate over the best timing.

Optic neuritis, new-onset demyelinating disease, demyelinating-like disorders and exacerbations of previously quiescent multiple sclerosis have all been reported in patients receiving TNF- $\alpha$  inhibitors. Demyelinating disease and optic neuritis are therefore contraindications to TNF- $\alpha$  inhibitor treatment.

A few cases of pancytopenia and aplastic anaemia have been reported with TNF- $\alpha$  inhibitors. If these problems occur, treatment should be stopped and patients evaluated for underlying diseases or other causative drugs. No monitoring is currently recommended, as these are rare events.

Although heart failure is associated with high levels of TNF- $\alpha$ , there is no evidence that TNF- $\alpha$  inhibitors are clinically useful in this setting; in fact they may even increase mortality. Biologic agents should therefore be used with caution in patients with significant heart failure.

Lymphoma has been reported with all three TNF- $\alpha$  inhibitors, but it remains uncertain whether there is a causal relationship because the incidence of lymphoma is increased in severe RA irrespective of immunotherapy. The types of lymphoma in RA patients treated with immunotherapy are similar to those seen in RA patients receiving other treatments. There is no evidence that TNF- $\alpha$  inhibitors are associated with malignancies other than lymphoma.

### **Immune responses to TNF- $\alpha$ inhibitors**

Patients develop antibodies to etanercept and adalimumab, but the clinical significance of this effect is unknown. As discussed above, human antichimeric antibodies to infliximab are common and increase the risk of infusion reactions. They also accelerate the clearance of infliximab; potentially this could reduce efficacy but the effect has not proved important in practice. These antibodies form less often when infliximab is given in combination with methotrexate, which is why this combination approach is standard for infliximab administration.

### **Interleukin-1-blocking agents**

Only one IL-1-blocking agent, anakinra, is currently available. Anakinra is a recombinant human IL-1 receptor antagonist. It is expressed in *Escherichia*

*coli* and has an amino acid sequence identical to native human IL-1 receptor antagonist (IL-1ra) except for the addition of an N-terminal methionine residue. Anakinra inhibits the action of IL-1 by competitively blocking the binding of IL-1 to IL-1 receptors on responsive target cells. The half-life of anakinra following subcutaneous administration ranges from three to six hours. There is no evidence of drug accumulation in RA patients after daily dosing for up to 24 weeks.

### Clinical use

Anakinra is used for treating active RA. Within Europe it is given in combination with methotrexate; in North America it can be given as monotherapy. Anakinra may be used after an adequate trial of another effective DMARD (eg, methotrexate), administered daily by subcutaneous injection. This drug leads to significant improvements in symptoms, signs and laboratory measures of RA within 2–16 weeks. There is an even more obvious effect on patient-related outcomes such as the disability measure Health Assessment Questionnaire (HAQ). Treatment should be continued if clinically relevant improvement occurs. There is no reason to combine anakinra with anti-TNF- $\alpha$  therapy; the available evidence suggests this approach has no enhanced effect. Anakinra is not widely used and, within the UK, is not recommended for use in routine clinical care because it is not sufficiently cost-effective.

### Side effects

Injection site reactions are frequent, affecting up to 70% of patients. These reactions rarely require treatment and seem to diminish with continued use.

Risk of infections, including serious infections, may be elevated slightly in association with anakinra. Treatment is contraindicated in the event of serious infection. There is no evidence of a treatment-related increased incidence of tuberculosis. Treatment with IL-1-blocking therapy in patients with any infection should only be resumed once that infection has been adequately treated.

## Novel biologic agents

A number of new biologics are under development. It is not possible to predict which will reach the clinical setting.

Four novel agents have been evaluated in detail:

- CDP 870 is a polyethylene glycol (PEG)ylated anti-TNF antibody fragment, which may have some advantages over the three existing anti-TNF- $\alpha$  inhibitors;

- rituximab is a B-cell inhibitor, which is currently used to treat lymphomas; initial controlled trials suggest it reduces RA disease activity;
- CTLA4-Ig is a fusion protein: the cytotoxic T lymphocyte-associated antigen 4-IgG1. It is the first in a new class of drugs known as co-stimulation blockers, and binds to specific sites on antigen-presenting cells, blocking their interaction with T cells – controlled trials are in progress;
- MRA is a recombinant human anti-IL-6 receptor monoclonal antibody that inhibits the function of IL-6 – controlled trials have shown it reduces disease activity in RA.

## **Economic considerations**

The biologics, particularly anti-TNF- $\alpha$  inhibitors, are effective and have a good tolerability profile; in the relatively short term (such agents have only been licensed for five years) they also have a fairly good risk profile. For these reasons, were they not so expensive, they might be first choice for many patients. The annual treatment cost of a biologic is a minimum of £10,000, compared with less than £2000 with conventional DMARDs such as methotrexate. However, this cost must be viewed in relation to the high impact of RA on healthcare budgets and on the quality of life of the patients. The argument over the cost-effective use of these new drugs is complex. At present, the consensus is that it is reasonably cost-effective to biologics in patients with active disease who have failed to respond to a number of conventional DMARDs.



# *Systemic and local steroids*

## **Introduction**

Steroids have been used to treat inflammatory arthritis for over 50 years. They rapidly became the leading treatment for active disease soon after they were shown to be effective in rheumatoid arthritis (RA). Steroids often show dramatic short-term effects on inflammation, but their clinical benefits diminish with time. Side effects limit their use.

Steroids are usually given orally. Intravenous pulses and intramuscular, soft tissue or intra-articular injections are also used, mainly to minimize or avoid side effects and to deal with acute or local problems. The choice of preparation depends on the required anti-inflammatory potency and duration of action. Cortisone and hydrocortisone are not recommended for long-term use in arthritis. Prednisolone has mainly glucocorticoid (anti-inflammatory) activity; it is the most commonly used oral corticosteroid for long-term treatment.

## **Pharmacology and mechanism of action**

Steroids have complex anti-inflammatory and immunomodulatory effects. They inhibit migration of leucocytes to sites of inflammation, and interfere with the function of leucocytes, endothelial cells and fibroblasts. In addition, they suppress production and release of factors involved in the inflammatory response, including cytokines, prostaglandins and leukotrienes.

Steroids are metabolized in the liver. Their effects may be reduced by drugs that induce liver enzymes (eg, phenytoin, phenobarbitone and rifampicin). Blood levels of steroids may be raised in liver failure. Anticoagulant doses may need to be reduced when given concomitantly with steroids.

## **Beneficial effects**

Steroids reduce the features of inflammatory synovitis, such as the number of swollen joints. They also reduce the erythrocyte sedimentation rate (ESR) and other acute phase markers. In high dose they reduce radiological erosive damage but such doses have unacceptable toxicity; there is some suggestion that lower doses may also have such an effect but the evidence is incomplete. In extra-articular disease, steroids can reduce inflammatory changes at other sites; for example, within the blood vessels in vasculitis.

## Systemic steroids

### Oral steroids in established disease

Oral steroids have an immediate benefit through reducing inflammatory synovitis and also some of the extra-articular features seen in a minority of RA patients. They are used in the following situations:

- in patients refractory to other treatments (including both non-steroidal anti-inflammatory drugs [NSAIDs] and disease-modifying drugs such as methotrexate) to obtain symptomatic control;
- in defined combination regimes particularly in early RA
- in elderly patients, in whom steroids may be better tolerated than anti-inflammatory drugs;
- during pregnancy, when other drugs may be contraindicated;
- to treat extra-articular features such as vasculitis.

In almost all circumstances, the dose should be low (in the region of 7.5 mg daily). The one exception is to control extra-articular features such as vasculitis, when high doses may be needed depending on the clinical situation.

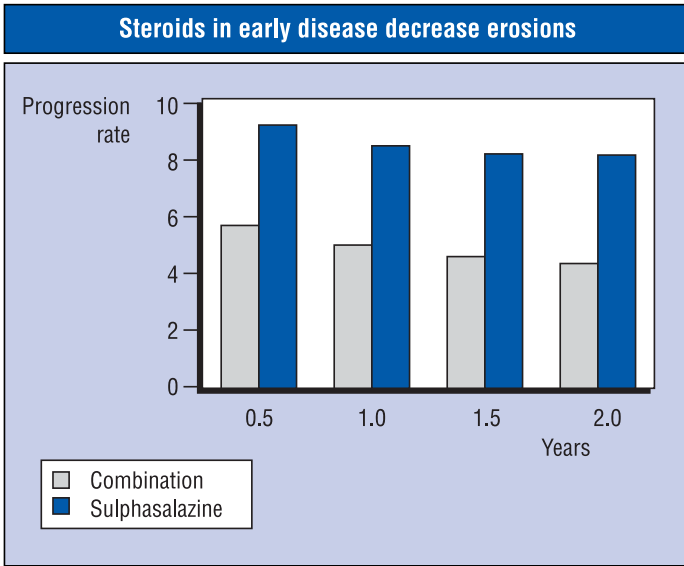
Some patients benefit symptomatically from the addition of low-dose oral prednisolone to disease-modifying drug therapy. However, such an approach is not usually beneficial in the longer term as the improvement is not sustained beyond six to nine months, there is often a rebound flare in disease activity as the dose is reduced, and there are concerns about long-term toxicity.

### Oral steroids in early RA

Debate continues over the value of oral steroids in the early phase of RA. Some trials in early disease have suggested that steroids reduce the progression of erosive damage when used alone or in conjunction with disease-modifying drugs (*see* Figure 6.1). This effect is preceded by a short-term reduction in the activity of inflammatory synovitis and an improvement of symptoms. The limitation of using steroids in this way, apart from the risk of adverse effects, is that the effect on erosions may be both small and short lived.

### Systemic steroid injections for flares

Intramuscular steroid injections, such as 120 mg methylprednisolone, are often used to treat an arthritis flare or given when disease-modifying drugs such as methotrexate are being started. This approach is simple to administer and rarely causes significant side effects if continued for up to four



**Figure 6.1.**

injections only. However, there is an incomplete body of evidence to support its use beyond three or four doses. A recent study did not demonstrate benefit from the addition of regular intra-muscular steroids over two years in patients whose disease was inadequately controlled; in contrast, steroid-induced side effects were clearly increased. Intravenous steroids are rarely used because, although rapidly effective, they often are followed by a severe rebound in symptoms after two to three months; there are also reports of fatalities due to arrhythmias.

### Side effects

The disadvantages of systemic steroid use are almost entirely related to their side effects, which are frequent and serious (*see* Table 6.1).

Patients are typically concerned by general changes such as weight gain and oedema. On balance, the cardiovascular risks, especially accelerated atherosclerosis, are the main threat to health.

Certain adverse events are preventable; this is particularly true for osteoporosis. Oral steroid treatment is associated with a significant increase in

Side effects of systemic steroids	
General	Weight gain Oedema Redistribution of body fat
Skin changes	Atrophy Acne Bruising Striae
Cardiovascular	Hypertension Hyperlipidaemia Thrombosis Accelerated atherosclerosis
Gastrointestinal	Dyspepsia Peptic ulceration Gastrointestinal bleeding Pancreatitis
Psychological	Mood changes Insomnia Depression/psychosis
Endocrine	Impaired glucose tolerance Suppression of the HPA axis Growth retardation in children
Bone	Osteoporosis Avascular necrosis
Other	Myopathy Glaucoma Cataracts Increased susceptibility to infection

**Table 6.1.** HPA, hypothalamo–pituitary–adrenocortical.

fracture risk at the hip and spine. Though the greatest increase in risk is seen with high-dose therapy, increased risk is also seen at doses of prednisolone <7.5 mg daily. Fracture risk increases rapidly after the onset of steroid treatment and declines equally rapidly after cessation of therapy. Loss of bone mineral density associated with oral steroids is therefore greatest in the first few months of their use. Patients at high risk of fracture, particularly those aged 65 years or over and those with a prior fragility fracture should commence bone-protective therapy at the time of starting steroids. In other individuals, measurement of bone mineral density using dual-energy X-ray absorptiometry (DEXA) is recommended for

assessment of fracture risk in individuals treated with glucocorticoids. General measures, such as good nutrition, adequate dietary intake of calcium and appropriate physical activity, should be encouraged as part of a preventive strategy. More specific preventive treatment includes calcium and vitamin D supplementation. Other treatments may be needed; most therapies indicated for osteoporosis can be used to prevent steroid-induced bone loss. Bisphosphonates are often used; the usual current regimes are weekly treatment with either alendronate (70 mg) or risendronate (35 mg) is effective.

## Local steroids

### Efficacy and usage

Steroid injections are used in individual joints to control local synovitis, as an adjunct to disease-modifying drugs. Patients usually show an improvement in symptoms that lasts for a few weeks to a few months. This approach is more commonly used for large joints such as the knee. The use of steroid injections is summarized in Table 6.2

Other sites that can be injected include entheses – where tendons are inserted into bones – and areas of compression, such as the carpal tunnel when there is median nerve compression.

Injection of the sacroiliac joints may be beneficial for patients with seronegative arthritis, who have sacroiliac joint pain as part of a spondylo-

Local steroid injections	
Sites	Peripheral joints Tendon insertions Carpal tunnel Sacro-iliac joints
Indications	Uncontrolled local inflammation Local compression
Adverse effects	Infection Tendon rupture Skin thinning Depigmentation

**Table 6.2.**

arthropathies (SpA). This is best carried out under X-ray imaging control or an alternative imaging method.

**Side effects**

Adverse effects of local steroid injections are uncommon. Iatrogenic infection is the most serious but least common complication, occurring in <1 in 10,000 cases. More common, but less clinically important complications include local irritation, atrophy of soft tissues at the sites of injection and post-injection flares. There have been isolated reports of weakening and even rupture of tendons after local steroid use. Some patients suffer a loss of pigmentation, which can be permanent; this can be a problem for dark-skinned individuals.

## Non-pharmacological therapy

### Multidisciplinary approach

The treatment of inflammatory arthritis is not entirely dependent on drug therapy. Instead, medication needs to be combined with a range of non-pharmacological management strategies, involving a multidisciplinary team of experts. Comprehensive rehabilitation involving a multidisciplinary team of clinic-based health professionals is as effective as inpatient team care programmes.

Members of the multidisciplinary team include:

- **Specialist rheumatologist** – to make initial diagnosis, establish a treatment plan and review its efficacy, detect complications and provide support for other team members
- **Specialist nurses** – to co-ordinate treatment, monitor the safety and tolerability of drug therapy, counsel patients and provide education and advice on the disease. These nurses provide long-term support for patients throughout their disease;
- **Physiotherapists** – to improve mobility by applying physical therapy on individual joints, and therefore to increase patient independence;
- **Occupational therapists** – to help patients achieve independent living by offering advice and providing a range of aids and adaptations for use in the home and at work;
- **Podiatrists** – to improve foot function by correcting deformity and abnormal pressure distribution by adapting footwear or by performing minor surgery on the feet.
- **Other Health Professionals** – less common members of the team include pharmacists (who can provide assistance with drug therapy and monitoring), orthotists (who provide and fit complex appliances) and psychologists (who can provide essential support in adapting to chronic disease)
- **General practitioners and primary care team** – to provide day-to-day care for patients, sharing care as appropriate with the secondary care team

A shared-care approach between primary and secondary care physicians, and facilitated by practice nurses and rheumatology nurse specialists,

ensures optimum monitoring of drug treatment efficacy and prompt identification of disease- or treatment-related complications.

## Communication

Effective communication between the patient and members of the health-care team is essential. Communication behaviours during the medical consultation are linked to patient satisfaction and health outcomes. Although there is limited information specifically on medical interactions with rheumatoid arthritis (RA) patients, the expertise on patient–doctor communication in chronic disease in general can be reliably applied in arthritis. The consensus is that patients' expectations of medical encounters are not always fulfilled and many patients desire better sharing of information and a greater participation in the decision-making process. Establishing such patient-centred care is a challenging but essential goal for all clinicians.

## Therapies

Table 7.1 summarizes the non-pharmacological therapies and their degree of effect in early or established RA.

Range of non-pharmacological therapies			
Therapy regimen		Early disease	Established disease
Patient education		++	+
Rest	Complete bed rest	+	+
	Resting affected joint	++	++
Physical therapy	Maintain range of movement	++	+
	Prevent muscle weakness	+	++
Occupational therapy	Joint protection	++	+
	Adaptation	+	++
Podiatry	Preventive treatment	++	+
	Footwear adaptations	+	++

**Table 7.1.** ++, strong evidence; +, weak evidence



## Patient education

- Members of the multidisciplinary team should follow a common approach to education to ensure the information provided to patients is consistent.
- Patient education leaflets are a useful resource to increase knowledge about the disease.
- Interventions that include a psycho-behavioural component in addition to providing information have enhanced results, improving pain relief and joint protection and reducing functional disability. However, these approaches require relatively intensive input from clinical staff.
- Patient-led self-management education programmes are increasingly popular but their effectiveness is uncertain and they are not useful in all settings.

## Rest

Historically, prolonged bed rest and joint immobilization in hospital were used to control disease activity in RA. This practice required extensive inpatient facilities such as those in the 'spa hospitals' of the past. This strategy no longer has a place in the management of arthritis. Rest helps symptom control in acute disease flares, but bed rest is not useful as it does not alter the course of the disease and may exacerbate deleterious musculoskeletal effects such as muscle weakness.

## Physical therapy

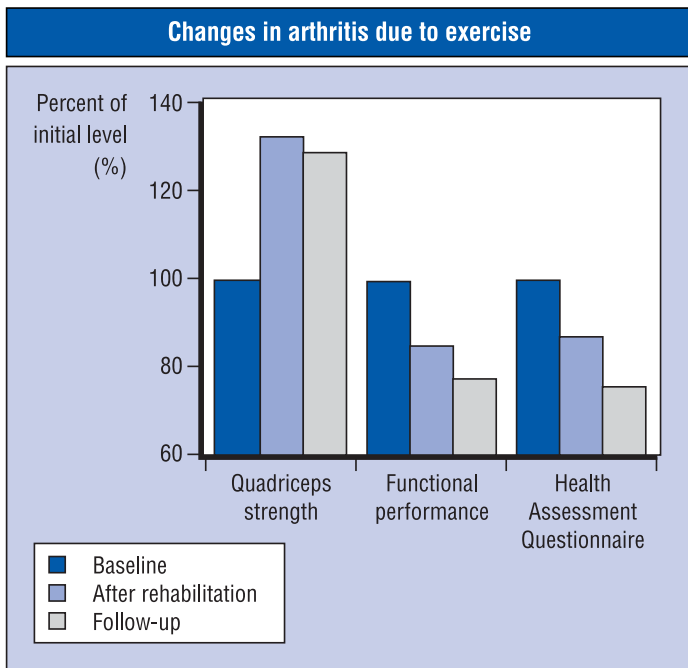
The principal aim of physiotherapy is to maintain function.

This mode of therapy benefits most patients with inflammatory arthritis, as they have pain, limited movement, impaired muscle function and consequent decreased fitness. A wide range of treatment modalities can be used:

- **massage** to improve flexibility, reduce swelling and enhance general well-being;
- **heat and cold** to reduce pain and stiffness, muscle spasm and swelling;
- **splinting** to reduce pain and inflammation, prevent deformities and support joints;
- **electrotherapy** to reduce pain. Treatment modalities such as interferential, ultrasound and low-power laser are often used. Some modalities (eg, diathermy treatment) produce local heat. Others (eg, transcutaneous electrical nerve stimulation [TENS]) alleviate pain by

reducing painful efferent nerve activation through increased afferent nerve stimulation;

- **exercise** to reduce joint pain and maintain joint function. A carefully graded programme is needed that avoids exacerbating joint symptoms and general fatigue, while increasing muscle strength, joint range of motion and general aerobic fitness. The chosen regime must be appropriate for the age, general fitness and level of disease activity in the individual patient. There is no evidence that exercise results in flares in disease activity scores. Aerobic exercise intensity should be 'moderate to hard' and increase maximum heart rate by 60–85%; three sessions per week, each lasting 30–60 minutes is reasonable. Strengthening exercises should also be 'moderate to hard' and focus on achieving 50–80% maximum voluntary contraction and be performed two or three times weekly. Figure 7.1 shows an example of the effects of exercise in arthritis.



**Figure 7.1.** Changes in arthritis due to exercise.

- Exercise is safe and effective in most patients with arthritis.
- Exercise can also improve cardiovascular fitness and general health.

Most physical treatment programmes utilize a combination of several different modalities over a number of sessions. A key issue is to encourage regular physical activity to reduce the risk of co-morbidities linked to the sedentary lifestyles too often adopted by people with established arthritis.

In contrast to drug therapy, there is limited evidence that physiotherapy benefits patients mainly due to the lack of research in this area. The main problem is that, unlike drug therapy, great variation exists both from the complex package of treatments a patient may receive and the ways in which each individual therapist may administer the treatment. Conventional trials may not be ideal in this setting and other methods of demonstrating clinical effectiveness are needed.

## Occupational therapy

Occupational therapists focus on:

- improving the patients' ability to perform daily activities;
- facilitating successful adaptations to RA-related disruptions in lifestyle;
- preventing losses of function;
- improving or maintaining an optimum psychological status.

Therapists work collaboratively with patients to achieve a balanced lifestyle within the context of the person's illness and disability. A range of interventions is used with particular focus on maintaining hand function, since they are used in almost every activity in life.

## Joint protection

Joint protection strategies aim to maintain functional ability through altering working methods, educating the patient on correct joint and body mechanics and encouraging the use of assistive devices. They are initially taught to patients by occupational therapists or other staff and should become part of each patient's self-management plan.

Theoretically, reducing the load and effort required to carry out daily activities should reduce strain on joint structures weakened by arthritis. Such joint protection can improve and maintain function and health status. Energy conservation training can also increase physical activity levels. As standard training techniques are not optimally effective in achieving joint protection, occupational therapists are developing new approaches including cognitive-behavioural training.

### Activities of daily living

This measure of activity performance incorporates personal care and extends to other activities such as home care and maintenance, shopping, family care, outdoor mobility, driving and communication. Therapists problem-solve with patients and provide training in alternative methods to perform an activity or in the use of assistive devices. They also facilitate environmental modifications, such as home reorganization and adaptation (eg, using stair rails and access ramps). A wide range of assistive devices is available, such as adapted knives and taps.

### Hand exercises and splinting

As mentioned previously, the importance of hand function for everyday living makes it a focus area for attention. Patients are taught a range of simple resistive hand exercises to maintain range of motion and strengthen muscles. Splints are also used to support the hands and wrists. Splinting may also be useful for supporting other joints.

## Podiatry

Feet are often the first areas to be affected in inflammatory arthritis. Specific problems can occur in the forefoot, midfoot or hindfoot; all of which can be treated by podiatrists to make walking less painful. For example, ulcers and corns that have been caused by foot deformities can be treated by debridement and similar approaches. Podiatrists can use various different assistive devices to improve foot function. These include:

- **Orthoses** – these special types of insole are fitted into normal shoes and improve walking by minimizing the pressure on affected joints.
- **Shoes** – as well as moulded insoles, shoes can be selected that are roomy enough to accommodate the feet and orthoses without adding unnecessary pressure. In a few patients special surgical shoes may be required
- **Protective shields** – these can act as guards for toes or provide padding to relieve pressure and reduce friction.

## Dietary intervention

Although patients with inflammatory arthritis often believe their diet is implicated in the onset or worsening of their arthritis, and collectively spend large sums of money on unproven dietary treatments, there is little evidence that dietary changes benefit inflammatory arthritis. The single exception to this is the possible benefit from fish oils which is discussed below.

However, healthy eating is a sensible policy for patients with arthritis and it is reasonable to advise patients to:

- eat a variety of foods;
- balance their food intake with physical activity;
- choose a diet:
  - with plenty of grain products, vegetables and fruits;
  - low in saturated fat and cholesterol;
  - with only moderate levels of sugars.

Patients with inflammatory arthritis are at nutritional risk for several reasons:

- they may have weight loss and cachexia linked to cytokine production;
- the medication may compound nutritional problems. For example, patients receiving methotrexate may have folic acid deficiency. Anti-inflammatory drugs often result in gastritis or peptic ulcer, and these frequently reduce the desire to eat;
- patients often have some vitamin or mineral deficiencies, with low levels of folic acid, vitamin C, vitamin D, vitamin B<sub>6</sub>, vitamin B<sub>12</sub>, vitamin E, calcium, magnesium, zinc and selenium. Food should always be the preferred source for such vitamins and minerals, but in some cases supplements may be needed. Examples include giving folic acid to patients taking methotrexate, or calcium and vitamin D supplements to those at risk of osteoporosis.

In a few patients, specific foods may exacerbate RA symptoms. Avoiding such foods or food groups has at least limited short-term benefits, and is probably not an unreasonable approach provided it does not result in a nutritionally inadequate diet.

Elimination diets, aiming to detect food hypersensitivities, are used by some patients. These avoid a specific food or group of foods (eg, milk, meat or processed foods) that commonly cause allergy. They are eliminated from the diet for a specific period of time and then gradually reintroduced one at a time to determine which, if any, cause a reaction. Despite the apparent logic of such an approach, it is time consuming and complex and runs some risk of nutritional deficiency unless carefully supervised. For the majority of patients, there is little to be gained from using exclusion diets.

The potential role of dietary fatty acids in modulating the inflammatory process is an area of current interest; in particular, omega-3 fatty acids that are found in fish oils. Taking such fish oils as dietary supplements has disadvantages, including changes in blood clotting, and triggering of diarrhoea and gastric disturbances, though overall they are relatively well-tolerated.

They have been proven to have a mild anti-inflammatory effect and there is no reason why interested patients should not use them.

## Complementary therapies

Patients with arthritis commonly use such treatments, possibly partly as a reflection of the perceived inadequacies of orthodox medical treatments for the condition, but also because it enables them to regain a greater level of control over their treatment choices. Commonly used therapies include homeopathy, manipulation, including chiropractic and osteopathy, acupuncture and herbal medicines; some patients also use less 'medical' treatments such as aromatherapy or massage.

There is little evidence for any of these in inflammatory arthritis. A recent systematic review of herbal medicines in RA suggested moderate support for gamma linolenic acid (found in some herbal medicines) in terms of reducing pain, stiffness and joint tenderness. The review also identified controlled trials of other agents, including capsaicin, curcumin, feverfew, flaxseed oil, *Boswellia serrata* and other traditional ayurvedic medicines, reumalex and *Tripterygium wilfordii*. However, because these were only single studies no definite conclusions could be drawn.

Acupuncture has been shown to reduce pain in a variety of circumstances. There are no controlled trials of manipulative therapies such as chiropractic or osteopathy in rheumatoid arthritis; however, patients considering such treatment should be warned of the potential for serious damage from neck manipulation since neck stability is reduced by RA. Previous studies of homeopathy in arthritis have been complicated by the difficulty in separating the effect of the treatment from the effect of the consultation; further studies are in progress.

## Orthopaedic surgery

Surgical intervention has been an important development in the management of inflammatory arthritis. Unlike medical care, surgery modifies the consequences of disease in the joints, reducing or eliminating pain for several decades. Although some patients require other procedures including cervical surgery and foot surgery, the main operations used in inflammatory arthritis are total and partial joint replacements.

Joint replacements are among the most effective surgical interventions ever devised and may allow patients to return to normal functioning. The available literature, most of which comes from observational studies rather than controlled trials, suggests surgery such as total knee arthroplasty results in

major improvements in pain, function and quality of life measures although the lack of controlled trials limits the evidence based in terms of comparison with other therapies.

The utilization of joint replacement varies widely between centres, even though the prevalence of severe joint damage in inflammatory arthritis is likely to be consistent. The reasons for this are unclear. The rationale, range and problems of orthopaedic surgery in arthritis are shown in Table 7.2. Strategies for increasing functional recovery from orthopaedic surgery in arthritis include optimization of pre-operative functional status, early surgical intervention and utilisation of specialist multidisciplinary teams.

Outcome of joint replacement surgery continues to improve due to better prostheses and better operative techniques. Prosthesis changes include improvements in the design of prosthetic components which can decrease stress shielding, hence preserving bone and diminishing the problems of the growing numbers of revision operations. Improvements in materials will decrease osteolysis. Metal-on-metal and ceramic-on-ceramic total joints may have turned the tide on osteolysis caused by polyethylene wear. Porous ingrowth is replacing cement fixation and is diminishing prosthetic loosening.

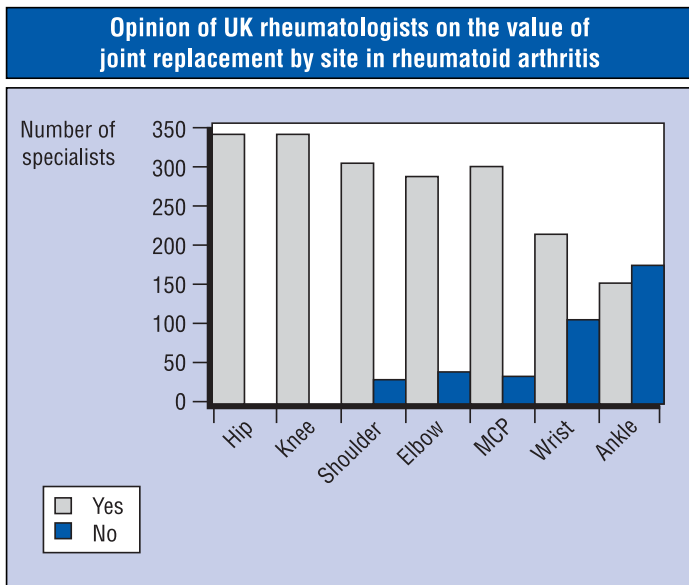
New surgical techniques are being developed. One important advance has been the introduction of unicompartmental knee arthroplasty. Some initial reports suggested that medial compartment replacement was not sufficiently effective to be a viable long-term option, although lateral compartment

<b>Orthopaedic surgery</b>	
<b>Reasons for surgery</b>	<b>Unacceptable pain</b>
Loss of range of movement	Functional limitation due to structural damage Specific localized problems (eg, carpal tunnel syndrome)
Types of surgery	Replacement arthroplasty Synovectomy Soft tissue release (eg, carpal tunnel syndrome) Resection (eg, metatarsal heads) Joint fusion
Complications	Infection Delayed wound healing Venous thrombosis Anaesthetic problems Surgical failure

**Table 7.2.**

replacement seemed to be promising. However, by the early 1980s, favourable initial results were being published for medial and lateral replacements and enthusiasm for the procedure rose. Unicompartmental knee arthroplasty now has a reliable ten-year outcome in properly selected patients with osteoarthritis who receive a skilfully implanted proper design. Unicompartmental knee arthroplasty can be an attractive alternative to osteotomy or total knee arthroplasty especially for middle-aged women. Another change has been the introduction of minimal incision hip replacement surgery, which enables the surgeon to perform hip replacement through one or two small incisions. Candidates for minimal incision procedures are typically thinner, younger, healthier patients who are anxious to have a quick recovery. Specially designed instruments are needed to prepare the socket and femur and to place the implants properly, in a similar method used for implanting an artificial hip. However, there is less soft-tissue dissection with this technique than with longer incisions.

Although replacement surgery can be undertaken on different joints, they are not all effective or beneficial. Figure 7.2 shows the views of UK rheumatologists about the merits of joint replacement surgery depending on the site.



**Figure 7.2.** MCP, metacarpophalangeal joint.



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