Chapter objectives

After studying this chapter you should be able to:

1. Explain the structure and function of synovial joints.
2. Understand the relevant anatomy of the hand and wrist joints.
3. Discuss the basic function of the immune system.
4. Understand the aetiopathogenesis of rheumatoid arthritis.
5. Describe the pathological changes that occur in inflammatory arthritis.
6. Recognize the common clinical presentations and features of rheumatoid arthritis and their pathophysiological basis.
7. Develop an approach to the differential diagnosis of inflammatory arthritis.
8. Describe extra-articular manifestations of rheumatoid arthritis and explain their pathophysiological basis.
9. Understand the principles that govern the team approach to the management of rheumatoid arthritis.
11. Discuss the place of orthopaedic surgery in the treatment of rheumatoid arthritis.
12. Appreciate the long-term prognosis of rheumatoid arthritis.
Introduction

Synovial joints, the most mobile type of joints in the body, are susceptible to inflammatory injury leading to arthritis. The synovium is a common target of a variety of insults including direct microbial infection, crystal deposition and autoimmune attack, e.g. in rheumatoid arthritis (RA). This chapter will review normal synovial joint structure and function, the processes that lead to inflammatory arthritis, an approach to differential diagnosis, and the principles of treatment of RA. The topic and discussion will be illustrated by a patient with inflammatory arthritis found to have RA. It is the commonest chronic inflammatory rheumatic disease, affecting 1–2% of the population. RA not only produces extensive morbidity, but also is associated with a reduction in life expectancy.

Essential anatomy and physiology

Synovial joint anatomy

There are three types of joints in the body: synarthroses, amphiarthroses and diarthroses (synovial joints). Synarthroses are joints that have an interlocking suture line between adjacent bones (e.g. skull bones)—this provides a very strong bond. The synarthrosis grows during maturation of the developing brain and is eventually replaced by bony union between the adjacent bones. Amphiarthroses are joints that have fibrocartilage between adjacent bones—this allows for flexibility. They are found in the rib cage, the sacroiliac joint and between vertebral bodies—the intervertebral discs.

Case 1.1 Rheumatoid arthritis: 1

Case history

Mrs Gale is a 43-year-old woman who, together with her husband, runs a domestic cleaning company. She presents with a 9-month history of painful hands and wrists. Her symptoms started with occasional early-morning stiffness and swelling in her right knee, followed shortly afterwards by similar symptoms in her hands and wrists. Mrs Gale says she is no longer able to help her husband in the cleaning business. The pain is getting worse. Physical examination reveals symmetrical soft-tissue swelling in all of the proximal interphalangeal and metacarpophalangeal joints of both hands and wrists. Her right knee joint is swollen and has an effusion. The metatarsophalangeal joints are tender to palpation.

A provisional diagnosis of an inflammatory arthritis, probably rheumatoid arthritis, is made. Interpretation of this presentation requires knowledge of synovial joint structure in general and the hands in particular as well as knowledge of the immune system in health and disease.

Synovial, or diarthrodial joints, are the commonest type of joint and are the most mobile. They possess a synovial membrane, have a cavity that contains synovial fluid, and are subclassified into ball and socket (e.g. hip), hinge (e.g. interphalangeal) and saddle (e.g. first carpometacarpal) types. These joints (Fig. 1.1) allow the cartilaginous surfaces of the joint ends to move efficiently and smoothly, with low frictional resistance. Different designs allow for different movements, including flexion (bending), extension (straightening), abduction (movement away...
from midline), adduction (movement towards midline), and rotation. They are more susceptible to inflammatory injury than are other types of joints.

Synovial joints are surrounded by a capsule that defines the boundary between articular and periarticular structures (Fig. 1.2). Reinforcing the capsule are ligaments and muscular tendons, which act across the joint. The joint capsule, ligaments and tendons are composed principally of type 1 collagen fibres—type 1 collagen is the major fibrous protein of connective tissue.

The synovial membrane has a lining layer that consists of special cells called synoviocytes and is normally one to three cells thick. There is no basement membrane separating the synoviocyte layer from the subintima (Fig. 1.3). There are at least two different types of synoviocyte cell: type A and type B. Type A are of bone marrow-derived macrophage (phagocyte or 'hungry cell') lineage and type B are fibroblast-like mesenchymal (connective tissue) cells. Other cell types in this layer include dendritic cells—antigen-processing cells involved in generating an immune response. The synoviocytes lie in a stroma composed of collagen fibrils and proteoglycans (a diverse group of glycosylated proteins that are abundant in the extracellular matrix of connective tissues), which is continuous with the subintima. The latter may be fibrous, fatty or areolar (contain loose connective tissue). It contains a dense network of fenestrated capillaries (small blood vessels) that facilitate the exchange of molecules between the circulation and the synovium. The vessels are derived from branches of the arterial plexus that supplies the joint capsule and juxta-articular bone. There is also a lymphatic supply—a vascular system involved in removing large molecules from the synovium. The latter is innervated and pain sensitive, particularly during inflammation.

**Synovial joint physiology**

Normal synovial joints are highly effective in allowing low-friction movement between articulating surfaces. Articular cartilage is elastic, fluid-filled and supported by a relatively impervious layer of calcified cartilage and bone. Load-induced compression of cartilage forces interstitial fluid to flow laterally within the tissue through adjacent cartilage. This assists in protecting the cartilage against mechanical injury.

Synovial fluid (Fig. 1.4) is present in small quantities in normal synovial joints. It is a clear, relatively acellular,
viscous fluid that covers the surface of synovium and cartilage. Synovial fluid is an ultrafiltrate of blood to which hyaluronic acid is added. Hyaluronic acid is secreted by synoviocytes and is the molecule responsible for synovial fluid viscosity, acting as a lubricant for synovial–cartilage interaction. Synovial fluid represents an important site for exchange of nutrients and metabolic by-products between plasma and the surrounding synovial membrane. The synovial cavity can be used to advantage as a site in which therapeutic agents are introduced, e.g. intra-articular corticosteroids to treat inflamed synovium, as well as for diagnostic aspiration.

Normal synovial fluid contains only small quantities of low molecular weight proteins compared with plasma. The barrier to the entry of proteins probably resides within the synovial microvascular endothelium (cells that line the synovial microcirculation).

### Interesting facts

**Anatomy of synovial joints**

Synovial joints are the commonest and most mobile type of joint in the body. They possess a synovial membrane and have a cavity that contains synovial fluid. They are subclassified into ball and socket (e.g. hip), hinge (e.g. interphalangeal) and saddle (e.g. first carpometacarpal) types.

**Synovial fluid**

Synovial fluid, present in small quantities in normal synovial joints, is a clear, relatively acellular, viscous fluid that covers the surface of synovium and cartilage. It is an ultrafiltrate of blood to which hyaluronic acid is added. Hyaluronic acid is secreted by synoviocytes and is the molecule responsible for synovial fluid viscosity, acting as a lubricant for synovial–cartilage interaction.

### Interesting facts

**Anatomy of the hand and wrist joints**

**Joints and synovial membranes**

The proximal and distal interphalangeal joints are true hinge joints whose movements are restricted to flexion and extension. Each joint has a thin dorsal (upper surface) capsular ligament strengthened by expansion of the extensor tendon, a dense palmar (under surface) ligament, and collateral ligaments on either side of the joint. The metacarpophalangeal joints are also considered hinge joints and their ligaments resemble those of the interphalangeal joints. When the fingers are flexed, the heads of the metacarpal bones form the rounded prominences of the knuckles, with the joint space lying about 1 cm distal (peripheral) to the apices of the knuckles. Figure 1.5 shows the relationship of the dorsal and lateral aspects of the joint space, synovial membrane and the articular capsule to adjacent structures.

The wrist or radiocarpal joint is formed proximally by the distal end of the radius and the articular disc, and distally by a row of carpal bones, the scaphoid, lunate, pisiform and triquetrum (Fig. 1.5A). The articular disc joins the radius to the ulnar and separates the distal end of the ulnar from the wrist joint proper. The wrist joint is surrounded by a capsule and supported by ligaments.

The distal radioulnar joint is adjacent to but not normally part of the wrist joint, since the articular disc divides these joints into separate cavities (Fig. 1.5A). The midcarpal joint is formed by the junction of the proximal and distal rows of the carpal bones. Limited flexion, extension and some rotation occur in the midcarpal joint. Pronation and supination occur primarily at the proximal and distal radioulnar articulations.

**Tendons**

The long flexor tendons of the muscles of the forearm are enclosed in a common flexor tendon sheath that begins proximal to the wrist crease and extends to the midpalm (Fig. 1.6). Part of the common flexor tendon sheath lies in the carpal tunnel and is bounded anteriorly by the flexor retinaculum (a ligament that lies on the volar surface of the wrist). Thickening of the synovial membrane of the flexor tendons because of synovitis can cause carpal tunnel syndrome (see Ch. 3).

The extensor tendons of the forearm pass through fibro-osseous tunnels on the dorsum of the wrist. These tunnels, which are lined with a synovial sheath, are bounded superficially by the extensor retinaculum and on the deep surface by the carpal bones and ligaments. A depression over the dorsolateral aspect of the wrist when the thumb is extended and abducted is called the anatomical snuffbox. It is formed by the tendons of abductor pollicis longus and extensor pollicis brevis muscles and is limited proximally by the radial styloid process. Tenderness in this region can be due to stenosing tenosynovitis of these tendons (a condition called de Quervain’s tenosynovitis). In this condition, placing the thumb in the palm of the hand, flexing the fingers over the thumb and adducting the wrist will usually produce severe pain (Finkelstein’s manoeuvre).

**Essential immunology**

The immune system has developed principally as a means to help the host combat microbial infection. The human body uses a number of mechanisms to achieve this objective, some innate and non-specific, others involving exquisitely precise targeted processes.

**Innate mechanisms**

Innate defence mechanisms include the protective effects of intact skin and mucosa in combating microbes. Normal skin acts as an impermeable barrier to most
infectious agents. Mucus secreted by the membranes lining the inner surfaces of the body (e.g., nasal and bronchial mucosa) acts as a protective barrier that prevents bacteria adhering to epithelial cells.

A variety of white blood cells, including polymorphonuclear neutrophils (PMNs) and macrophages, can act as important lines of defence against microbial attack. These cells, derived from bone marrow precursors, are capable of eliminating microbes following their phagocytosis (uptake). The cells are rich in digestive enzymes that aid in elimination of these microbes. PMNs are short-lived cells, whereas macrophages may remain in connective tissues for prolonged periods. PMNs are principally involved in host defence against pus-forming bacteria, while macrophages are better at combating intracellular microbes, including certain bacteria, viruses and protozoa. No prior exposure to the microorganism is necessary for these leukocytes to act.

Another innate line of defence against microbes is the complement system. This comprises over 20 proteins. The complement system is able to respond rapidly to a trigger stimulus, resulting in activation of a sequential cascade in which one reaction is the enzymatic catalyst of the next (Fig. 1.7). The most important complement component is C3, which facilitates the uptake and removal of microbes by enhancing their adherence to the surface of phagocytic cells. Biologically active fragments of C3—C3a, and C5a are able to attract PMNs (called chemotaxis) as well as activating these cells. Activated complement components later in this sequence, C6, 7, 8 and 9, form a complex—the membrane attack complex—on the surface of target cells and this is able to punch holes in the cell membrane, resulting in target cell lysis.

There are a variety of other humoral defence mechanisms mediated by soluble factors that assist in containing microbial infection. These include acute phase proteins such as C-reactive protein, alpha-1-antiprotease and alpha-2-macroglobulin and the interferons. The latter are a family of broad-spectrum antiviral agents that are synthesized by cells when infected by viruses. They limit the spread of virus to other cells.

Humans as well as many lower-order animals have developed more selective mechanisms to combat infection, involving humoral or antibody and cellular systems.

**Antibodies**

Antibodies are remarkable proteins produced by bone-marrow derived B lymphocytes, which are able to differentiate into plasma cells. Antibodies are adaptor molecules that are capable of binding to phagocytic cells, activating complement and binding to microbes. Each antibody has a unique recognition site for a particular microbe—the Fab end of the molecule, which binds microbes (Fig. 1.8). Molecules in the microorganism that evoke and react with antibodies are called antigens. The Fc end of the antibody molecule contains domains capable of binding and activating the first component of complement
as well as binding to phagocyte Fc receptors. There are five antibody subtypes, classified by variations in the structure of the Fab region: IgG, IgM, IgA, IgD and IgE.

There is an enormous variety of B lymphocytes, each programmed to synthesize a single antibody specificity. These antibodies are expressed on the lymphocyte cell surface and act as a receptor for antigens. This process is highly selective; for example, antibodies that recognize tetanus toxoid antigen do not recognize influenza virus, and vice versa. On exposure to antigen, B lymphocytes with the corresponding cell surface antibody specificity, bind to the cell and deliver activation signals. This leads to their differentiation into plasma cells and synthesis and secretion of specific antibodies. The activated B lymphocytes also undergo proliferation, resulting in expansion of the number of clones capable of producing the same antibody. Antibody production in response to antigenic challenge is referred to as an acquired immune response.

Even after the elimination of a microbial antigen trigger, some B lymphocytes remain and have a ‘memory’ of this exposure. On subsequent challenge with the same antigen, the body responds by synthesizing antibody faster and in greater quantities than on the first exposure. This is the secondary immune response.

The ability to recognize a particular antigen and distinguish it from a different antigen is related to the ability to distinguish between self-antigen and non-self (i.e. foreign) antigens. There is an active process by which self-antigen fails to induce an immune response, known as tolerance.
In some circumstances, tolerance is broken and the individual produces self-directed antibodies known as autoantibodies. These may give rise to autoimmune diseases. Another autoimmune disease, systemic lupus erythematosus, is discussed in Chapter 9.

Cell-mediated immunity

Many microbes live inside host cells out of the reach of antibodies. Viruses can live inside host cells, such as macrophages, where they replicate. Thus a different form of immune defense, known as cell-mediated immunity, is required to combat intracellular infection. This involves T or thymus-derived lymphocytes. T cells only recognize antigen when it is presented on the surface of a host cell. There are T cell receptors present on the cell surface, distinct from antibody receptors, which recognize antigen. A further complexity is that antigen is recognized in association with another cell surface molecule known as the major histocompatibility complex (MHC) expressed on the target cell. The MHC plays an important role in organ transplant rejection.

A macrophage that has been infected with a virus is able to process small antigenic components of the virus and place these on its surface. A subpopulation of T lymphocytes, known as T helper cells, primed to that antigen, recognize and bind to the combination of antigen and class 2 MHC molecules. These T cells also secrete a range of soluble products known as lymphokines. The latter include gamma interferon, which stimulates microbicidal mechanisms in the macrophage that help to kill the intracellular microbe.

There is also another subpopulation of T lymphocytes, known as cytotoxic T cells, which recognize antigen expressed on the surface of target cells in association with MHC class 1 molecules (Fig. 1.9). The cytotoxic T cell comes into direct contact with the target cell and kills it. Just as is true for B cells, T cells selected and activated by binding antigen undergo clonal proliferation and mature to produce T helper and cytotoxic cells and produce memory cells. The latter can be reactivated upon further antigenic challenge.

For maximal T cell responses, second signals are usually required. Two of the co-stimulatory molecules through which these signals are provided are CD28 and CD40 ligand. Both of these molecules are expressed by synovial T cells in RA. One of the newer biological therapies for RA, Abatacept, specifically targets this interaction.

In summary, a wide range of innate and adaptive immunological mechanisms has evolved to protect the host against microbial infection. In some circumstances the host becomes a target for these responses, resulting in autoimmune disease.

Pathology

Synovitis

To gain a better appreciation of the processes occurring within an inflamed joint, it is necessary to understand synovial pathology. However, in clinical practice a synovial biopsy is not routinely performed as part of the diagnosis of inflammatory arthritis.

In RA, the classical example of an inflammatory arthropathy, the synovium undergoes characteristic histological changes, but these are not disease-specific. Eventually, they may progress to destruction of articular cartilage and result in joint subluxation or ankylosis (bridging of adjacent bones).

In the early stages of RA, the synovium becomes edematous (contains excess fluid), thickened, hyperplastic (cells multiply excessively) and develops villus-like projections as found in normal small intestine (Fig. 1.10A). The synovial lining layer undergoes cellular proliferation and becomes multilayered. One of the earliest histological changes is injury to the synovial microvasculature, with swelling of endothelial cells, widened interendothelial gaps and luminal occlusion. There is dense synovial cellular infiltration with prominent perivascular T lymphocytes, plasma cells and macrophages, but few neutrophils (Fig. 1.10B). Prominent fibrin deposition is characteristic. Lymphoid nodular aggregates composed principally of CD4 T (helper) cells may be found in the synovial stroma (Fig. 1.10C), but are more likely to develop later in the disease. By contrast, in the synovial fluid there is a predominance of neutrophils. RA often involves periarticular structures including tendon sheaths and bursae.

In the later stages of RA, the inflamed synovium develops a hyperaemic, fibrovascular granulation tissue known as pannus (Latin: 'piece of cloth'), which includes new blood vessel formation (angiogenesis). This spreads over and subsequently invades the articular cartilage. The pannus eventually destroys articular cartilage and invades bone, causing juxta-articular erosions and subchondral cysts. These can be seen on plain radiography and at an even earlier stage of disease using magnetic resonance imaging (MRI). It may lead to fibrosing ankylosis and loss of joint mobility. Joint instability and subluxation (partial dislocation) may arise from damage to the joint capsule, ligaments and tendons, as the inflammatory process extends. This may subsequently heal with fibrosis and
Although RA predominantly involves synovial joints, it is a systemic disease and may affect many tissues and organs including skin, blood vessels, heart, lungs, muscles and eyes. The most characteristic extra-articular feature is the rheumatoid nodule, found in 25% of patients, typically in subcutaneous tissues over pressure areas. Rheumatoid nodules have a characteristic microscopic appearance, consisting of three distinct layers—a central zone of fibrinoid necrosis (pink-staining dead material) surrounded by palisading (fence-like) phagocytes arranged radially, and granulation tissue with inflammatory cells.

The synovium in the seronegative spondyloarthropathies may be difficult to distinguish microscopically from RA. Typically there is inflammation both in the synovium and bony entheses (the site of ligamentous and capsular insertion into bone)—enthesitis. The synovium does not usually develop extensive pannus formation and consequently, there is less invasion of bone and articular cartilage compared with RA. The enthesis becomes infiltrated by a non-specific granulation tissue. In severe forms of the disease, enthesopathy is followed by calcification and ossification, particularly in the spine and capsules of peripheral joints.

**Differential diagnosis of inflammation of the synovium**

Synovial joints are susceptible to inflammatory injury, probably because of their rich network of fenestrated...
Microorganisms may lodge in the joint from a direct penetrating injury or, more commonly, by haematogenous (blood-borne) spread from a distant site during bacteraemia. Clinical pointers include fever and constitutional symptoms—sweating, rigors (shivers), malaise. However, these symptoms are not specific for infection and may occur in patients with RA. A cutaneous source of infection may give a clue, e.g., a boil or carbuncle. In the case of sexually active young women, *Neisseria gonorrhoeae* infection needs to be considered. This subject is covered in more detail in Chapter 11.

Sudden onset of monoarthritis, particularly in the big toe, in an older male raises the suspicion of crystal-induced arthritis due to sodium urate deposition. Uric acid, the end product of purine metabolism, may precipitate out of its usually soluble state, deposit in the synovium and produce acute inflammation. An acute attack is typically triggered by agents (alcohol and certain drugs) that raise serum uric acid levels and precipitate sodium urate crystal deposition. Clinically it presents with the sudden onset of exquisite pain in a joint—frequently the first metatarsophalangeal joint. The patient exhibits the classic signs of inflammation—local heat, erythema (redness), tenderness, swelling and loss of function. Another type of crystal that commonly produces monoarthritis is calcium pyrophosphate dihydrate. This usually affects middle-aged females and involves the knee joint. Crystal arthritis is covered in greater depth in Chapter 7.

Involvement of one or a limited number of joints in an asymmetric distribution raises the possibility of seronegative (i.e., rheumatoid factor negative) spondyloarthritis. The spondyloarthropathies, as the name implies, often have spinal involvement and include ankylosing spondylitis, psoriatic arthritis, colitic arthritis and reactive arthritis. These conditions typically manifest as an asymmetric arthritis involving one or several joints, including the spine and/or sacroiliac joints. There are often associated features that give clues to the diagnosis, e.g., presence of psoriasis (a red, scaly skin rash) or a history of inflammatory bowel disease (e.g., episodes of bloody diarrhoea). A recent episode of non-specific urethritis or bowel infection with *Salmonella* or *Shigella* microorganisms should raise the possibility of reactive arthritis. Patients may give a history of eye inflammation (e.g., iritis—inflammation of the iris) resulting in episodes of painful red eyes, or inflammation of ligamentous or tendinous insertions into bone (enthesitis) resulting in painful heels, for example. Patients with seronegative spondyloarthropathies frequently have a family history of the condition and there is an association with the white blood cell marker (histocompatibility locus antigen) HLA-B27. The latter is found in over 95% of Caucasian males with ankylosing spondylitis, but in only 6–8% of the normal population. How this genetic marker leads to disease predisposition is poorly understood. Tests for the autoantibody rheumatoid factor are negative—hence the term seronegative.

The pattern of disease onset in RA is quite variable. Although it often presents insidiously with the development of a symmetrical inflammatory arthritis involving capillaries. The synovium has only a limited number of ways in which it can respond to injury.

The synovium may be the target of a large number of insults including microbes, e.g., *Staphylococcus aureus* leading to septic arthritis; crystals, e.g. sodium urate leading to gouty arthritis; or autoimmune attack, e.g. RA in which the trigger is unknown (Box 1.1).

Determining the aetiological basis for synovitis may be difficult. Tender soft-tissue swelling and fluid (effusion) of synovial joints (as seen with Mrs Gale) indicates that the joint is inflamed, i.e. synovitis. Information on the following may enable a more precise diagnosis to be made:

- the pattern and distribution of joint involvement (symmetrical versus asymmetrical)
- the number of joints involved—one (monoarthritis), a few (<6—oligoarthritis) or multiple (>6—polyarthritis)
- the duration of inflammation (days, weeks or months)
- the type of trigger; and
- the presence of extra-articular features, e.g. fever, rashes.

The sudden onset of painful swelling of one joint—monoarthritis—raises the possibility of infection.
multiple joints over weeks to months, a monoarticular onset, especially involving the knee (as in Mrs Gale’s case), may antedate the development of symmetrical arthritis. The joints most commonly affected in polyarthritis with RA are the small joints of the hands (proximal interphalangeal and metacarpophalangeal joints), wrists, elbows, feet, knees and ankles. Later in the disease, large joints such as the hip and shoulder may be involved, but not usually at presentation. A family history of RA is often present. The patient usually complains of joint stiffness, especially in the morning, joint swelling and pain. The patient may also have systemic symptoms, such as weight loss and fatigue.

Polymyalgia rheumatica is an inflammatory arthropathy characterized by pain and stiffness, usually of sudden onset, predominantly affecting the limb girdle areas (shoulders and hips). It usually occurs in older subjects, is generally associated with a moderate to markedly elevated erythrocyte sedimentation rate (ESR) and C-reactive protein levels and is rapidly responsive to corticosteroids. It is often associated with giant cell arteritis, especially in the temporal arteries but any artery can be affected. Headache is the most common symptom but visual symptoms suggesting arteritis include transient and permanent visual loss. Biopsies characteristically show infiltrations of macrophages, T cells and multinucleated giant cells, the hallmark of the disease.

**Aetiopathogenesis of rheumatoid arthritis**

There are a diverse range of aetiologies for inflammatory arthritis—infection, crystal and autoimmune. The first two are discussed in the chapters on bone and joint infection (Ch. 11) and crystal arthritis (Ch. 7), respectively. Here, the aetiopathogenesis of RA is discussed (Fig. 1.11).

Although the cause of RA is unknown, genetic, microbial and immunological factors are thought to play a role in disease susceptibility. RA is one of a group of conditions in which immunogenetic responses are important.

As such, it joins the majority of autoimmune diseases in which genes known to exert influence on the immune response (immune response genes) are involved in disease pathogenesis. However, because the antigen(s) that trigger RA are unknown, the precise details remain elusive.

Major histocompatibility complex (MHC) genes, present on chromosome 6 in man, are important in determining host immune responses to foreign antigens. They play a vital role in organ transplantation and determine whether rejection of a graft occurs. They are also

**Fig. 1.11 Schematic diagram of the pathogenesis of RA.**

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**Case 1.1 Rheumatoid arthritis: 2**

**Establishing the diagnosis**

It comes to light that Mrs Gale’s mother had severe RA and was disabled by her disease. Mrs Gale complains of fatigue, but gives no history of rashes, weight loss or change in bowel habit. The history of polyarthritis of insidious onset, symmetrical pattern of joint involvement, prominent early morning joint stiffness and positive family history of RA suggest a diagnosis of RA. However, to establish the diagnosis, radiological and laboratory investigation are warranted. A number of investigations are usually performed; the focus here is on synovial fluid analysis and joint X-rays.

**Synovial fluid analysis**

Synovial fluid aspiration, performed at the bedside, using a sterile no-touch technique is often helpful in determining the cause of inflammatory arthritis (Table 1.1). Typically in RA, the fluid is macroscopically (i.e. to the naked eye) cloudy, owing to the increased number of white cells it contains, and of low viscosity because of the biochemical degradation of hyaluronic acid (Fig. 1.4). This contrasts with normal synovial fluid, which is clear, colourless and highly viscous. Other features of the fluid may provide a diagnosis for the inflammatory arthritis, e.g. the presence of needle-shaped birefringent crystals in gout, or bacteria in septic arthritis.
involved in predisposition to autoimmune diseases such as RA and systemic lupus erythematosus. There is a linkage of certain genes in this complex, known as DR, with susceptibility to RA. The best-described association of RA is with HLA-DR4.

Family studies have found that HLA haplotype sharing (i.e. individuals sharing the same genetic markers) is increased in family members affected by RA. Molecular analysis of the DR alleles (variations at this gene locus) associated with RA suggests that the genetic contribution of MHC genes to RA is approximately 25%. Other genes thought to play a role in disease susceptibility to RA include immunoglobulin genes, genes controlling glycosylation patterns of immunoglobulin (i.e. the different type and amount of carbohydrate present) and T cell receptor genes. It must be remembered that RA has a complex multifactorial pathogenesis and, while immune response genes are important, environmental factors also play a role.

A microbial aetiology of RA has been postulated for many decades. Microorganisms that have been proposed

| Table 1.1  | Synovial fluid analysis in inflammatory arthritis |
| --- | --- | --- | --- | --- |
| Normal | RA | Gout | Septic |
| Colour | Colourless | Yellow | Yellow | Yellow |
| Clarity | Clear | Cloudy | Cloudy | Purulent |
| Viscosity | High | Low | Low | Low |
| White cell count (/mm$^3$) | <1500 | 2–50000 | 5–50000 | 50–500000 |
| % neutrophils | <5 | 30–80 | 50–80 | >95 |
| Crystals | No | No | Yes | No |
| Bacteria | No | No | No | Yes |

Joint X-rays

Plain X-rays of the hands and feet often provide useful diagnostic information in patients with inflammatory arthritis. The earliest changes in RA involving the hands are soft-tissue swelling of proximal interphalangeal and metacarpophalangeal joints. This corresponds with synovitis of affected joints. There is periarticular osteoporosis (bone thinning) thought to be secondary to increased blood flow through inflamed joints and local release of cytokines (molecules that are released by activated cells and are involved in signalling to other cells). However, these changes are not specific for RA and simply reflect joint inflammation. The most characteristic feature is the development of bony erosions that start at the periphery of the joint where the synovium reflects off the joint capsule. Erosions correspond with the site of local invasion by inflammatory synovial tissue, known as pannus, which grows into the adjacent bone and cartilage (Fig. 1.12), discussed below.

Fig. 1.12 X-ray showing bony erosion of metacarpophalangeal joint and proximal interphalangeal joint.
RHEUMATOID ARTHRITIS AND THE HAND

Macrophages, neutrophils and fibroblasts produce large quantities of proteolytic enzymes including matrix metalloproteinases (MMPs)—enzymes that require cleavage by other proteases to become active. The matrix metalloproteinases—collagenase, gelatinase and stromelysin—mediate the degradation of joint tissues that accompanies the development of pannus.

Large quantities of antibody are present within the joint, including local production of rheumatoid factors (RF). The latter are autoantibodies of the IgM, IgG and IgA classes characterized by antigenic binding determinants on the constant region of human IgG. IgM RF are found in the serum of 70% of patients with RA and are associated with severe joint disease and extra-articular features, e.g. vasculitis (inflammation of blood vessels). Patients who have IgM RF in their serum are said to be seropositive. RF may participate in some of the clinical phenomena that occur in RA, e.g. vasculitis leading to leg ulcers or nodules. However, they are not specific for RA and may occur in other autoimmune diseases, e.g. Sjögren’s syndrome, and occasionally in infectious diseases, e.g. bacterial endocarditis.

Recently, another auto-antibody has been described in the serum of patients with RA, namely anti-citrullinated protein antibodies and are highly specific for that disease. Citrullination is catalysed by peptidyl arginine deamidase. Citrullinated proteins are found in the synovium of patients with RA, but are not unique to that site or to that disease. Diagnostic kits which detect cyclic citrullinated protein antibodies are now challenging RFs as the most valuable test in the diagnosis of RA.

Pathophysiological basis of symptoms and signs of rheumatoid arthritis

Although RA is an autoimmune multisystem disease, its primary clinical manifestation usually relates to the involvement of synovial joints. The clinical features vary in severity between patients, as well as fluctuating over time in individual patients. The initial presentation of the disease is most commonly as a symmetrical inflammatory polyarthritis involving the hands (Fig. 1.13). Why the disease causes symmetrical joint involvement is unknown. The patient experiences pain, stiffness and swelling in the joints, that is characteristically worse in the morning. Joint swelling and pain are due to the presence of active inflammation in the synovium, i.e. synovitis or effusion. Systemic symptoms may be due to the presence of circulating cytokines such as TNF-α.

Joint deformity is not a typical feature of early disease and usually occurs only after the disease has been present for some time. Deformity arises secondary to damage caused by the pannus invading cartilage and bone. Radiological bone erosions may not be present at the time of diagnosis, but usually develop over months, or longer, with ongoing active disease. They reflect invasion of bone by pannus. Typical deformities include ulnar deviation of the digits at the metacarpophalangeal joints.

to play a role include mycoplasma, mycobacteria and a number of viruses, e.g. Epstein–Barr virus. However, there is no convincing evidence for a microbial cause of RA.

That immunological and inflammatory processes play a role in the pathological expression of RA is undisputed. Although RA is a systemic disease, its hallmark is chronic inflammation in the synovium of multiple joints. It is best viewed as being an autoimmune disease, triggered by an unknown antigen. The initiating event of joint damage is thought to be triggering of autoreactive CD4 T helper lymphocytes by antigen(s) presented to these T cells. In early lesions, activated/memory T cells predominate in pericapillary sites beneath the synovial membrane. Accompanying the T cells are neutrophils, mast cells and mononuclear phagocytes that mature to activated macrophages.

In the earliest lesions, there is an increase in vascularity driven by angiogenesis-stimulating factors released from macrophages and fibroblasts. Both vessels and infiltrating cells have enhanced expression of intercellular adhesion molecules, especially intercellular adhesion molecule-1 (ICAM-1). As the lesion progresses, lymphoid cells organize into microenvironments similar to that seen in lymph nodes. Dendritic cells (specialized cells that present antigens to the immune system effectively) are found in these environments and are thought to provide the basis of local antibody production by B cells and ongoing T cell activation. Mature memory T cells promote antibody synthesis with little negative feedback.

Despite the importance of T cell involvement, the most active cells in synovial lesions are macrophages. The macrophage-derived cytokines interleukin (IL) -1, -6 and -8, tumour necrosis factor-alpha (TNF-α), and granulocyte-macrophage colony-stimulating factor (GM-CSF) are found in abundance within the rheumatoid synovium. Interleukins are a group of peptides that signal between cells of the immune system. By contrast, only low levels of T cell-derived cytokines, e.g. IL-2, IL-4 and interferon-gamma, can be detected. TNF-α is thought to be a central cytokine in the perpetuation of the inflammatory response. Indeed, anti-TNF treatment by monoclonal antibodies to TNF-α or TNF receptor blockade has been demonstrated to have a dramatic effect in reducing inflammatory disease activity in RA. Fibroblast-like cells also contribute to the cytokine network, particularly IL-6 and transforming growth factor beta (TGF-β). The latter is a downregulatory cytokine (i.e. it decreases inflammatory activity).

Pro-inflammatory cytokines predominate in rheumatoid synovium. They are responsible for:

- activation of adhesion molecule expression on blood vessels
- synovial recruitment of inflammatory cells (lymphocytes and other leukocytes)
- continuing activation of macrophages, fibroblasts and dendritic cells
- promoting angiogenesis.

Large quantities of proteolytic enzymes including matrix metalloproteinases (MMPs)—enzymes that require cleavage by other proteases to become active. The matrix metalloproteinases—collagenase, gelatinase and stromelysin—mediate the degradation of joint tissues that accompanies the development of pannus.

Large quantities of antibody are present within the joint, including local production of rheumatoid factors (RF). The latter are autoantibodies of the IgM, IgG and IgA classes characterized by antigenic binding determinants on the constant region of human IgG. IgM RF are found in the serum of 70% of patients with RA and are associated with severe joint disease and extra-articular features, e.g. vasculitis (inflammation of blood vessels). Patients who have IgM RF in their serum are said to be seropositive. RF may participate in some of the clinical phenomena that occur in RA, e.g. vasculitis leading to leg ulcers or nodules. However, they are not specific for RA and may occur in other autoimmune diseases, e.g. Sjögren’s syndrome, and occasionally in infectious diseases, e.g. bacterial endocarditis.

Recently, another auto-antibody has been described in the serum of patients with RA, namely anti-citrullinated protein antibodies and are highly specific for that disease. Citrullination is catalysed by peptidyl arginine deamidase. Citrullinated proteins are found in the synovium of patients with RA, but are not unique to that site or to that disease. Diagnostic kits which detect cyclic citrullinated protein antibodies are now challenging RFs as the most valuable test in the diagnosis of RA.

Pathophysiological basis of symptoms and signs of rheumatoid arthritis

Although RA is an autoimmune multisystem disease, its primary clinical manifestation usually relates to the involvement of synovial joints. The clinical features vary in severity between patients, as well as fluctuating over time in individual patients. The initial presentation of the disease is most commonly as a symmetrical inflammatory polyarthritis involving the hands (Fig. 1.13). Why the disease causes symmetrical joint involvement is unknown. The patient experiences pain, stiffness and swelling in the joints, that is characteristically worse in the morning. Joint swelling and pain are due to the presence of active inflammation in the synovium, i.e. synovitis or effusion. Systemic symptoms may be due to the presence of circulating cytokines such as TNF-α.

Joint deformity is not a typical feature of early disease and usually occurs only after the disease has been present for some time. Deformity arises secondary to damage caused by the pannus invading cartilage and bone. Radiological bone erosions may not be present at the time of diagnosis, but usually develop over months, or longer, with ongoing active disease. They reflect invasion of bone by pannus. Typical deformities include ulnar deviation of the digits at the metacarpophalangeal joints.

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and swan-neck deformities of the fingers. Ulnar deviation results from the fingers being pulled in the ulnar direction by the natural pull of the forearm muscles in the presence of subluxation (partial dislocation) at the metacarpophalangeal joints. In a swan-neck deformity, the proximal interphalangeal joint is hyperextended and the distal interphalangeal joint flexed.

The temporal pattern of these clinical manifestations varies between patients. About one-third experience prolonged periods of remission. Another third demonstrate fluctuating disease activity characterized by periods of active joint inflammation interspersed with periods of more quiescent disease. The remaining third manifest progressive deforming joint damage with declining functional status over time. Mortality rates are increased in those with the most severe forms of the disease.

**Rheumatoid arthritis as a systemic disease**

RA may be more accurately termed rheumatoid disease, as it is a multisystem disease (Fig. 1.14), with the major clinical manifestation being polyarthritis. In addition to joint pain, stiffness and swelling, patients with RA often have systemic clinical features that can include fatigue, weight loss, low-grade fever and myalgia (muscle pain). Lymphadenopathy (enlarged lymph glands) is present in about 30% of patients with active disease, usually of axillary, epitrochlear (near the elbow) oringuinal regions, and biopsy shows reactive hyperplasia.

Patients often have a normochromic (normal colour), normocytic (normal-sized red blood cells) anaemia. This occurs commonly in patients with chronic inflammatory or infectious diseases and is due to ineffective bone marrow production of red blood cells. It is known as the anaemia of chronic disease. If the haemoglobin level drops below 10 g/L, other explanations besides RA should be looked for. Thrombocytosis (elevation of platelet count), common in active disease, returns to normal when the arthritis is controlled. The erythrocyte sedimentation rate (ESR) and serum C-reactive protein levels are often elevated and are used as markers of disease activity. The ESR is determined by counting the number of millimetres the red blood cells have settled from the top of the serum in a capillary tube after 60 minutes.

**Case note: Management**

Mrs Gale reports that she has noticed the development of small painless nodular lumps over the extensor surfaces of both elbows. Her general practitioner explains that she has RA and that the lumps are rheumatoid nodules. She will need to be treated with a comprehensive management programme. She is referred to the local branch of the Arthritis Foundation for information and is advised to attend their patient education programme. She is recommended to undertake a period of rest and commenced on naproxen 500 mg b.d., a non-steroidal anti-inflammatory drug. She is referred to a rheumatologist for advice about the use of disease-modifying anti-rheumatic drugs.
Rheumatoid nodules occur in 25% of patients, most commonly on the extensor surfaces of the forearms, but they can occur at any site where there is pressure (Fig. 1.15). Subcutaneous nodules are usually only removed if they cause discomfort or become ulcerated, and may recur if the arthritis remains active. They are also found in internal organs, e.g. in the lungs, spleen, heart valves, eyes, and other viscera.

Vasculitis may also occur in RA. The most common type is a mild obliterator endarteritis (the vessels are occluded), which produces painless infarcts in the finger-nail beds and paronychia. These lesions frequently appear in crops, heal without tissue damage and, accordingly, do not require specific treatment. Leukocytoclastic vasculitis (inflammation of small blood vessels with ‘nuclear dust’) in the skin may also occur and manifest as palpable purpura (small raised purple lesions). This type of vasculitis most commonly occurs in the legs and heals without scarring. The most serious type of vasculitis in RA is a necrotizing vasculitis of small to medium-sized arteries and requires aggressive treatment. Its manifestations depend upon the site of involvement but include necrotizing skin lesions and ulcers when dermal vessels are affected, intestinal infarction and mononeuritis multiplex—involvement of multiple discrete peripheral nerves.

RA can also involve the heart, pericarditis (inflammation of the sac that surrounds the heart) being the most common cardiac manifestation. Small, usually asymptomatic, pericardial effusions have been reported in up to 40% of patients with RA. Histology shows a fibrinous pericarditis. Only a very small number of patients have larger pericardial effusions that become symptomatic. A mild myocarditis (inflammation of the heart muscle) can also occur in RA. It is rarely symptomatic and usually associated with a normal electrocardiogram. Valvular abnormalities occasionally occur in RA, most frequently of the aortic valve, and are usually due to fibrous valvular scarring.

The most common respiratory manifestation of RA is pleural involvement, typically manifesting as an asymptomatic pleural effusion. Occasionally, it can produce frank pleurisy (pleuritis). Rheumatoid nodules may also be found in the lung and can be difficult to distinguish from other causes of pulmonary nodules. Pulmonary fibrosis may occur secondary to chronic lymphocytic and monocytic infiltrate in the pulmonary interstitium or rarely as an adverse reaction to treatment with agents such as gold or methotrexate.

There are several types of eye involvement. Scleritis, or inflammation of the sclera, results in a painful, red eye (Fig. 1.16). Scleritis can lead to thinning of the sclera, called scleromalacia, which may rarely perforate the eye—scleromalacia perforans. Episcleritis, or inflammation in the loose connective tissue that lies between the conjunctiva and the sclera, is less likely to be symptomatic or as serious as is scleritis. It usually resolves rapidly with no residual abnormalities.

Several neuropathies can occur as part of RA, including a peripheral neuropathy (glove and stocking pattern of involvement), entrapment neuropathy caused by soft tissue swelling (the commonest example being carpal tunnel syndrome—see Ch. 3) and mononeuritis multiplex.

**Treatment of rheumatoid arthritis**

The management of patients with RA is very complex. This section is restricted to providing the principles
guiding management. For a more comprehensive coverage of this subject, the reader is directed to textbooks of rheumatology.

Modern approaches involve recognition of the importance of the therapeutic team in the optimal management of patients with RA. The team comprises of a rheumatologist (who usually acts as team leader), family physician, orthopaedic surgeon, allied health members including physiotherapist, occupational therapist, social worker, nurse and patient educator, the patient and his or her immediate family. While not all members of this team are required in the management of every patient, at times each may be called on to contribute his or her expertise.

Rest is therapeutic during periods of active disease. Controlled trials of rest therapy have demonstrated its therapeutic benefit. This does not imply that bed rest is required for all patients. Therapy may simply involve rest periods taken during the day. Exactly how rest reduces inflammation is unknown. Rest has to be balanced with exercise, best supervised by an experienced physiotherapist. Exercises include passive joint movement during periods of active disease, which are used to preserve a full range of joint motion, and active exercises including isometrics to reverse muscle wasting. The latter often develops in muscles adjacent to inflamed joints as a result of disuse.

Patients often experience depressive symptoms, marital disharmony and financial hardship as a result of having a chronic painful debilitating disease. The social worker can help with these aspects of the patient’s care. In more advanced cases, the orthopaedic surgeon plays an important role, usually in performing synovectomy for a chronically inflamed joint that has failed to respond to medical therapy or in reconstructive surgery to replace irreversibly damaged joints.

Pharmacological treatment principles (Table 1.2) include providing analgesia, reducing joint inflammation, preventing joint damage and inducing remission.

### Analgesics

Analgesics, including paracetamol/acetaminophen, have no anti-inflammatory effects. They can be used every 4–6 hours for pain relief if necessary. They seldom produce side-effects and are well tolerated.

#### Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs), of which aspirin is the historical prototype, inhibit the cyclooxygenase enzymes. NSAIDs act quickly (within hours to a few days) and reduce joint inflammation by inhibiting the production of inflammatory cyclooxygenase products, particularly the prostaglandins—small lipid molecules with potent effects on many steps in the inflammatory process. This provides symptomatic relief, with a reduction in joint pain, stiffness and swelling. They do not, however, prevent the development of joint erosions or damage. Furthermore, their effect rapidly reverses on drug cessation. Nevertheless, they have made an important contribution to the symptomatic treatment of patients with RA.

These drugs, of which there are a large number, are potent anti-inflammatory agents. Commonly used agents include diclofenac, naproxen, ketoprofen, sulindac, piroxicam, indomethacin and ibuprofen. They vary in their plasma half-lives, potency and degree of gastrointestinal toxicity. NSAIDs are usually administered orally, in conjunction with food, sometimes as an enteric-coated formulation to reduce gastrointestinal toxicity. They are occasionally given as a suppository, which also reduces, but does not eliminate, upper gastrointestinal toxicity. Unfortunately, many RA patients do not have the manual dexterity to insert a suppository. A number of NSAIDs are available as gels that can be applied topically to inflamed joints.

As a class of drugs, their use has been limited by adverse effects, particularly upper gastrointestinal toxicity, e.g. gastritis and peptic ulcer formation. In susceptible individuals, NSAIDs are nephrotoxic, by inhibiting prostaglandin-dependent compensatory renal blood flow. Some NSAIDs have characteristic adverse effects, e.g. headaches with indomethacin. By contrast, other NSAIDs have certain advantages, e.g. relative renal sparing with sulindac.

Two classes of cyclooxygenase enzymes have been described: COX-1 and COX-2. COX-1 enzymes are expressed constitutively in gastric mucosa, kidneys and other organs and are not inducible. By contrast, COX-2 enzymes are not usually constitutively expressed in tissues, but can be induced by certain molecules, e.g. cytokines at sites of inflammation. Traditional NSAIDs, as described above, inhibit both COX-1 and COX-2 enzymes (Fig. 1.17). However, selective COX-2 inhibitors have been developed, which have minimal effects on the COX-1 enzyme. These agents provide anti-inflammatory effects with less upper gastrointestinal toxicity. Celecoxib and rofecoxib were the first of this novel class of compounds. However, Rofecoxib was withdrawn because of a higher risk of patients developing myocardial infarction. The cardiovascular safety of Celecoxib and of

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<td><strong>Drug type</strong></td>
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<td>Analgesics</td>
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non-selective NSAIDs remains under a cloud. At time of writing, a definitive statement on their cardiovascular safety cannot be made. It seems wise to minimize or avoid their use in patients at high risk or with a previous history of cardiovascular disease.

### Interesting facts

#### NSAIDs and cardiovascular risk

Over the past 30 years, the main toxicity concern of NSAIDs has been the upper gastrointestinal toxicity system. However, since 2000 there has been increasing interest in the cardiovascular risk of NSAIDs, particularly the COX-2 selective inhibitor Rofecoxib (Vioxx). This culminated in its international withdrawal from the market. The cardiovascular risk of NSAIDs, whether COX-2-selective or not remains under a cloud.

#### Corticosteroids

The corticosteroids (or glucocorticoids) are hormones produced by the adrenal glands. They have potent anti-inflammatory and immunosuppressive properties. Their effect in RA, when used at high doses, is dramatic. Corticosteroid analogues have been produced synthetically by chemical modification of the natural hormone cortisol. This has resulted in a range of compounds with varying potencies and differential toxicities. By far the most commonly used compound is prednisone, which is cortisol. This has resulted in a range of compounds with varying potencies and differential toxicities. By far the most commonly used compound is prednisone, which is four to five times as potent as cortisol and has less mineralcorticoid activity, resulting in less fluid retention.

Prednisone is administered orally and acts rapidly to reduce inflammation, resulting in a lessening of joint swelling, pain and stiffness in RA. They bind to cytoplasmic cortisol receptors and are transported into the nucleus where they interfere with RNA processing of protein molecules. Corticosteroids act on a wide variety of target cells including leukocytes. They inhibit leukocyte chemotaxis (directed motion towards a stimulus), preventing circulating polymorphs, monocytes and lymphocytes from reaching sites of inflammation. They reduce vascular permeability and inhibit the production of cytokines and arachidonic acid metabolites, such as prostaglandins and leukotrienes.

Despite clinical efficacy, corticosteroids are toxic if used at high doses for prolonged periods. Corticosteroids have important effects on bone metabolism resulting in osteoporosis and eventual non-traumatic fractures (discussed in Ch. 5). They interfere with glucose metabolism and are diabetogenic. Corticosteroids cause salt and water retention and may precipitate or exacerbate hypertension. They interfere with ocular lens metabolism resulting in cataract formation. Their immunosuppressive action, while beneficial in reducing inflammation in RA, results in increased susceptibility to a wide range of bacterial and opportunistic infections, e.g. herpes zoster virus and fungal infections.

In general, corticosteroid side-effects are dose- and time-related. In order to limit toxicity, corticosteroids should be used for as short a time and at as low a dose as possible to achieve an anti-inflammatory effect. In recent years, a number of different regimens have been introduced to improve efficacy, while minimizing toxicity. These include the use of intermittent pulses of high-dose corticosteroids, e.g. monthly intravenous methylprednisolone. It has recently been demonstrated that continuous low-dose daily oral prednisone (≤7.5 mg/day) retards the development of bony erosions with minimal toxicity.

Another route frequently used to administer corticosteroids is intra-articular injection of depot preparations. This approach aims to deliver a high dose of corticosteroid, which is retained within the joint and reduces local inflammation with limited systemic absorption. This approach is effective in controlling local disease activity.

In patients with life- or major organ-threatening rheumatoid vasculitis, high-dose systemic treatment with

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**Case 1.1 Rheumatoid arthritis: 4**

**Case note: Corticosteroid treatment**

Despite 2 weeks of complete rest and a course of naproxen, Mrs Gale has only partly improved, remains in pain and cannot function effectively. After a telephone call by her general practitioner to a rheumatologist, she is advised to commence oral prednisone 10 mg per day as a morning dose.

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Fig. 1.17 The cyclooxygenase system: arachidonic acid is converted to prostaglandins by the enzyme cyclooxygenase (COX). There are two forms of this enzyme: COX-1 and COX-2. COX-1 produces prostaglandins responsible for maintaining normal stomach, kidney, intestine and platelet function. COX-2 produces prostaglandins found at inflammatory sites. Conventional NSAIDs block both COX-1 and COX-2. COX-2-specific inhibitors block only COX-2; thus they inhibit only those prostaglandins responsible for inflammation.
Disease-modifying anti-rheumatic drugs

Disease-modifying anti-rheumatic drugs (DMARDs) are a group of disparate compounds that in general share an important feature—the potential to retard the development of bony erosions in RA. Drugs in this category include gold compounds, sulfasalazine and the anti-malarial drug hydroxychloroquine. Immunosuppressive drugs are also sometimes considered in this group. These include the folic acid antagonist methotrexate, the antimetabolite azathioprine, the alkyllating agent cyclophosphamide, cyclosporin, which inhibits the production of IL-2 by T lymphocytes, and recently the pyrimidine antagonist leflunomide. Methotrexate is the most widely prescribed drug in this group.

There is no single mechanism by which these agents work. In general, they have a delayed onset of clinical action, measured in weeks to months rather than hours to days as with NSAIDs and corticosteroids. They all have potential toxicity and require careful and regular monitoring. Their initiation should be under the guidance of a rheumatologist. A detailed description of these drugs, their mechanism of action and toxicity profile is beyond the scope of this chapter.

There is a changing view on the way in which anti-rheumatic drugs, especially the DMARDs, are best used in RA. These agents are now introduced at the time of diagnosis rather than waiting for the appearance of radiological erosions, as was formerly done. The radiological and clinical outcome of patients with RA treated with DMARDs early in disease has improved. DMARDs are now being used in combination rather than as single agents, much as oncologists have used combination chemotherapy to treat haematological malignancy. Combinations of drugs with different mechanisms of action and different profiles of toxicity have been chosen. Combinations shown to be superior to single-agent DMARD treatment include: hydroxychloroquine, sulfasalazine plus methotrexate; and cyclosporin plus methotrexate.

Case note: Treatment with a disease-modifying anti-rheumatic drug

Mrs. Gale has her first appointment with the rheumatologist. She has had a good symptomatic response to oral prednisone and has markedly reduced joint pain and stiffness. Nevertheless, the rheumatologist recommends that she be commenced on a disease-modifying anti-rheumatic drug. He discusses the various options available and they decide to add enteric-coated sulfasalazine initially at 500mg per day. She is told about possible adverse drug effects and the need for regular blood counts to monitor for toxicity.

Interesting facts

Biological therapy for rheumatoid arthritis

At the time of writing the first edition of The Musculoskeletal System in 2000, the clinical role of biological therapy for RA was still unclear. However, that position has changed. There has been a dramatic expansion in both the range of diseases in which it is being applied and the range of agents that are now available. In the rheumatic field this has broadened to include psoriatic arthritis, anklylosing spondylitis as well as RA. Targets have now broadened from those directed against TNF-α to include B cells, co-stimulatory molecules, IL-1 receptor antagonist and IL-6 receptor.

Biological treatments

A new era is emerging with the introduction of biological agents in the treatment of RA. These include monoclonal antibodies directed against B cells (e.g. Mabthera) or co-stimulatory molecules (e.g. Abatacept) and those against inflammatory cytokines, e.g. TNF-α. Another approach is the use of soluble cytokine receptors, e.g. soluble TNF receptors, IL-1 receptor antagonists and IL-6 receptor. This approach is proving to be highly effective in both suppressing joint inflammation and in preventing the development of bony erosions. The main reservations are their high cost and uncertainty about their long-term safety.

In summary, the biological treatment of RA is complex and not for the occasional practitioner. It involves the use of specialized drugs with significant toxicity and requires considerable expertise in their appropriate use.

Surgery for rheumatoid arthritis

A significant number of RA patients require the skills of an orthopaedic surgeon at some stage of their disease. Two types of surgery are commonly used—synovectomy and reconstructive or joint-replacement surgery.

Synovectomy is the surgical removal of synovium from an inflamed joint. It can be performed as an open procedure or by arthroscopy, depending on the joint involved and the skill of the surgeon. The main indication is persistent arthritis in a joint, which fails to settle, despite medical therapy, including repeated intra-articular depot corticosteroid injections. The site most commonly treated is the knee. Less commonly treated are other joints or inflamed tendon sheaths—tenosynovitis requires synovectomy. Results are good with better symptomatic and radiographic outcome for an involved joint, compared with medical therapy, even after 3 years.
Reconstructive or joint-replacement surgery is reserved for patients with irreversibly damaged joints and severe articular cartilage loss, who are experiencing pain on using the joint, e.g. when walking short distances, and loss of function. The joints most commonly replaced are: the knee, hip, shoulder and metacarpophalangeal joints of the hands. There are many types of artificial joints with different biomechanical properties. Some require the use of cement to hold the joint prosthesis in place, while uncemented prostheses have been developed more recently. The results of surgery, particularly for knee and hip joint replacement, are excellent with markedly reduced pain and improved joint function. Half-lives for cemented knee and hip prostheses are approximately 8–10 years. Surgical revision is now a common procedure. The main local adverse outcomes of joint replacement surgery are cement loosing and, uncommonly, but very seriously, secondary bacterial infection. It is hoped that the use of uncemented prostheses will eliminate loosening of prostheses and result in longer prostheses half-life.

Other types of surgery are performed less commonly on RA patients, including bony fusion, particularly for unstable wrists, and carpal tunnel release for a median nerve entrapped in the carpal tunnel by persistently inflamed synovium (see Ch. 3).

Case note: Response to drug treatment
Some 3 years later, Mrs Gale is managing reasonably well on treatment with prednisone 5mg per day, sulfasalazine 2g per day, vitamin D and a calcium supplement. She is able to help with the family business, but has persistent synovitis in her right knee, despite repeated intra-articular depot corticosteroid injections. The latter produce only temporary relief of symptoms. She is referred to an orthopaedic surgeon for consideration of a synovectomy.

Case note: Response to surgical treatment
Mrs Gale undergoes an arthroscopic synovectomy with a good result. One year later she notices a recurrence of generalized joint pain, stiffness and fatigue. Blood tests indicate that her inflammatory parameters (ESR and C-reactive protein) have worsened. Her rheumatologist advises revision of her anti-rheumatic medications, with the addition of methotrexate.

Prognosis
The natural history of untreated RA is poor. It is associated not only with severe morbidity, but a shortening of life expectancy by 7–10 years. Patients die as a result of premature cardiovascular disease, infection or extra-articular disease. It has been claimed that the prognosis for untreated RA is similar to that of treated Hodgkin’s disease.

DMARDs slow disease progression, both clinically and radiologically, although complete remission off therapy is seldom achieved. It is thought that the earlier introduction of DMARDs and the use of combination therapy or biologicals can substantially improve the long-term prognosis and reduce mortality.

Further reading