“以器官系统为中心”原版英文教材

SYSTEMS OF THE BODY

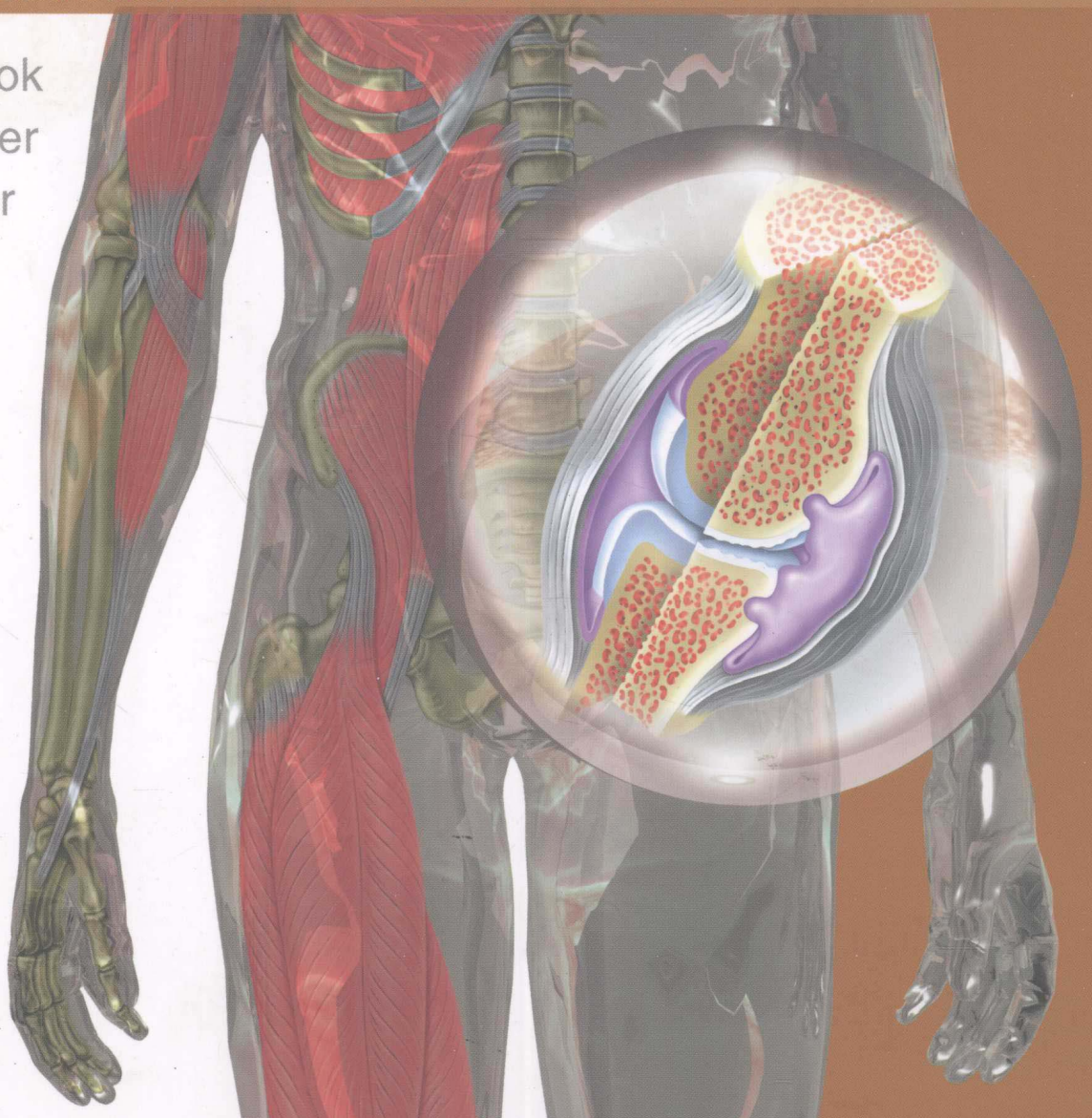
骨骼肌肉系统·第2版

The Musculoskeletal System

SECOND EDITION

BASIC SCIENCE AND CLINICAL CONDITIONS

Philip Sambrook
Leslie Schrieber
Thomas Taylor
Andrew Ellis



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骨骼肌肉系统 · 第2版

The Musculoskeletal System SECOND EDITION

BASIC SCIENCE AND CLINICAL CONDITIONS

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出版说明

“以器官系统为中心”的医学教学模式是国际医学教育的趋势。本系列书是世界著名医药卫生出版集团爱思唯尔公司出版的一套“以器官系统为中心”的医学基础课程教材，共分为骨骼肌肉系统、心血管系统、呼吸系统、消化系统、泌尿系统、神经系统、内分泌系统七个分册。该套教材第1版出版后受到世界各地许多医学院校的欢迎，并被多家进行“以器官系统为中心”教学的医学院校选定为教材。第2版根据第1版出版后教师和学生的反馈意见，结合医学知识的更新进行了全新修订。在编写内容上，该系列教材强调基础与临床的整合。每一章节都是围绕着一个临床病例展开，通过对病人问题的呈现以及解决过程引出对相关知识的探究，从而使与器官系统结构、功能以及疾病相关的重要的基础医学知识得到了完善的整合。在版式安排上，图框中的病例资料与正文中的医学知识完美匹配，一步一步地激起读者的求知欲望。

当前，我国很多医学院校都在进行“以器官系统为中心”的医学课程教学改革，为了借鉴国外教材的经验，北京大学医学出版社通过版权引进影印出版了这套“SYSTEMS OF THE BODY”原版英文教材。该系列书可以作为医学院校“以器官系统为中心”教学的教材和教学参考书，也可以作为医学院校进行英语授课的教材或供学生自学使用。

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This book is aimed primarily at medical students. In the past, many medical courses have been structured to teach, progressively, anatomy, physiology, pathology, pharmacology and, finally, clinical medicine. In line with new curricula of many medical schools, the aim of this book is to integrate basic with clinical science, using a problem-based learning approach. The first edition was a great success with much positive feedback and we have kept that model in the second edition, while updating the book to reflect the many new advances in the field. However, the self-assessment material now appears on the book's website.

Since musculoskeletal disorders account for about 20% of all visits to primary care physicians, it is essential that medical students have a good working knowledge and understanding of the relevant basic and clinical sciences to allow them to diagnose and treat such disorders. We believe that the ideal approach is problem-based learning and each chapter is devoted to a specific musculoskeletal pathology, illustrated by an appropriate case or cases. The book has been developed for that purpose. It is not a comprehensive textbook of rheumatology or orthopaedics, however many primary care physicians will find it useful to revise and update their knowledge about specific diseases.

In each chapter, a major rheumatic disease is introduced by a clinical case. This is followed by the relevant basic science in an integrated fashion so that the anatomy, biochemistry and physiology necessary to understand that disease are explained. Each of the chapters is written by a different experienced clinician; however, the approach to each follows a similar format that makes it easy for the reader to understand.

We are proud of the second edition of this book and confident that it represents a novel and practical guide to the teaching of musculoskeletal disorders in most medical schools. We anticipate that this will translate to better management of musculoskeletal conditions by primary care physicians.

1

RHEUMATOID ARTHRITIS AND THE HAND

Leslie Schrieber

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.
10. Describe the clinical pharmacology and use of non-steroidal anti-inflammatory drugs, corticosteroids, disease-modifying anti-rheumatic drugs and biological therapies in the treatment 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

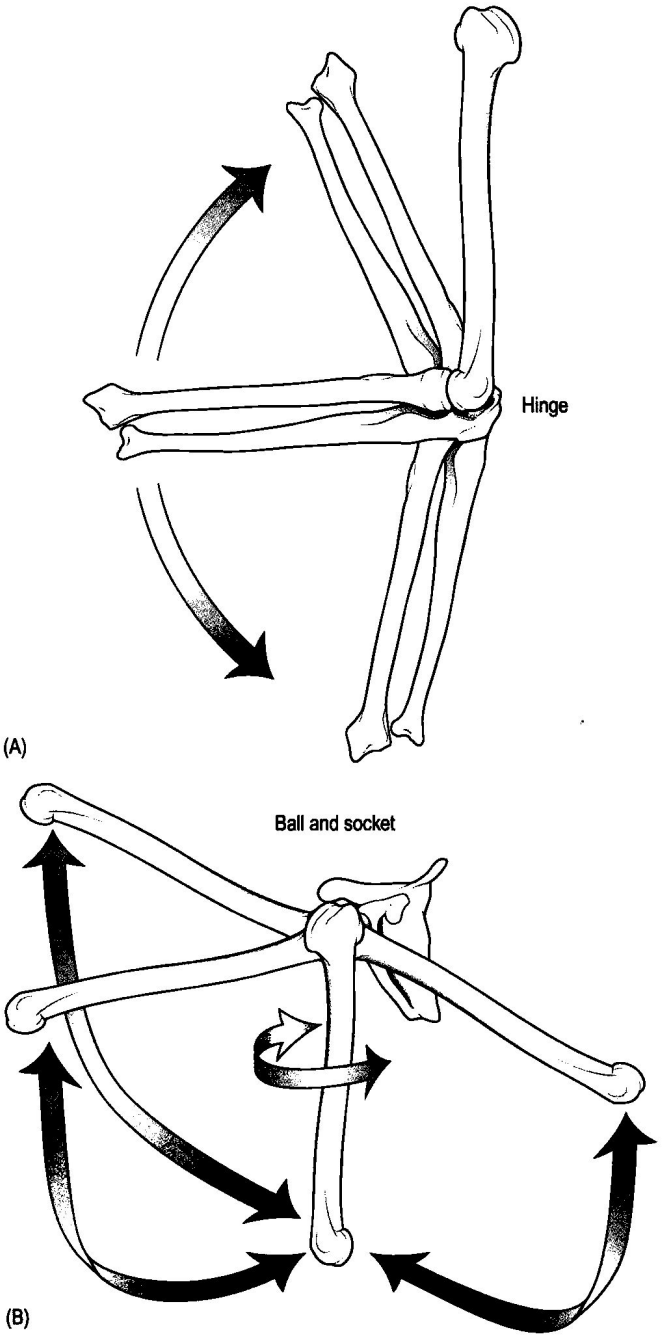


Fig. 1.1 Types of synovial joint: (A) hinge joint; (B) ball and socket joint.

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 synovium 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.

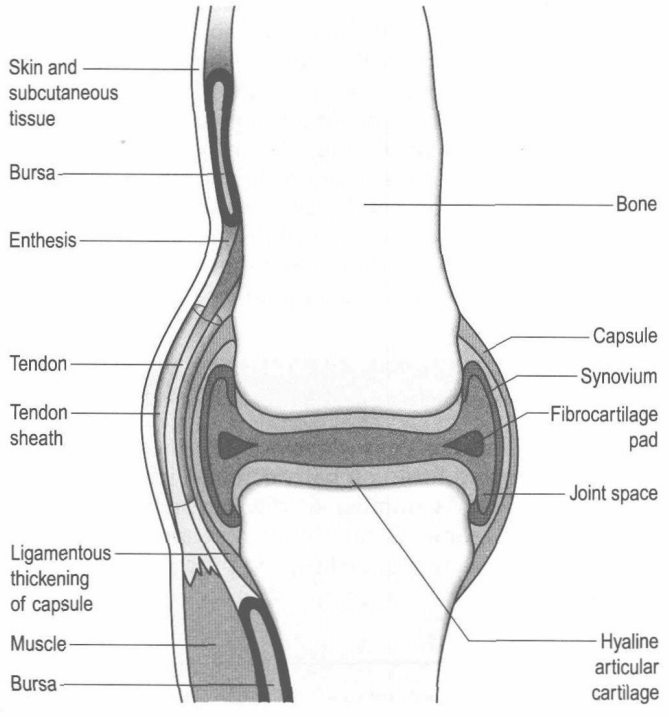


Fig. 1.2 Structure of a synovial joint.

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,

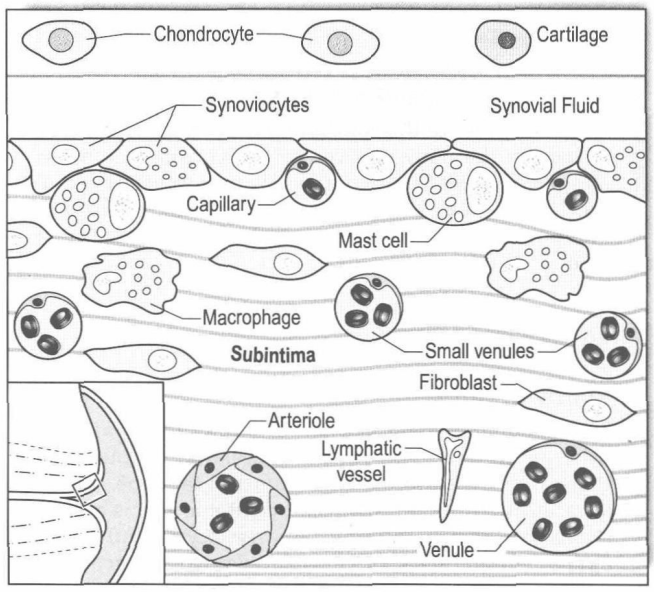


Fig. 1.3 Histology of a normal synovial joint.

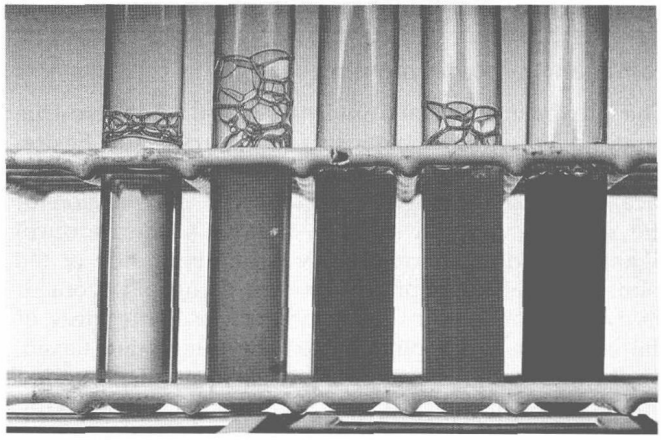


Fig. 1.4 Synovial fluid—macroscopic appearance, from left to right: normal or osteoarthritis; inflammatory (e.g. rheumatoid arthritis); gout; septic; and haemarthrosis (blood).

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.

Interesting facts

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.

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

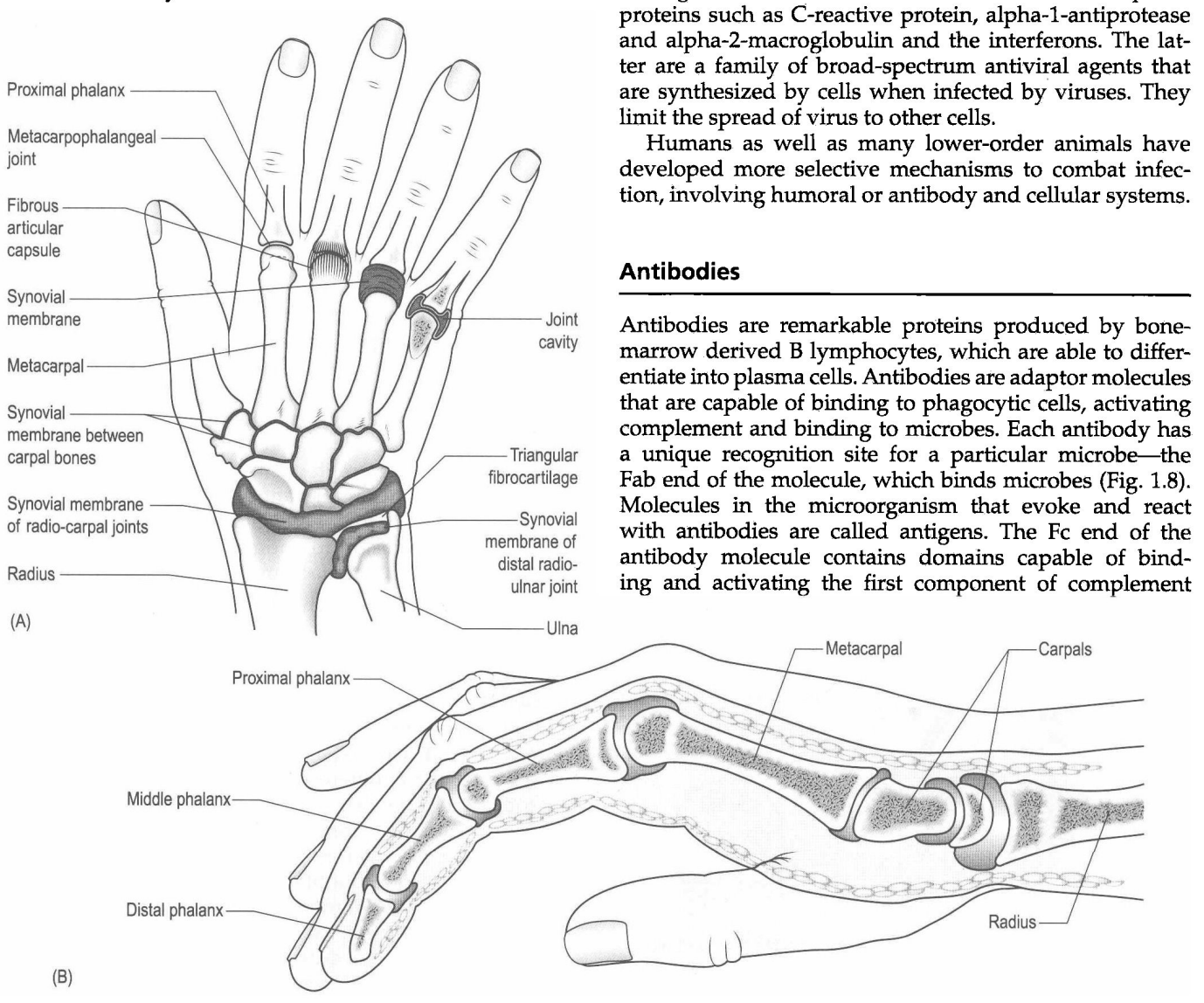


Fig. 1.5 Relationship of the synovial membranes of the wrist and metacarpal joints to adjacent bones: (A) dorsal view; (B) sagittal view showing in addition proximal and distal interphalangeal joints.

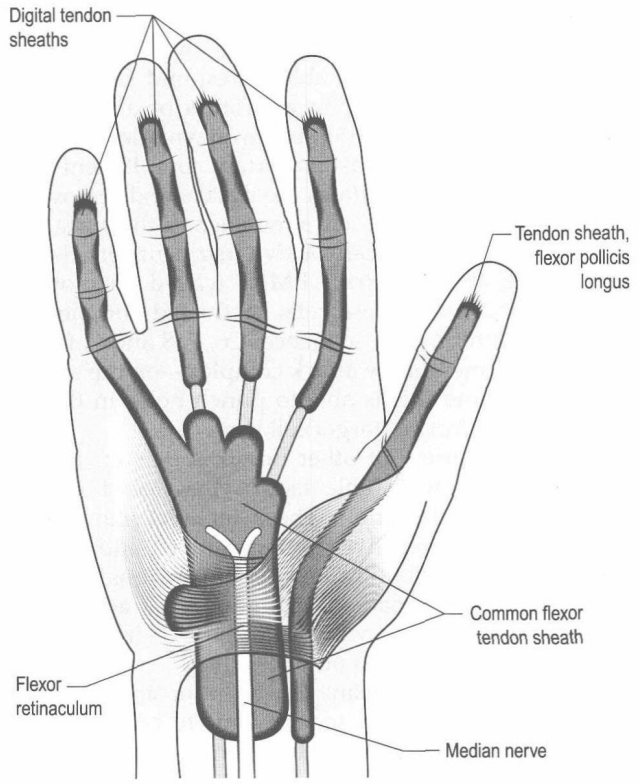


Fig. 1.6 Palmar view of the hand showing distribution of the synovial sheaths and flexor tendons.

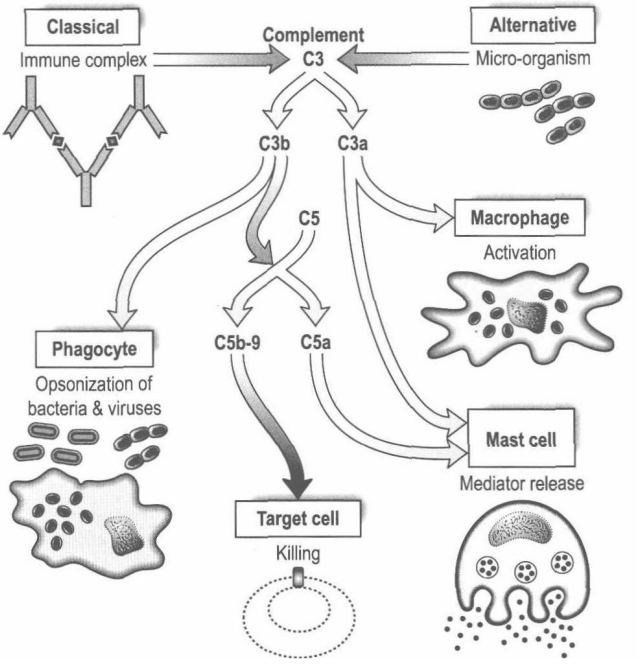


Fig. 1.7 The complement system: the classical complement pathway is activated by immune complexes of antibodies and antigens, while the alternative pathway is promoted by the lipopolysaccharide component of the cell wall of bacteria. Both result in conversion of C3 to C3b, which activates the terminal lytic complement sequence.

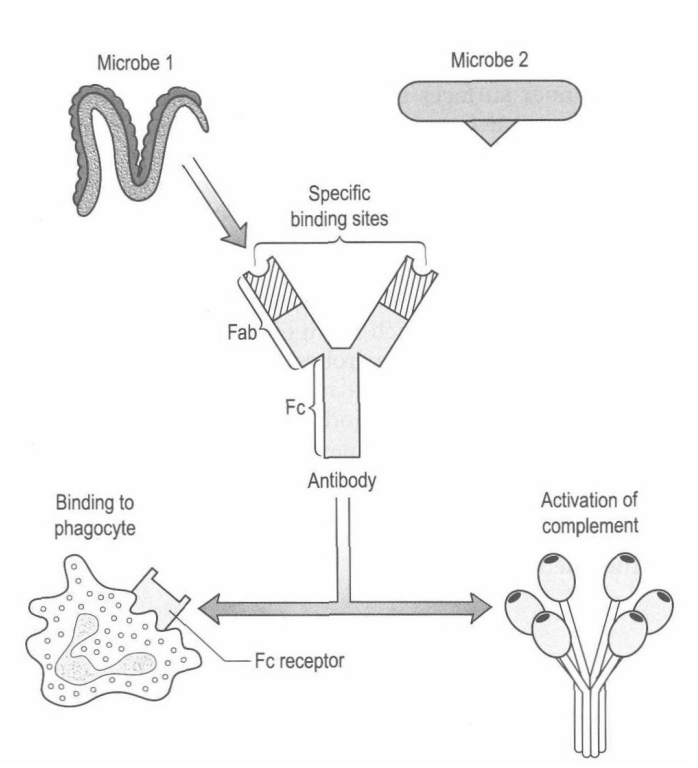


Fig. 1.8 The structure of an immunoglobulin: the antibody is an adaptable molecule able to bind specifically to microbial antigen 1, but not antigen 2 via its Fab end. The Fc end is able to activate complement and to bind to the Fc receptor on host phagocytic cells.

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.

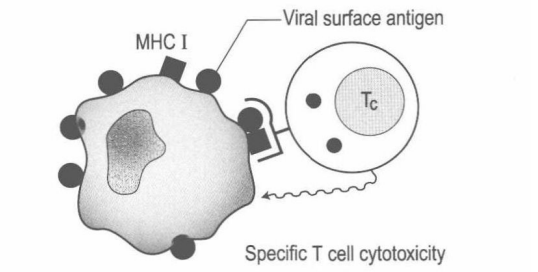


Fig. 1.9 Cytotoxic T cells are able to recognize viral surface antigen in association with MHC class 1 molecules and subsequently lyse the target cell.

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 defence, 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

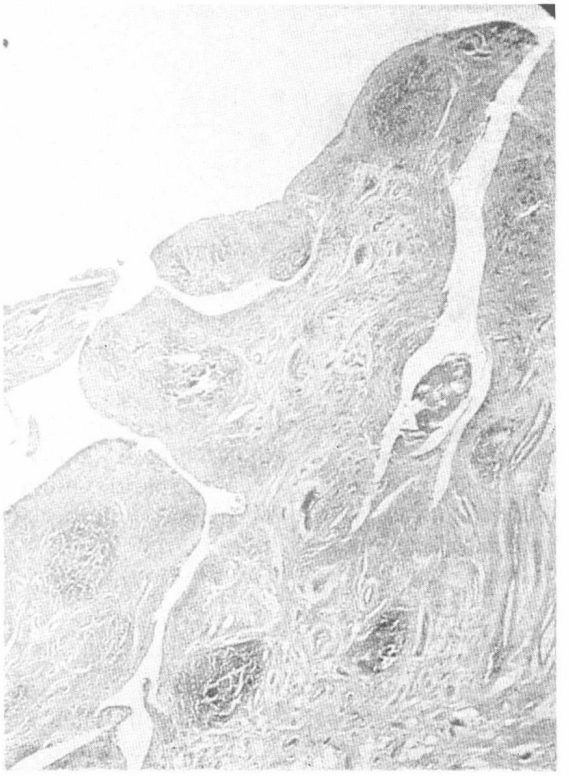
To gain a better appreciation of the processes occurring within an inflamed joint, it is necessary to understand synovial pathology. However, in clinical practice a synovial biopsy is not routinely performed as part of the diagnosis of inflammatory arthritis.

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).

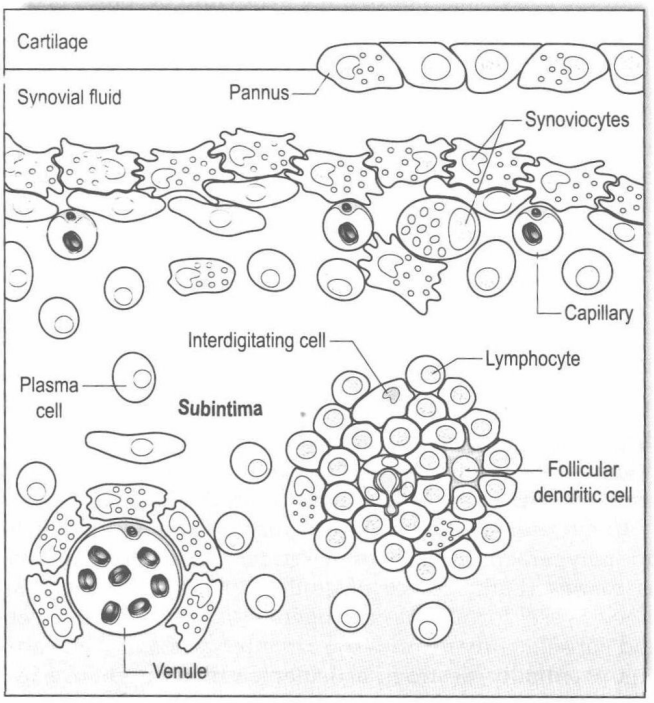
In the early stages of RA, the synovium becomes oedematous (contains excess fluid), thickened, hyperplastic (cells multiply excessively) and develops villus-like projections as found in normal small intestine (Fig. 1.10A). The synovial lining layer undergoes cellular proliferation and becomes multilayered. 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 CD4T (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

(A)



(B)



(C)

Fig. 1.10 Histopathology of a joint with rheumatoid arthritis. (A) Early disease: low-power micrograph of inflamed synovium. (B) Lymphoid nodular aggregates in synovial stroma (C) Diagram of the histopathology of a rheumatoid joint.

lead to fixed deformities. The destruction of cartilage predisposes to secondary osteoarthritis.

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