Processes in Pathology

AN INTRODUCTION FOR STUDENTS OF MEDICINE

MICHAEL J. TAUSSIG

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MICHAEL J. TAUSSIG
MA PhD
Principal Scientific Officer,
Department of Immunology,
Institute of Animal Physiology,
Babraham, Cambridge; and
Fellow of Trinity College,
University of Cambridge

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Preface

The original impetus to write an introductory textbook of General Pathology came out of teaching the subject to undergraduates at Trinity College, Cambridge. As all medical students are aware, there are several excellent comprehensive textbooks of General Pathology, most of which are daunting in their size and content. Compared with these, my aims were relatively modest, namely to describe concisely the most important pathological processes which it is essential for the student to understand, and to present them in a way which would both inform and stimulate. Some five years ago I approached Mr Per Saugman of Blackwell Scientific Publications and was encouraged by him in the conviction that a need existed for an introductory book to supplement, rather than supplant, the more exhaustive texts already available. In those far off days I probably considerably underestimated my task, for an adequate introduction to Pathology, however modest, demands a synthesis of most branches of medical science. Indeed I soon realised that the aim of a short book on General Pathology was almost a contradiction in terms. Accordingly, I restricted myself to five main areas, as the section headings make clear. The first two sections deal with the basic processes of response to injury and defence against infectious agents. The next two describe the non-infectious diseases which are the principal pathological causes of human mortality, namely those of the circulation and of neoplastic origin. The final section deals with the role of inheritance in disease. The reader will find that besides introducing basic concepts of Pathology, I have stressed the cellular, molecular and genetic mechanisms as far as possible and tried to convey the dynamic nature of the processes involved. Our understanding of mechanisms is progressing rapidly in some areas and hitherto established concepts are changing; I hope that the content of this book reflects this element of rapid progress in many fields, without losing sight of the fundamental principles on which that progress is based.

I wish to express my gratitude to several colleagues who have been kind enough to read parts of the manuscript and offer their comments and corrections. They are Dr Donald Kellaway, Dr David Bowyer, Dr David Brown, Professor Robin Coombs, Professor John Edwards, Professor Peter Lachmann, Dr Arnold Feinstein, Dr Brian Mahey, Dr Richard Binns and Dr Hugh Davies. I am especially indebted to Donald Kellaway, who read the entire manuscript and made a host of invaluable suggestions, and was the originator of Figure 1.16 and Figure 4.1. I am also indebted to Dr Arnold Feinstein, Dr Edward Munn and

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The debt I owe to my wife Hanna for her support, patience and understanding can be acknowledged but not adequately repaid.

Contents

Section 1
Inflammation

Introduction

Inflammation is the response of living tissue to injury. It is a fundamental pathological process, in Florey's words 'the backbone of pathology'. The term covers the progressive changes which occur when a tissue is damaged, but not destroyed, from the time of the original injury to final healing. Inflammation is thus a process not a state. The stimuli which give rise to inflammation may be physical, as in a cut or a burn, or chemical, after contact with noxious substances; they may be bacterial, as in infection by pathogenic micro-organisms, or immunological, in the conditions known as hypersensitivity. The basic events which follow these diverse stimuli, however, are generally similar. The end results of inflammation are often beneficial in that the inflammatory response leads, as far as possible, to the return of tissues to normal functioning after physical and chemical injury, and is a main line of defence against pathogenic microbes. A beneficial outcome is not always the case, however; inflammation can lead to fibrous scarring, and especially where hypersensitivity is involved, the inflammatory response can itself be a major cause of tissue damage.

Terminology

The occurrence of inflammation in a tissue or organ is indicated by the suffix *-itis*, as in appendicitis, meningitis, glomerulonephritis, and so forth. Inflammation is divided on the basis of duration into *acute* and *chronic*: acute inflammation lasts for hours or days, while chronic inflammation persists for weeks or months.

The stimuli which give rise to acute or chronic inflammation, and the course of events in each are often sufficiently distinctive to justify describing the acute and chronic process separately.

ACUTE INFLAMMATION

Main features of acute inflammation

The major or 'cardinal' signs of acute inflammation have been recognised for literally thousands of years. Celsus (30 B.C.–A.D. 38) formulated them as *rubor* (redness), *tumor* (swelling), *calor* (heat) and *dolor* (pain). To these is generally added *functio laesa* (loss of function) traditionally ascribed to Galen (A.D. 130–200). The understanding of the biological changes underlying these signs had to wait for detailed microscopic observations, the pioneering description being that of Cohnheim (1882). The main features of acute inflammation which he described in the tongue or foot-web of the frog hold good for inflammation as it occurs in many different situations in the human body. They may be summarised as follows.

1 Dilatation of blood vessels in the injured area. As a result flow of blood through the area is at first greatly increased, though with time the loss of fluid from the blood leads to progressive reduction in blood flow.

2 Increased permeability of vessel walls to protein. Blood vessel walls normally permit the free passage of water and low molecular weight solutes, but are only slightly permeable to plasma proteins. This permeability is increased during inflammation and leads to the accumulation of a protein-rich fluid termed the *inflammatory exudate*, in the extravascular space.

3 Emigration of white blood cells from the blood vessels into the exudate. Typically, leucocytes line up on the inner surface of the blood vessel, a process known as *pavementing* or *margination*, pass through the vessel wall between endothelial cells, and then migrate by amoeboid movement through the extravascular space towards the site of injury.

Thus acute inflammation is essentially a vascular phenomenon and all the changes which occur, including pavementing and emigration of leucocytes, are a consequence of the primary vascular responses. The outward signs of inflammation can also be explained on this basis. Redness and heat are both due to increased blood flow through the inflamed area resulting from vasodilatation. Swelling is caused by the accumulation of exudate. Pain is the result of the increase in tissue tension and the action of chemical substances released during inflammation. Swelling, pain and cell death can lead to loss of function of the inflamed part.

The triple response

Clearly, vascular changes play a major role in acute inflammation. The triple response, described first by Lewis (1927), is often used as an example of the vascular change in the skin to mild mechanical injury. It can readily be produced by a firm stroke with a ruler on the forearm or back. An immediate reddening or flush occurs at the site of injury; a zone of redness, known as a flare, then spreads outwards from the injured area; finally, a swelling or weal develops inside the injured area. The reaction reaches its peak within a few minutes of the injury being given. The triple response illustrates three of the cardinal signs—redness, heat and swelling. Briefly, the mechanism is as follows. As a result of the injury, various chemical substances, termed the *chemical mediators* of inflammation and including vasoactive amines and kinins (p. 25) are released locally. Their immediate effect is to cause vasodilatation at the site of the injury, producing the observed flush. The flare which follows, an area of surrounding vasodilatation, is of nervous origin, and is due to an axon reflex which results from stimulation of local nerve endings in the skin by the chemical mediators. In acute inflammation in general, however, the nervous contribution is not considered vital, since the main features of inflammation can occur in denervated tissue. The weal is the result of local increased permeability of the blood vessels, again caused by chemical mediators, resulting in local accumulation of a fluid exudate.

The small blood vessels

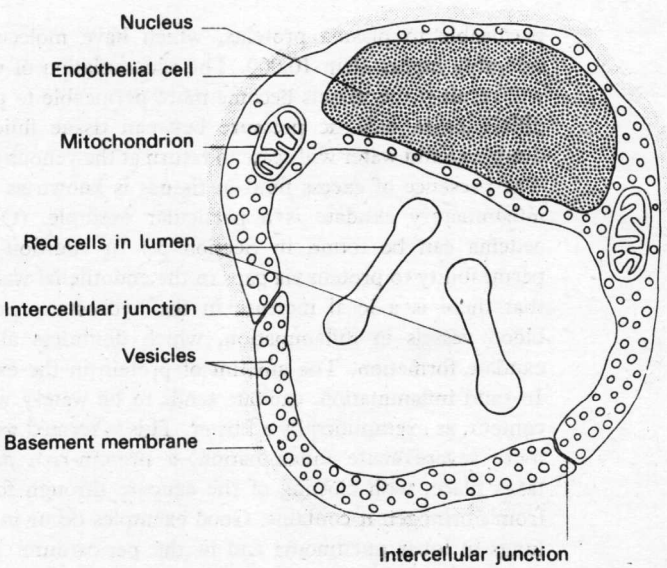
The arterioles, capillaries and venules of the microcirculation are the blood vessels mainly involved in inflammation. The dilatation of local

vessels is an essential early feature of acute inflammation. After very brief initial contraction, the arteriolar walls relax to increase blood flow. In the case of capillaries, which in their normal state often contain plasma but not red cells, the term dilatation really means the relaxation of precapillary sphincters to allow them to fill with blood. The basic structure of capillaries consists of a layer of endothelium surrounded by a basement membrane and pericapillary cells (Figure 1.1). An important feature of the vessel wall shown in Figure 1.1 is the intercellular junction between endothelial cells. These junctions are normally closed, but during inflammation they separate to produce gaps between the endothelial cells, which can be visualised by electron microscopy as shown in Figure 1.2. These gaps, which form under the influence of the chemical mediators of inflammation, are the physical basis of increased permeability of capillaries and venules during inflammation.

Normal tissue fluid and exudate

It is important here to understand the mechanism of formation of normal tissue fluid. This was described by Starling as the result of a balance between the hydrostatic pressure at the arteriolar end of a tissue blood supply tending to force water out of the blood vessels, and the resulting increased osmotic pressure of the blood, due principally to the plasma proteins, which tends to draw water back into the vessels from the tissues at the venous end. This is illustrated in Figure 1.3a. It is important to note that under normal circumstances, the capillaries allow water, salts and solute up to molecular weight of about 10,000 to pass freely into the surrounding tissue; they are only very slightly

Figure 1.1. Cross-section of a capillary as seen in the electron microscope (at about × 20,000 magnification).



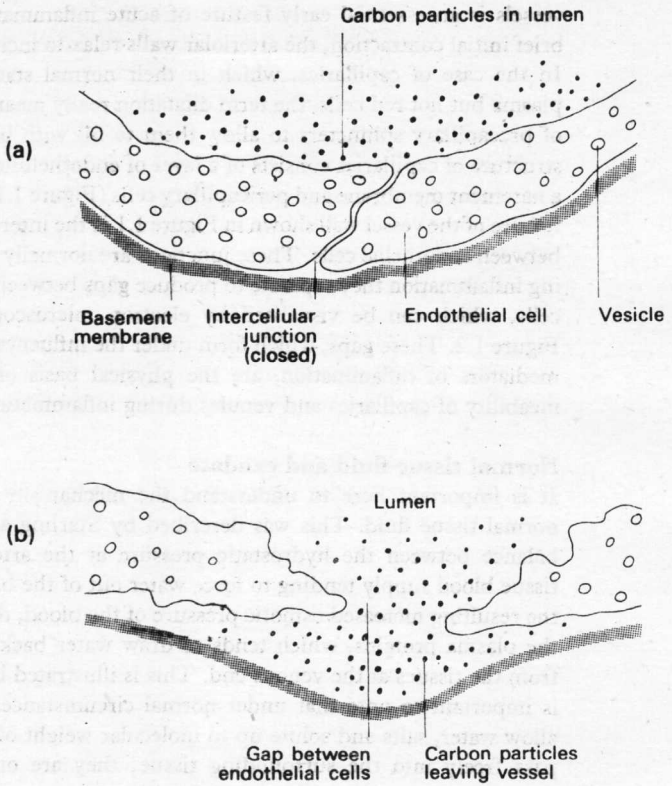


Figure 1.2. Wall of small blood vessel (a) in normal state, and (b) in inflammation. Carbon particles have been injected to demonstrate permeability change (as seen in electron micrographs approximately × 30,000).

permeable to plasma proteins, which have molecular weights considerably higher than 10,000. The accumulation of excess tissue fluid will result if the vessels become more permeable to proteins, since the difference in osmotic pressure between tissue fluid and blood will disappear and water will cease to return at the venous end (Figure 1.3b). The presence of excess fluid in tissues is known as *oedema*, of which inflammatory exudate is a particular example. (Other examples of oedema can be found in Section 3.) In addition to the increased permeability to protein via gaps in the endothelial wall, it can be shown that there is a local increase in the hydrostatic pressure inside the blood vessels in inflammation, which doubtless also contributes to exudate formation. The amount of protein in the exudate is variable. In mild inflammation, exudate tends to be watery with a low protein content, as exemplified by a blister. This is termed *serous* exudation. In more severe acute inflammation, a protein-rich *fibrinous* exudation takes place, with clotting of the exudate through formation of fibrin from fibrinogen it contains. Good examples occur in the alveoli of the lungs in lobar pneumonia and in the pericardium in fibrinous peri-

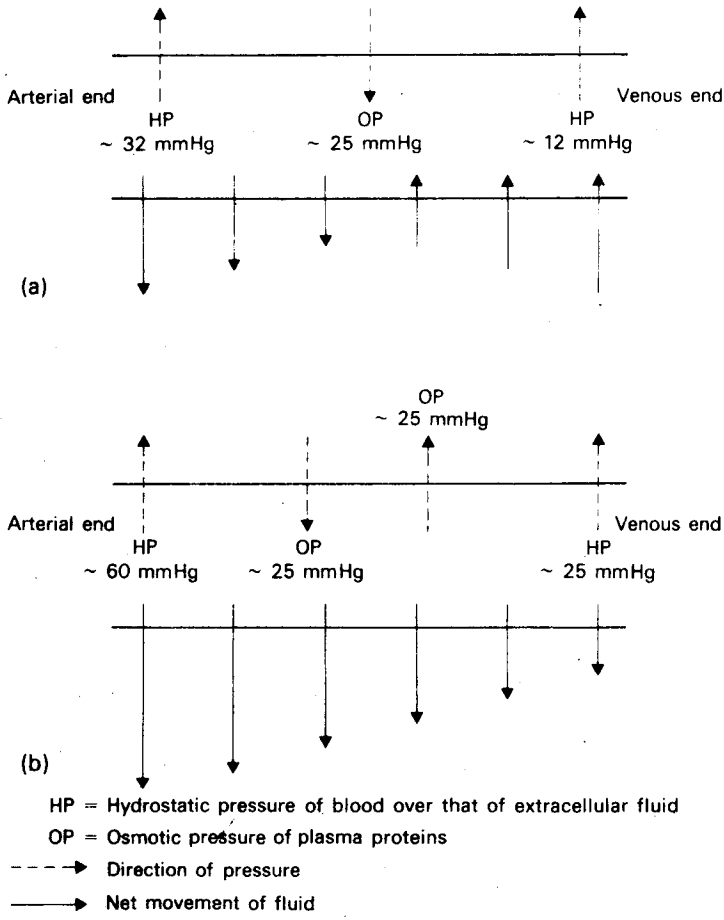


Figure 1.3. Exchange of fluid across walls of small blood vessels (a) under normal conditions, and (b) in acute inflammation.

carditis. A third type of exudation, in which pus is formed, *suppurative* or *purulent* exudation, is described on page 23.

Function of exudate

The inflammatory exudate has several important functions, particularly in relation to infection by pathogenic bacteria. Bacteria often produce tissue-damaging toxins which will be diluted by the exudate. As noted above, the exudate frequently clots, with deposition of fibrin which creates a mechanical obstruction to the spread of bacteria. Other very important protein components of exudate are the gamma globulins which include the *antibodies* to neutralise toxins (antitoxins) and assist in the uptake of bacteria by phagocytic cells (opsonins, described further below). Finally, the exudate is continuously drained off by the lymphatic vessels, and antigens such as bacteria and their toxins are thereby carried to the lymph nodes where immune responses can be mounted.

Lymphatics

The draining of the exudate during acute inflammation and resolution takes place mainly through the lymphatic system. The lymphatic vessels form an extensive network in practically all the tissues of the body. In the tissues themselves, the terminal lymphatics are blind-ending, thin-walled tubes with a wall of endothelium and basement membrane very similar to the blood vessels of the microcirculation. The colourless fluid they contain—lymph—drains from them into larger collecting lymphatics, eventually to still larger collecting channels and finally into the thoracic duct or the right lymph duct. These in turn discharge into veins at the root of the neck. Situated on the path from terminal lymphatics to the thoracic duct are the lymph nodes, about which more will be said in Section 2. Part of the function of the lymph nodes is to act as filters of the lymph, removing foreign proteins, particles, bacteria, etc., and initiating immune responses to them.

In normal tissues the function of lymphatics is to drain the extracellular fluid as it forms, eventually returning it and the small amount of protein it contains, to the blood. In acute inflammation, lymphatic drainage is greatly increased in volume and richer in protein. Despite their thin-walled structure, lymphatics do not collapse as the pressure of the inflammatory exudate on them increases; instead they are held open by fine fibres attached to the vessel wall which stretch as the tissue fills with exudate. Protein enters lymphatics through gaps between adjacent endothelial cells, in much the same way as it leaves the blood vessels. Bacteria are often transported in the lymph to the local lymph nodes. Virulent organisms, such as *Streptococcus pyogenes*, may cause inflammation in the walls of lymphatic vessels, which can then be seen as thin red streaks in the skin extending from the focus of infection (*lymphangiitis*); acute inflammation in the lymph nodes also frequently occurs, resulting in painful swelling of the nodes (*lymphadenitis*). This latter process greatly increases the filtering capacity of the node by jamming the sinus channels with neutrophils and later macrophages.

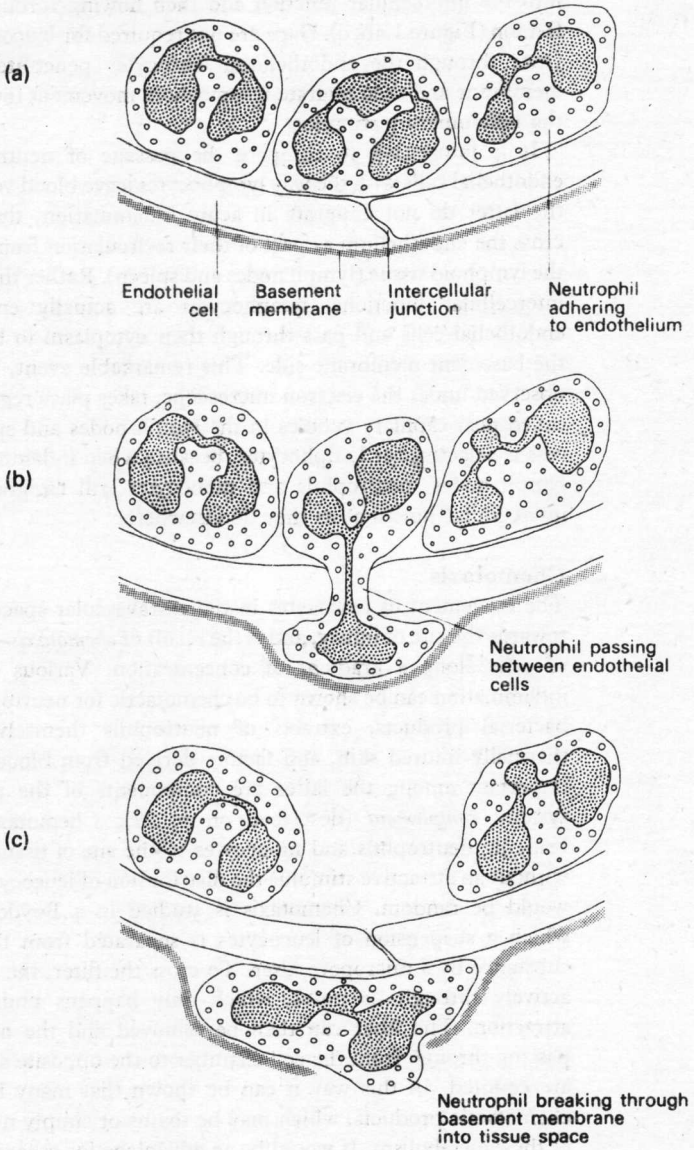
Migration of leucocytes into the exudate

In addition to proteins, the main component of inflammatory exudate is cellular, the most prominent cell types involved being the neutrophil polymorphonuclear leucocytes (neutrophils) and macrophages.* The cellular component is most pronounced in bacterial infection, especially with pyogenic (pus-forming) organisms such as *Streptococcus pyogenes* and *Staphylococcus aureus*, and rather less in purely physical injury. We have seen that as a result of initial vasodilatation, the blood flow through an area of inflammation is at first much increased. Typically, the cellular components of the blood are found centrally in the blood stream (axial flow) while the plasma flows peripherally and adjacent to the vessel wall. With time, the loss of plasma through the endothelium, due to its increased permeability, causes a slowing of the blood flow, which in turn results in more contact between blood cells and the endothelium

* Derived from blood monocytes.

of the vessel. It is then observed that leucocytes adhere to the endothelium, the inner surface of which may eventually become lined with a layer of adherent leucocytes (pavementing of leucocytes) as shown in Figure 1.4a. Since this process is only observed during inflammation, it is assumed that a change in the endothelium renders it 'sticky' for leucocytes at this time. Calcium is required, but the details of the mechanism of leucocyte adherence are unknown. It is mainly the

Figure 1.4. Emigration of leucocytes in inflammation. (a) Margination (pavementing) of neutrophil polymorphonuclear leucocytes; (b) and (c) stages in emigration.



neutrophils and monocytes which adhere to the wall in this way; lymphocytes, which are not generally found in acute inflammatory exudates, do not adhere to endothelium. Having adhered, the leucocytes actively traverse the vessel wall, a process known as *emigration.* (The term *diapedesis* is used by some authors to describe leucocyte emigration. The correct use of diapedesis, however, is the passive loss of red cells from the vessels under pressure, which takes place through the intercellular junctions and may occur as a late event in acute inflammation in severe injury). It can be shown by electron microscopy, that the leucocyte passes between endothelial cells, by thrusting a pseudopod into the intercellular junction and then flowing through in amoeboid fashion (Figure 1.4b, c). Gaps are not required for leucocyte emigration. Once through the endothelium, leucocytes penetrate the basement membrane and then migrate by amoeboid movement towards the site of the inflammatory stimulus.

It is interesting to compare the passage of neutrophils between endothelial cells with the way lymphocytes leave blood vessels. Although the latter do not emigrate in acute inflammation, they do regularly cross the endothelium as part of their recirculation from the blood into the lymphoid tissue (lymph nodes and spleen). Rather than pass through intercellular junctions, lymphocytes are actually engulfed by the endothelial cells and pass through their cytoplasm to be deposited on the basement membrane side. This remarkable event, which has been observed under the electron microscope, takes place regularly in vessels called post-capillary venules in the lymph nodes and spleen. The process is selective for lymphocytes, because when inflammation occurs in lymph nodes, neutrophils and monocytes still emigrate through the intercellular junctions as they do elsewhere.

Chemotaxis

The movement of leucocytes in the extravascular space is directional, towards the site of injury, and is the result of *chemotáxis*—the movement of cells along a gradient of concentration. Various components of inflammation can be shown to be chemotactic for neutrophils, including bacterial products, extracts of neutrophils themselves, extracts of thermally injured skin, and factors derived from blood plasma. Most important among the latter are components of the plasma enzyme system, *complement* (described on p. 27). Chemotaxis is vital in bringing neutrophils and monocytes to the site of tissue damage, since without an attractive stimulus the distribution of leucocytes in the tissue would be random. Chemotaxis is studied in a Boyden chamber, in which a suspension of leucocytes is separated from the chemotactic substance by a micropore filter. To cross the filter, the cells must pass actively through its pores, which only happens under chemotactic attraction. The filter can then be removed and the number of cells passing through from the cell chamber to the opposite side of the filter are counted. In this way it can be shown that many bacteria release chemotactic products, which may be toxins or simply normal products of their metabolism. It would be an advantage for organisms to prevent

chemotaxis, and some toxins such as streptococcal streptolysin have the ability to inhibit neutrophil chemotaxis. Their effectiveness *in vivo*, however, is not known. Neutrophils migrate rapidly along a chemotactic gradient, whereas monocytes move rather slowly. This may account in part for the delay in appearance of monocytes in inflammatory exudates. Neutrophils contain a substance which attracts monocytes, which could also explain the sequential appearance of these cells in acute inflammation. Sensitised lymphocytes also produce monocyte chemotactic factors which are important in cell-mediated immunity (p. 115). The absence of lymphocytes from acute inflammatory exudate reflects selectivity of chemotactic factors for different cell types.

Leucocytes involved in acute inflammation

The morphology of the cells involved in acute inflammation is shown in Figure 1.5. The neutrophils are granulocytes which arise from specific precursors in the bone marrow; they are end cells incapable of further division. Their important morphological feature, besides the typical lobed nucleus, is the presence in the cytoplasm of two types of granule, the azurophilic *lysosomal granules* and the neutrophilic *specific granules*. The lysosomes contain degradative enzymes which play a major role in neutrophil function, including phosphatases, myeloperoxidase, nucleases, nucleotidase, lysozyme, cathepsin, β-glucuronidase, collagenase, elastase, kallikrein and plasminogen (precursor of plasmin or fibrinolysin). The more numerous specific granules contain lactoferrin and lysozyme. Because of their short life-span (3–4 days) neutrophils often tend to die at the site of inflammation, and in so doing release their lysosomal enzymes which then proceed to digest both the dead neutrophils themselves (autolysis) and dead tissue cells round about, as well as extravascular fibrin. The solubilisation of debris is the main role of neutrophils in sterile inflammation, such as mild thermal burns. The other major function of neutrophils is their ability to take up, kill and intracellularly digest pathogenic bacteria by the process known as *phagocytosis*. This is of paramount importance in infectious disease, where neutrophils are often the first line of defence against bacterial invaders. Neutrophils also contain, and release, a substance called *endogenous pyrogen* which is partly responsible for the development of fever during acute inflammation. This is a lipoprotein probably released during phagocytosis which acts on the thermoregulatory centres of the brain. Fever during inflammation is probably of little advantage and rarely harmful.

Sometimes eosinophil polymorphonuclear leucocytes (eosinophils) rather than neutrophils are found in areas of inflammation, particularly in helminth infections and in hypersensitivity reactions such as hay fever and allergic asthma. In addition to other enzymes, eosinophil granules contain some which degrade certain mediators of inflammation such as histamine (see p. 25).

The other major cell type in acute inflammation is the macrophage. Macrophages are derived from blood monocytes, and apart from obvious morphology (Figure 1.5) they differ from polymorphs both in