2. Acute inflammation, healing and repair

Introduction

Inflammation is an almost universal response to tissue damage by a wide range of harmful stimuli including mechanical trauma, tissue necrosis and infection. The purpose of inflammation is to destroy (or contain) the damaging agent, initiate repair processes and return the damaged tissue to useful function. Inflammation is somewhat arbitrarily divided into ***acute*** and ***chronic inflammation*** but in reality the two often form a continuum. Many causes of tissue damage provoke an acute inflammatory response but some types of insult may bring about a typical chronic inflammatory reaction from the outset (e.g. viral infections, foreign body reactions and fungal infections). Acute inflammation may ***resolve*** or ***heal by scarring*** but may also progress to chronic inflammation and it is common for a mixed acute and chronic response to coexist. This chapter describes acute inflammation and its sequelae, while chronic inflammation is discussed in Chapter 3. Many examples of acute and chronic inflammation are illustrated in Chapter 4.

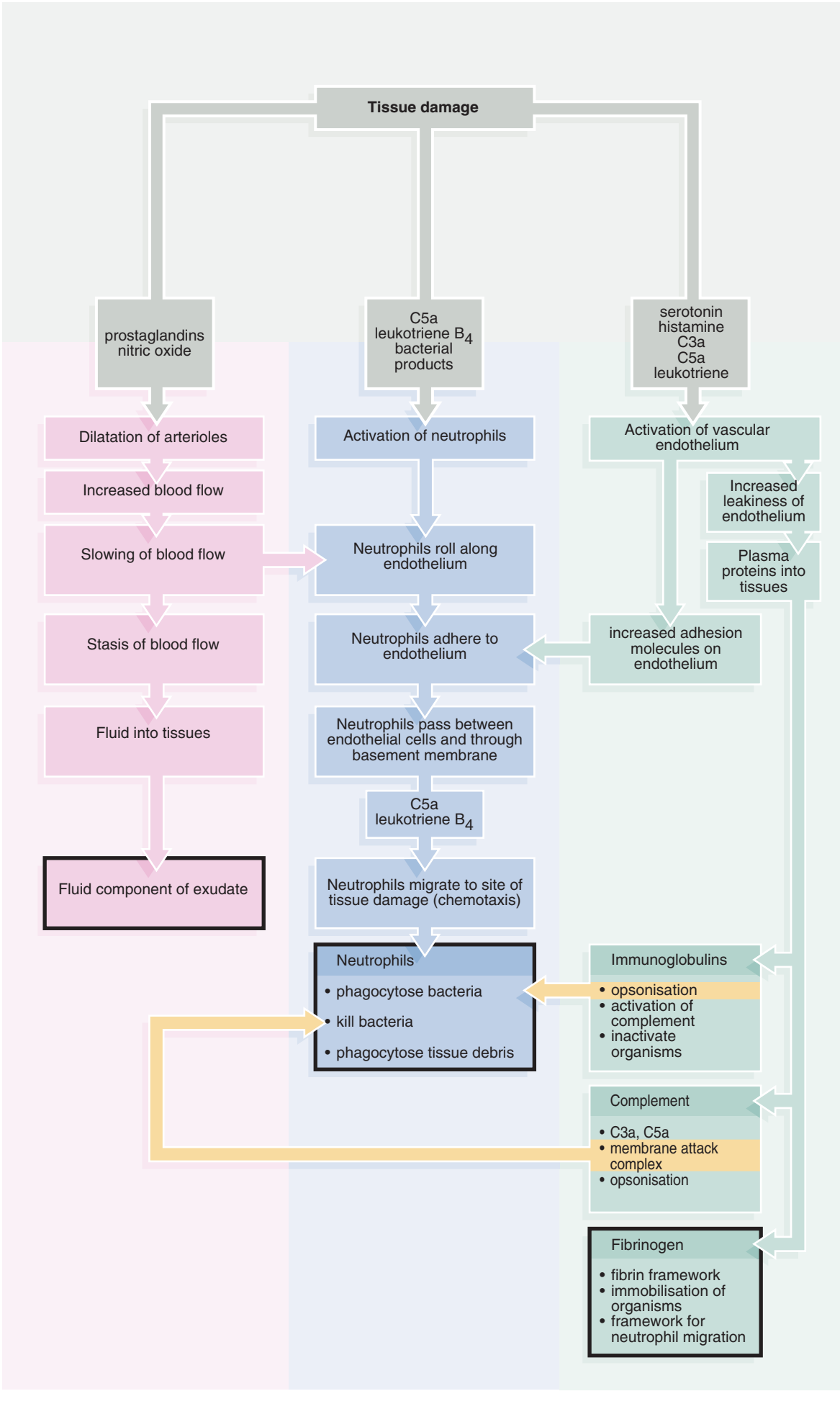
There are three major and interrelated components of acute inflammation:

- **Vascular dilatation**
  - relaxation of vascular smooth muscle leading to engorgement of tissue with blood (*hyperaemia*).
- **Endothelial activation**
  - increased endothelial permeability allows plasma proteins to pass into tissues
  - expression of adhesion molecules on the endothelial surface mediates neutrophil adherence
  - production of factors which cause vascular dilatation.
- **Neutrophil activation**
  - expression of adhesion molecules causes neutrophils to adhere to endothelium
  - increased motility allows emigration from vessels into surrounding tissues
  - increase capacity for bacterial killing.

Fig. 2.1 **Mechanism of early acute inflammation**

Acute inflammation may develop over minutes or hours depending on the type and severity of the tissue damage and generally lasts hours to days. Vascular dilatation, increased vascular permeability and neutrophil activation and migration are interdependent processes and all three are required for the full response. Immediately after the tissue damage has occurred, there may be a brief phase of constriction of arterioles but this is followed within seconds by arteriolar dilatation, which leads to increased blood flow to the area. At much the same time, gaps form between endothelial cells of the capillaries allowing protein-rich plasma to leak into the tissue. The dilated capillaries become engorged with red cells and blood flow slows and then stops. The slowing of blood flow brings neutrophils into contact with the endothelial cells, which have been busy inserting adhesion molecules into their plasma membranes. As the neutrophils come into contact with the endothelium, ***adhesion molecules*** on the neutrophil plasma membrane bind to their complementary receptors on the endothelial cells and become stuck. Activation of the neutrophils plays a role here so that activated neutrophils are more likely to stick. Meanwhile in the tissues, the plasma-derived proteins undergo various changes. The ***complement cascade*** is initiated (alternative pathway) forming components with a wide range of activities. ***Immunoglobulins*** bind to any causative organisms immobilising them, and forming immune complexes that further activate complement (classical pathway). ***Fibrinogen*** is cleaved to form a network of ***fibrin*** that impedes the movement of fibrin monomers which polymerise to form a pathogenic organisms and provides a framework for the migration of neutrophils. The increased fluid in the tissue causes an increased flow of lymph to carry immune complexes and antigenic material to the lymph nodes where a specific immune response is initiated over a matter of days. The neutrophils pass through the basement membrane of the endothelium and move along a concentration gradient of ***chemotactic factors***. When they arrive at the site of injury, the activated neutrophils phagocytose necrotic tissue debris and pathogenic organisms. The activation of the neutrophils makes them more efficient at phagocytosis and killing. Opsonisation of bacteria by complement and immunoglobulins renders them more readily phagocytosed.

This entire process is orchestrated by a plethora of chemical mediators derived from injured tissues, bacteria, plasma proteins and leucocytes. The most important of these mediators are indicated at their sites of action. Note that some mediators have multiple actions.


Tissue damage
prostaglandins
nitric oxide
C5a
leukotriene B4
bacterial
products
serotonin
histamine
C3a
C5a
leukotriene
Dilatation of arterioles
Activation of neutrophils
Activation of vascular endothelium
Increased blood flow
Increased leakiness of endothelium
Slowing of blood flow
Neutrophils roll along endothelium
Plasma proteins into tissues
Stasis of blood flow
Neutrophils adhere to endothelium
increased adhesion molecules on endothelium
Fluid into tissues
Neutrophils pass between endothelial cells and through basement membrane
C5a
leukotriene B4
Fluid component of exudate
Neutrophils migrate to site of tissue damage (chemotaxis)
Neutrophils
• phagocytose bacteria
• kill bacteria
• phagocytose tissue debris
Immunoglobulins
• opsonisation
• activation of complement
• inactivate organisms
Complement
• C3a, C5a
• membrane attack complex
• opsonisation
Fibrinogen
• fibrin framework
• immobilisation of organisms
• framework for neutrophil migration

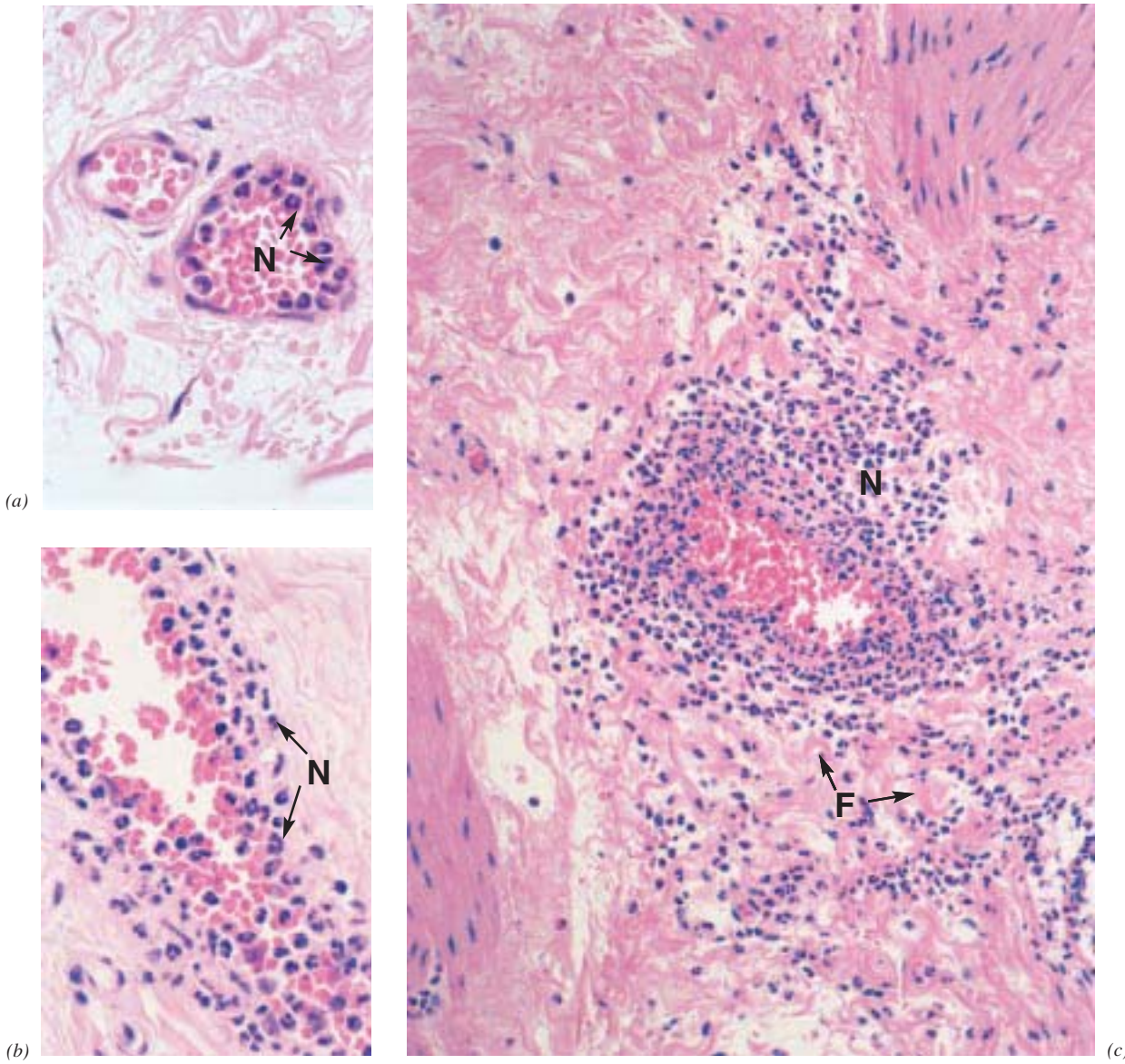
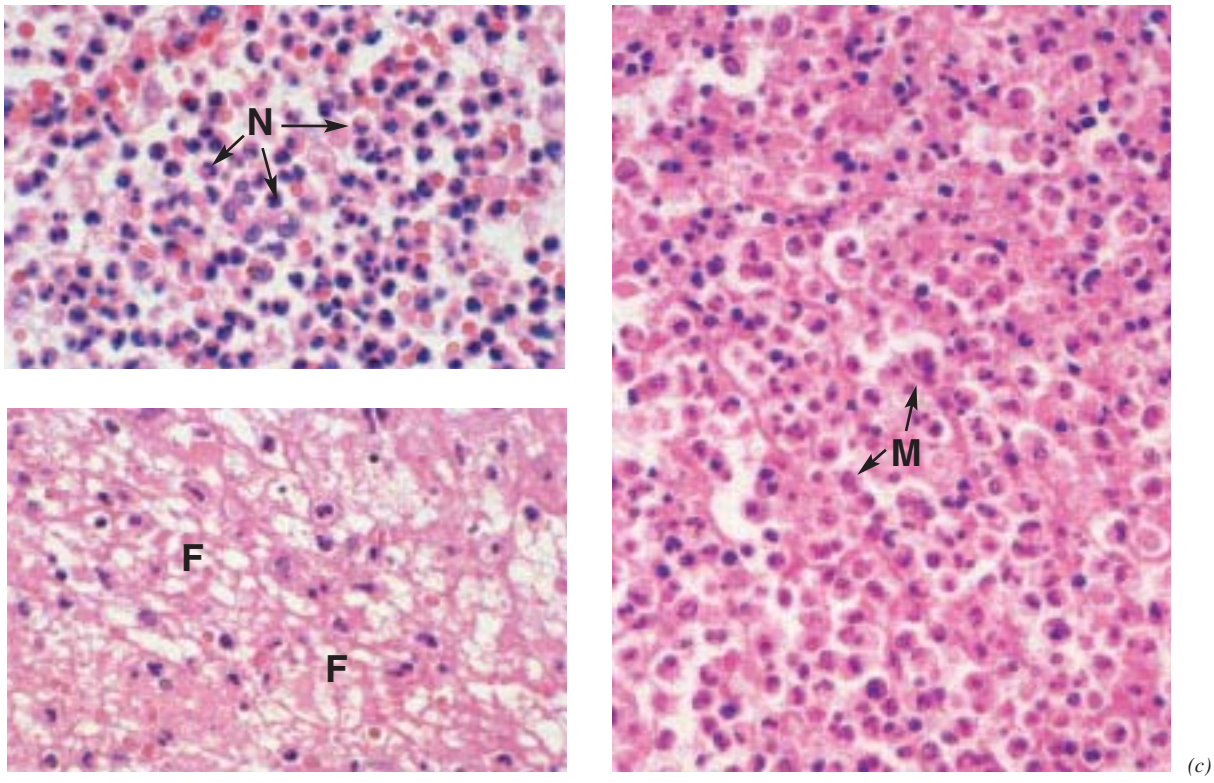


Fig. 2.2 Formation of the acute inflammatory exudate
(a) Early vascular changes (HP) (b) Migration of neutrophils (HP) (c) Early formation of exudate (LP)

This set of micrographs illustrates the sequence of events during the initial phases of the acute inflammatory response described in Figure 2.1. In micrograph (a), two small capillaries are shown. Both vessels are dilated and in the larger, neutrophils **N** line up around the periphery of the vessel, a process termed ***pavementation***. These neutrophils are adherent to the endothelium. The surrounding fibrous connective tissue contains clear spaces owing to the accumulation of fluid (***oedema***) between the collagen bundles. Plasma proteins, although not visible, are also found free within the tissue. These include the blood coagulation protein ***fibrinogen*** which is converted to insoluble ***fibrin*** which will later form a meshwork within the tissue.

The neutrophils pass through the vessel wall by extending their pseudopodia between adjacent endothelial cells. The neutrophils then penetrate the endothelial basement membrane and move into the perivascular connective tissue as shown in micrograph (b). Once in the extravascular tissues, the neutrophils are attracted to the site of tissue damage by chemotactic agents such as the complement component ***C5a*** and migrate actively towards higher concentrations of these agents (***chemotaxis***); this is shown in micrograph (c). At the site of tissue damage, neutrophils play an important role in destruction of microorganisms. Phagocytosis of organisms is promoted by a coating of immunoglobulin and complement (***opsonisation***) and activated neutrophils are more effective at killing pathogens. These three components, namely water, proteins (including fibrin) and neutrophils, form the typical ***acute inflammatory exudate***.

Chemical mediators, although not visible, control this process. Vasodilatation is mediated by ***prostaglandins*** and ***nitric oxide***. Increased vascular permeability is controlled by substances such as the vasoactive amines, serotonin and histamine, complement components ***C5a*** and ***C3a, leukotrienes C_4, D_4, and E_4, platelet activating factor (PAF)*** and ***substance P***. Leucocyte activation and chemotaxis are influenced by ***C5a***, ***leukotriene B_4***, various ***chemokines*** and bacterial products.



(a) (b) (c)

Fig. 2.3 Acute inflammatory exudate
(a) Neutrophilic exudate (HP) (b) Highly fibrinous exudate (HP) (c) Mixed neutrophil–fibrin exudate (MP)

The quality of an acute inflammatory exudate varies depending on the state and nature of the injured tissue and the type of noxious agent involved. These micrographs show established acute inflammatory exudates differing from one another in the number of neutrophils **N** and amount of fibrin **F** present; fibrin strands stain bright pink with H&E staining.

Micrograph (a) shows an acute inflammatory exudate in which neutrophils are the main component, usually the case when the damaging stimulus is a bacterial infection; this neutrophil-rich exudate is commonly called '***pus***', and this pattern therefore often called ***acute purulent inflammation***.

Micrograph (b) shows a acute inflammatory exudate in which fibrin is the main component (***fibrinous exudate***); this occurs most commonly on serosal surfaces (see Fig. 2.6b).

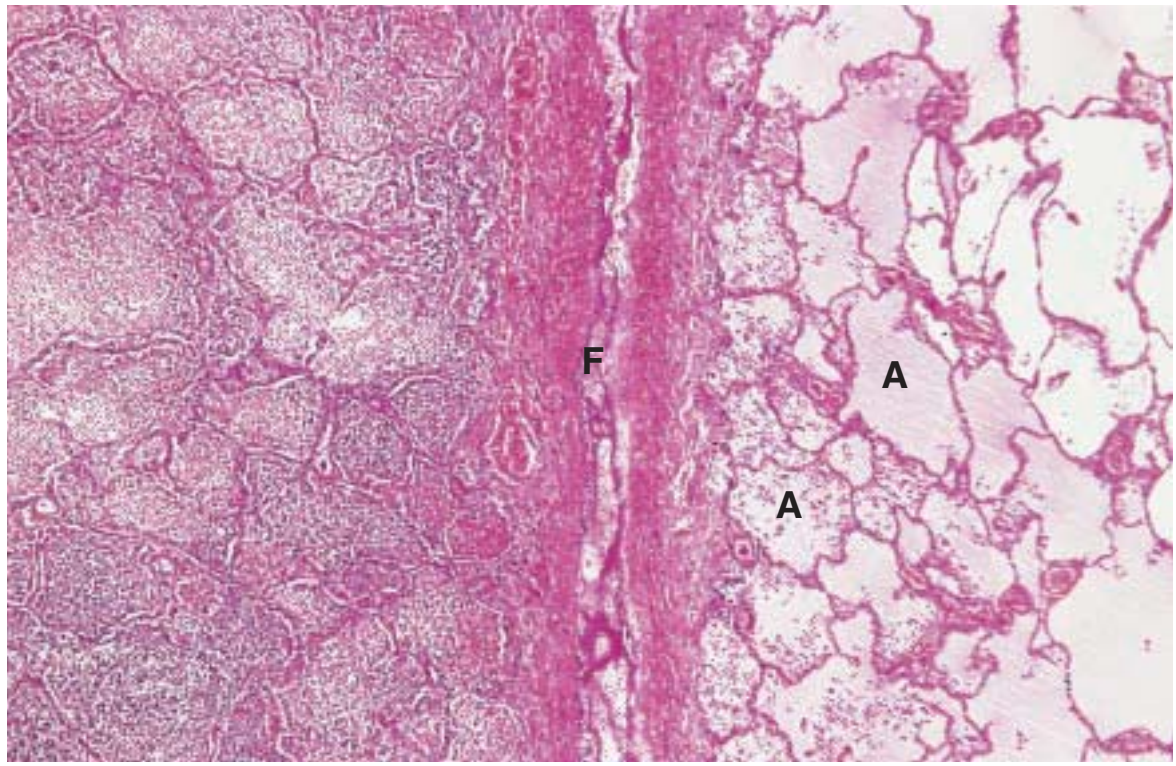
Micrograph (c) shows a mixed neutrophilic/fibrinous exudate at a late stage, with some macrophages entering the picture.

Once in the extravascular tissues, neutrophils engulf necrotic fragments of damaged tissue, breaking them down with their lysosomal enzymes. When tissue damage has been caused by bacteria, as in lobar pneumonia (Fig. 2.4), neutrophils phagocytose and kill the causative organisms. The activity of neutrophils is limited by their inability to regenerate lysosomal enzymes and, after a ***respiratory burst*** which generates the hydrogen peroxide used to kill bacteria, the neutrophils degenerate. Mature neutrophils only survive for 3 days but their numbers are maintained in acute inflammation by new arrivals from the circulation; the systemic response to acute inflammation is release of neutrophils from bone marrow into the blood, resulting in a ***neutrophil leukocytosis***. Degenerate neutrophils can be recognised by condensation (pyknosis) and fragmentation (karyorrhexis) of the nuclei and, eventually, cytoplasmic disintegration; this is best seen in micrograph (b).

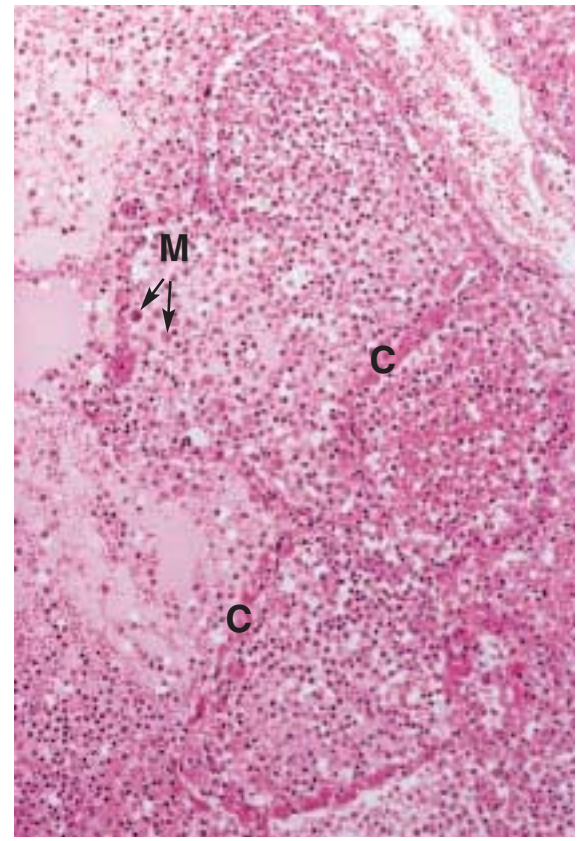
Although the dominant cell type in the early phases of acute inflammation is the neutrophil, within 24 hours macrophages also begin to migrate into the damaged tissue and by 48–72 hours are the predominant cell type. The macrophages are derived from circulating blood monocytes. Macrophages **M**, a few of which can be seen in micrograph (c), continue the phagocytic work begun by neutrophils and ultimately mop up the degenerate neutrophils and fibrin strands. Unlike neutrophils, macrophages can regenerate their lysosomal enzymes and are capable of sustained activity. The monocytes may also act as antigen-presenting cells to initiate specific immunological responses.

The fate of the acute inflammatory exudate depends on a variety of factors including the nature and destructibility of the injurious agent, the extent of tissue damage and the properties of the tissue in which the damage has occurred.

The process of acute inflammation terminates by one of four main processes: ***resolution***, ***organisation and repair***, ***abscess formation*** or ***chronic inflammation***.



(a)



(b)

Fig. 2.4 Acute inflammation of lung: lobar pneumonia (a) LP (b) MP

An important cause of acute inflammation in the lung parenchyma is bacterial infection causing lobar pneumonia. However, the most common type of pneumonia is bronchopneumonia (Fig. 12.5) where infection spreads from the bronchi into adjacent lung tissue. In lobar pneumonia, which is less common now than previously, a whole lobe becomes solidified as a result of a massive outpouring of fluid, fibrin and neutrophils into the alveolar spaces. This pattern of pneumonia is most commonly caused by pneumococcus (*Streptococcus pneumoniae*).

In micrograph (a), a portion of lung is shown with an interlobar fissure **F** running vertically. The lung tissue on the left shows obliteration of alveolar spaces by purple-staining masses of inflammatory cells (mainly neutrophils) with associated fibrin; this is termed ***consolidation***. Alveolar walls can just be discerned. The dense inflammatory exudate is sharply limited by the interlobar fissure. The lung on the right of the fissure shows the earliest changes of acute inflammation, with faint pink-staining serous exudate in alveoli **A** and early neutrophil emigration giving rise to a few scattered cells within the alveolar spaces.

At higher magnification in micrograph (b), alveolar wall capillaries **C** are seen engorged with blood. The alveolar spaces are obliterated by an acute inflammatory exudate rich in neutrophils and lesser amounts of wispy pink-stained fibrin. Occasional large, rounded mononuclear cells, macrophages **M**, can also be seen, but these are few in the acute phase of the disease.

If untreated, there are three possible outcomes to lobar pneumonia: death may occur (as in this patient), there may be complete resolution (Fig. 2.8), or, rarely, the exudate may become organised with consequent permanent fibrosis of the lung tissue.

Clinical features and nomenclature of acute inflammatory processes

The vascular and exudative phenomena of acute inflammation are responsible for the clinical features and were described by Celsus in the first century AD. The ***cardinal signs of Celsus*** are:

- ***redness*** (*rubor*) caused by hyperaemia
- ***swelling*** (*tumor*) caused by fluid exudation and hyperaemia
- ***heat*** (*calor*) caused by hyperaemia
- ***pain*** (*dolor*) resulting from release of bradykinin and PGE_2

Galen later added:

- ***loss of function*** (*functio laes*a) caused by the combined effects of the above.

Clinically, patients who have significant acute inflammation feel unwell and have a fever. This is mediated by cytokines released into the blood (***interleukins 1 & 6, tumour necrosis factor (TNF)*** and ***prostaglandins***), acting on the hypothalamus. Laboratory investigations commonly reveal a raised neutrophil count in the blood.

The nomenclature used to describe inflammation in different tissues employs the tissue name (or its Greek or Latin equivalent) and the suffix '***-itis***'. For example, inflammation of the appendix is referred to as ***appendicitis***, inflammation of the Fallopian tube is termed ***salpingitis***, and inflammation of the pericardium is termed ***pericarditis***. While this holds true for most tissues and organs, there are notable exceptions in traditional clinical usage. For example, inflammation of the pleura is usually termed ***pleurisy***, while inflammation of subcutaneous tissues as a result of infection is usually termed acute ***cellulitis***. Many examples of acute inflammatory diseases are presented in the systems pathology chapters, which form the second half of this book. In addition, the nomenclature applied to common forms of acute inflammation is presented in Figure 2.5; the causes given in this table illustrate the most common factors initiating each type of inflammatory response.

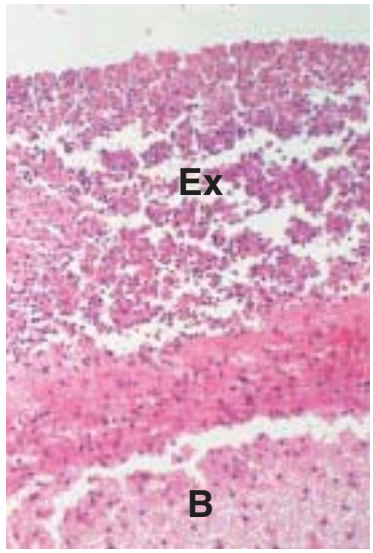
Fig. 2.5 Nomenclature and aetiology of common types of inflammation

Tissue	Acute inflammation	Typical causes
Meninges	Meningitis	Bacterial and viral infections
Brain	Encephalitis	Viral infections
Lung	Pneumonia	Bacterial infections
Pleura	Pleurisy	Bacterial and viral infections
Pericardium	Pericarditis	Bacterial and viral infections, myocardial infarction
Oesophagus	Oesophagitis	Gastric acid reflux, fungal infections
Stomach	Gastritis	Alcohol abuse, *Helicobacter pylori* infection
Colon	Colitis	Bacterial infections, ulcerative colitis
Rectum	Proctitis	Ulcerative colitis
Appendix	Appendicitis	Faecal obstruction
Liver	Hepatitis	Alcohol abuse, viral infections
Gallbladder	Cholecystitis	Bacterial infections, chemical irritation
Pancreas	Pancreatitis	Pancreatic enzyme release
Urinary bladder	Cystitis	Bacterial infections
Bone	Osteomyelitis	Bacterial infections
Subcutaneous tissues	Cellulitis	Bacterial infections
Skin	Sunburn	UV radiation
Joints	Arthritis	Bacterial and viral infections, immune complex deposition
Arteries	Arteritis	Immune complex deposition

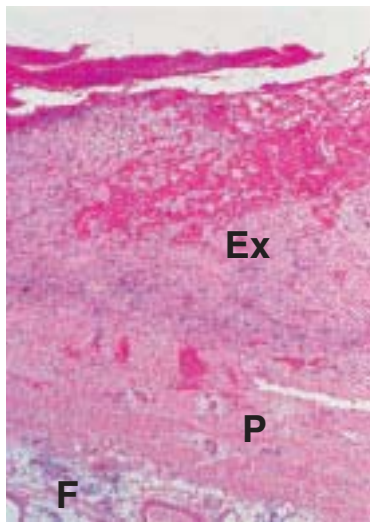
Morphological types of acute inflammation

While the basic process of acute inflammation is the same in all tissues, there are frequently qualitative differences in the inflammatory response seen under different circumstances. Terms describing these variations are widely used in clinical practice and are summarised below:

- ***Suppurative inflammation (purulent inflammation)*** refers to acute inflammation in which the acute inflammatory exudate is particularly rich in neutrophil leucocytes. Suppurative inflammation is most commonly seen as a result of infection by bacteria where the mixture of neutrophils (viable and dead), necrotic tissue, and tissue fluid in the acute inflammatory exudate form a semi-liquid material referred to as ***pus***; hence, the term ***purulent inflammation***. This is illustrated in Figure 2.6a. Within tissues, a circumscribed collection of semi-liquid pus is termed an ***abscess*** (Fig. 2.13). The destruction of tissue may be due as much to release of neutrophil lysosomal enzymes as to tissue destruction by bacteria. Bacteria which produce purulent inflammation are described as ***pyogenic bacteria***. They initiate massive neutrophilic infiltration with subsequent destruction of infected tissues. Pyogenic bacteria include *Staphylococci*, some *Streptococci (S. pyogenes, S. pneumoniae), Escherichia coli* and the *Neisseriae* (meningococci and gonococci).
- ***Fibrinous inflammation*** refers to a pattern of acute inflammation where the acute inflammatory exudate has a high plasma protein content. Fibrinogen derived from plasma is converted to fibrin, which is deposited in tissues. This pattern is particularly associated with membrane-lined cavities such as the pleura, pericardium and peritoneum where the fibrin strands form a mat-like sheet causing adhesion between adjacent surfaces. This is illustrated in Figure 2.6b.
- ***Serous inflammation*** describes a pattern of acute inflammation where the main tissue response is an accumulation of fluid with a low plasma protein and cell content. This is often called a ***transudate***, which by definition has a specific gravity of <1.012 in contrast to an exudate with a specific gravity >1.020. This pattern of response is most commonly seen in the skin in response to a burn.



(a)



(b)

Fig. 2.6 Purulent and fibrinous inflammation
(a) Purulent inflammation: acute meningitis (LP) (b) Fibrinous inflammation: acute pericarditis (LP)

These micrographs contrast examples of purulent and fibrinous inflammation. Acute inflammation in the meninges (a) surrounding the brain illustrates an example of an exudate in which very little fibrin is formed. In acute meningitis, the exudate is almost entirely composed of oedema fluid and neutrophils.

Acute meningitis may be caused by bacterial infection (e.g. *Neisseria meningitidis* or *Streptococcus pneumoniae*). Viral and mycobacterial (tuberculous) meningitis are characterised by a chronic inflammatory reaction from the outset and this is reflected clinically by a much more subtle presentation. The presence of pathogenic bacteria in the meninges excites an acute inflammatory exudate in the subarachnoid space in which neutrophils predominate. Macroscopically, this appears as a creamy thick fluid, and the term ***acute purulent inflammation*** is often used to describe such a reaction. In the micrograph, note the densely cellular exudate **Ex** lying on the surface of the brain **B** in the subarachnoid space.

When an acute inflammatory exudate forms on a serosal surface, the exudate is usually dominated by the presence of large amounts of fibrin. Macroscopically, a shaggy layer of fibrin coats the formerly smooth surface. This is seen in acute pericarditis (b) and also in acute pleurisy and acute peritonitis. In this low magnification photomicrograph, the exudate **Ex** is well established on the epicardial aspect of the pericardium **P**. No myocardium is seen in this micrograph, but epicardial fat **F** is readily identifiable. Acute pericarditis most commonly occurs secondary to death of underlying cardiac muscle (***myocardial infarction***). The acute inflammatory exudate is made up of dense masses of pink-staining fibrin with comparatively few neutrophils.

The usual fate of serosal exudates is organisation via ingrowth of granulation tissue, and eventual formation of collagenous scar tissue binding adjacent serosal surfaces together. If this process occurs in the peritoneal cavity, then bowel loops can be obstructed by these fibrous adhesions.

Outcomes of acute inflammation

The process of acute inflammation is designed to neutralise injurious agents and to restore the tissue to useful function. There are four main outcomes of acute inflammation if the patient survives: ***resolution, healing by fibrosis, abscess formation,*** and ***progression to chronic inflammation.*** Three factors determine which of these outcomes occurs:

- the severity of tissue damage
- the capacity of specialised cells within the damaged tissue to divide and replace themselves, a process termed ***regeneration***
- the type of agent which has caused the tissue damage.

Resolution involves complete restitution of normal architecture and function. This can only occur if the connective tissue framework of the tissue is intact and the tissue involved has the capacity to replace any specialised cells that have been lost (regeneration). Examples of resolution are recovery from sunburn (acute inflammatory response in the skin as a result of UV radiation exposure) and the restitution of normal lung structure and function following lobar pneumonia (see Fig. 2.8). ***Regeneration*** of tissues can play an important part in resolution, for example regrowth of alveolar lining cells following pneumonia. Another example of regeneration is seen in the peripheral nervous system where axonal processes can regrow following damage. This function depends on viability of the cell body of the neurone and is an example of regeneration of one part of a cell, not the formation of new cells.

Healing by fibrosis (scar formation) occurs when there is substantial damage to the connective tissue framework and/or the tissue lacks the ability to regenerate specialised cells. In these instances, dead tissues and acute inflammatory exudate are first removed from the damaged area by macrophages (see Fig. 2.7), and the defect becomes filled by ingrowth of a specialised vascular connective tissue called ***granulation tissue*** (see Fig. 2.9). This is termed ***organisation***. The granulation tissue gradually produces collagen to form a ***fibrous*** (collagenous) ***scar*** constituting the process of ***repair*** (see Figs 2.10 and 2.11). Despite the loss of some specialised cells and some architectural distortion by fibrous scar, structural integrity is re-established. Any impairment of function is dependent on the extent of loss of specialised cells. Modified forms of repair occur in bone after a fracture when new bone is created (Fig. 2.12), and in brain with the formation of an astrocytic scar (Fig. 23.2).

Abscess formation takes place when the acute inflammatory reaction fails to destroy/remove the cause of tissue damage and continues with a component of chronic inflammation. This is most common in the case of infection by pyogenic bacteria. As the acute inflammation progresses, there is liquefaction of the tissue to form ***pus.*** At the periphery of this area, a chronic inflammatory component surrounds the area and fibrous tissue is laid down walling off the suppuration (see Fig. 2.13).

Chronic inflammation may result following acute inflammation when an injurious agent persists over a prolonged period causing concomitant tissue destruction, inflammation, organisation and repair. Some injurious agents elicit a chronic inflammatory type of response from the outset. Chronic inflammation is discussed fully in Chapter 3.

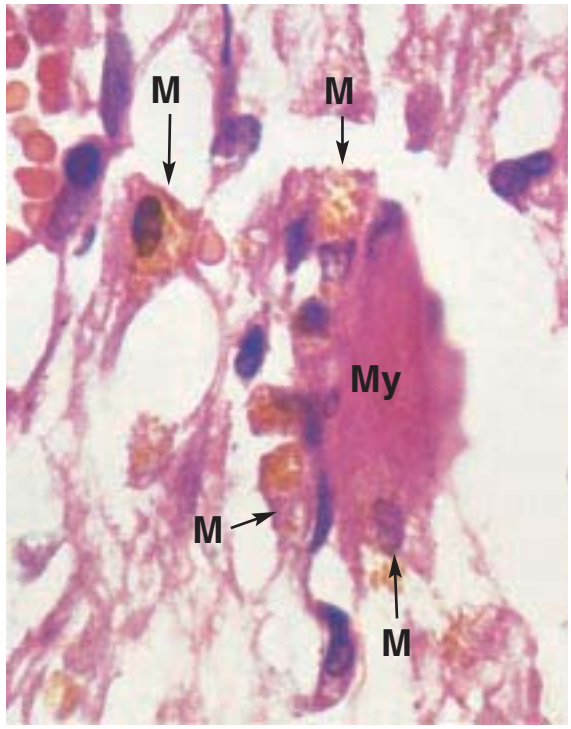


Fig. 2.7 Early outcome of acute inflammation: macrophage accumulation (HP)

As early as the second or third day of the acute inflammatory response, macrophages accumulate in increasing numbers. These enter the tissue in a similar fashion to neutrophils under the influence of chemotactic factors. Macrophages phagocytose cell debris, dead neutrophils, and fibrin. At the same time, lymphocytes begin to enter the damaged area, reflecting an immune response to any introduced antigens.

This micrograph shows an area of cardiac muscle, which has undergone necrosis following blockage of its arterial supply (***myocardial infarction***). The acute inflammatory response has almost run its course, and the neutrophils and fibrin predominant in the earlier stages have been removed by macrophages. All that remains is a soft, loose tissue containing a few necrotic myocardial remnants **My**, one of which is shown here being engulfed by macrophages **M**. The macrophages can be identified under these circumstances by the foamy appearance of their cytoplasm, which also often contains brownish pigment granules. These brown granules are iron-containing pigments (***haemosiderin***) derived from haemoglobin. Further details of the events following myocardial infarction are shown in Figure 10.2.

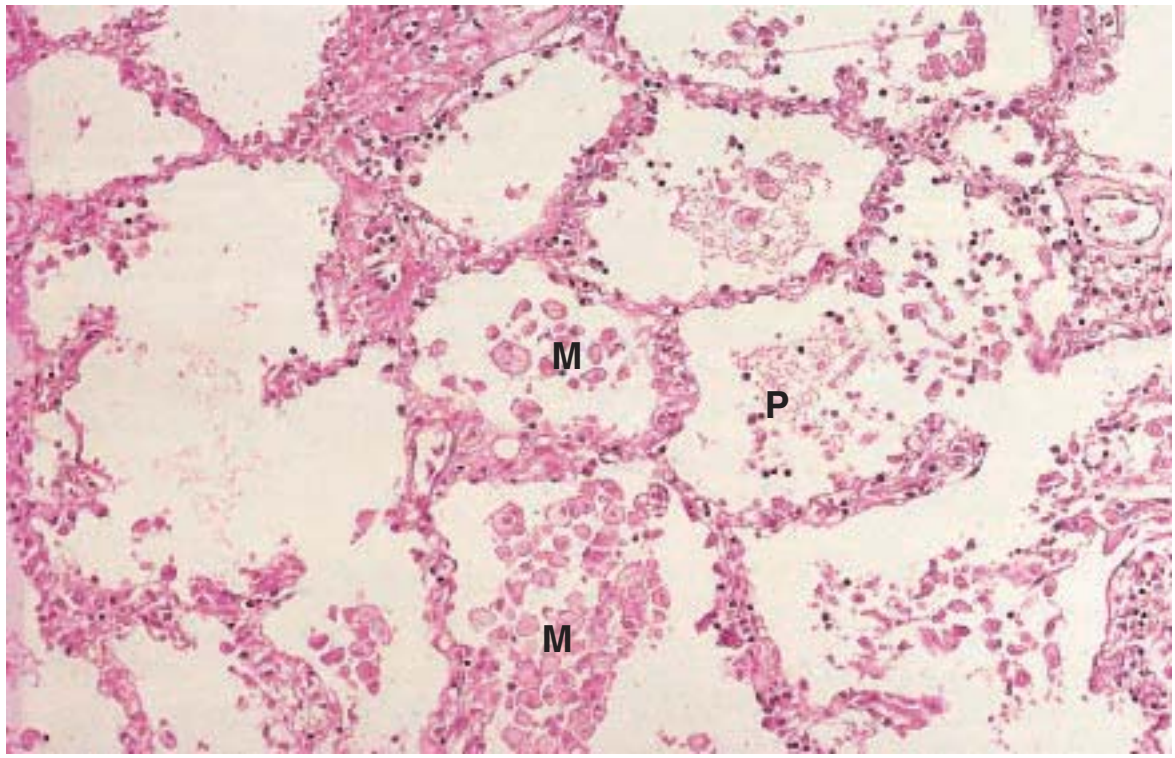
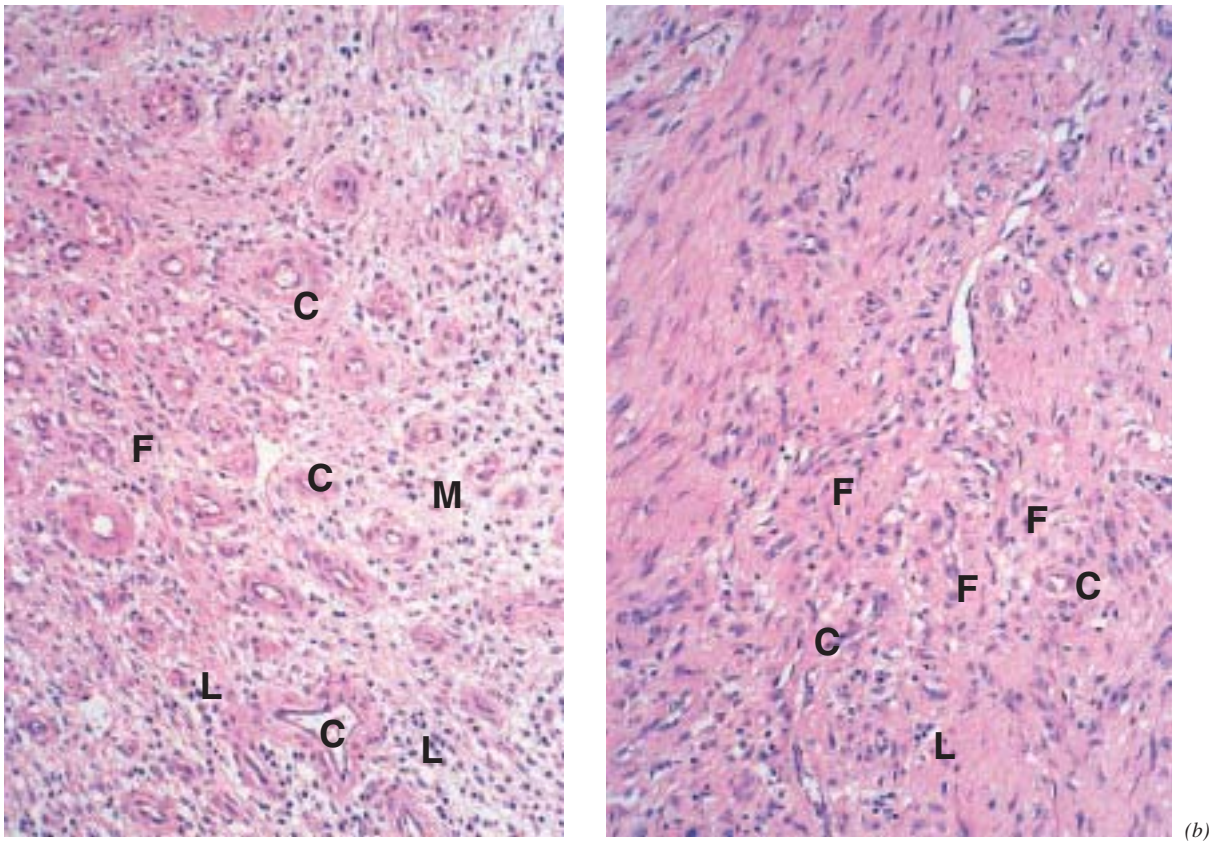


Fig. 2.8 Resolution of acute inflammation: lobar pneumonia (HP)

Occasionally, a damaging stimulus may excite a strong acute inflammatory response with minimal tissue damage. In such circumstances, resolution of the exudate may occur without any need for organisation and repair, thereby leaving no residual tissue scarring.

This phenomenon occurs in lobar pneumonia in which the acute inflammatory response is due to infection by a bacterium, commonly the pneumococcus (see Fig. 2.4). The alveoli of one or more lobes of the lung are filled with acute inflammatory exudate and the loss of respiratory function may be so great as to cause fatal ***hypoxia***. This was a common cause of death in previously fit young people in the pre-antibiotic era.

Bacteria are engulfed by neutrophils, and fibrin strands are broken down by ***fibrinolysins*** derived from plasma and neutrophil lysosomes. Macrophages **M** are recruited and phagocytose necrotic neutrophils, extravasated red cells and other cell debris. Fluid and degraded proteinaceous material **P** together with the macrophages are then resorbed into the circulation via alveolar wall vessels and interstitial lymphatics or may be coughed up as brown-coloured sputum. Alveolar spaces are thus cleared of exudate and can participate in gaseous exchange. Regeneration of alveolar lining cells completes the return to normal structure and function.



(a) (b)

Fig. 2.9 Granulation tissue
(a) Vascular granulation tissue (HP) (b) Fibrous granulation tissue (HP)

Where there is significant damage to the connective tissue framework, the former site of active tissue damage and acute inflammation becomes occupied by a mixture of proliferating capillaries, fibroblasts, macrophages, lymphocytes and plasma cells, termed ***granulation tissue***.

Capillaries **C** are derived by budding from vessels at the periphery of the damaged area (***angiogenesis***) and form an interconnected network shown in micrograph (a). In this early form, termed ***vascular granulation tissue***, spaces between the capillaries are occupied by macrophages, lymphocytes, proliferating fibroblasts and a loose connective tissue matrix. At this stage, the capillaries are thin-walled and relatively leaky, leading to extravasation of erythrocytes and fluid into the tissue.

With time, the vessels regress, collagen is laid down, and the inflammatory cells return to the circulation. The effect of this progression is seen in micrograph (b), where numerous plump activated fibroblasts **F** can be seen with a few residual lymphocytes and relatively inconspicuous capillaries **C**. This is now termed ***fibrous granulation tissue*** in recognition of the presence of mature collagenous fibrous tissue. Collagen, laid down by the fibroblasts, is remodelled in an orderly pattern and the fibrous granulation tissue takes on the characteristics of an early ***fibrous scar*** as seen in Figure 2.11.

Granulation tissue is also involved in healing of wounds whatever the cause and site of the tissue defect. In the case of a simple skin incision, where the wound edges are in close apposition and the actual defect is minimal: this is termed ***healing by primary intention***. In other situations, the tissue defect will be large and filled with blood clot and a variable amount of tissue debris. In this case, described as ***healing by secondary intention***, organisation and filling of the defect by granulation tissue take considerably longer (see Fig. 2.10).

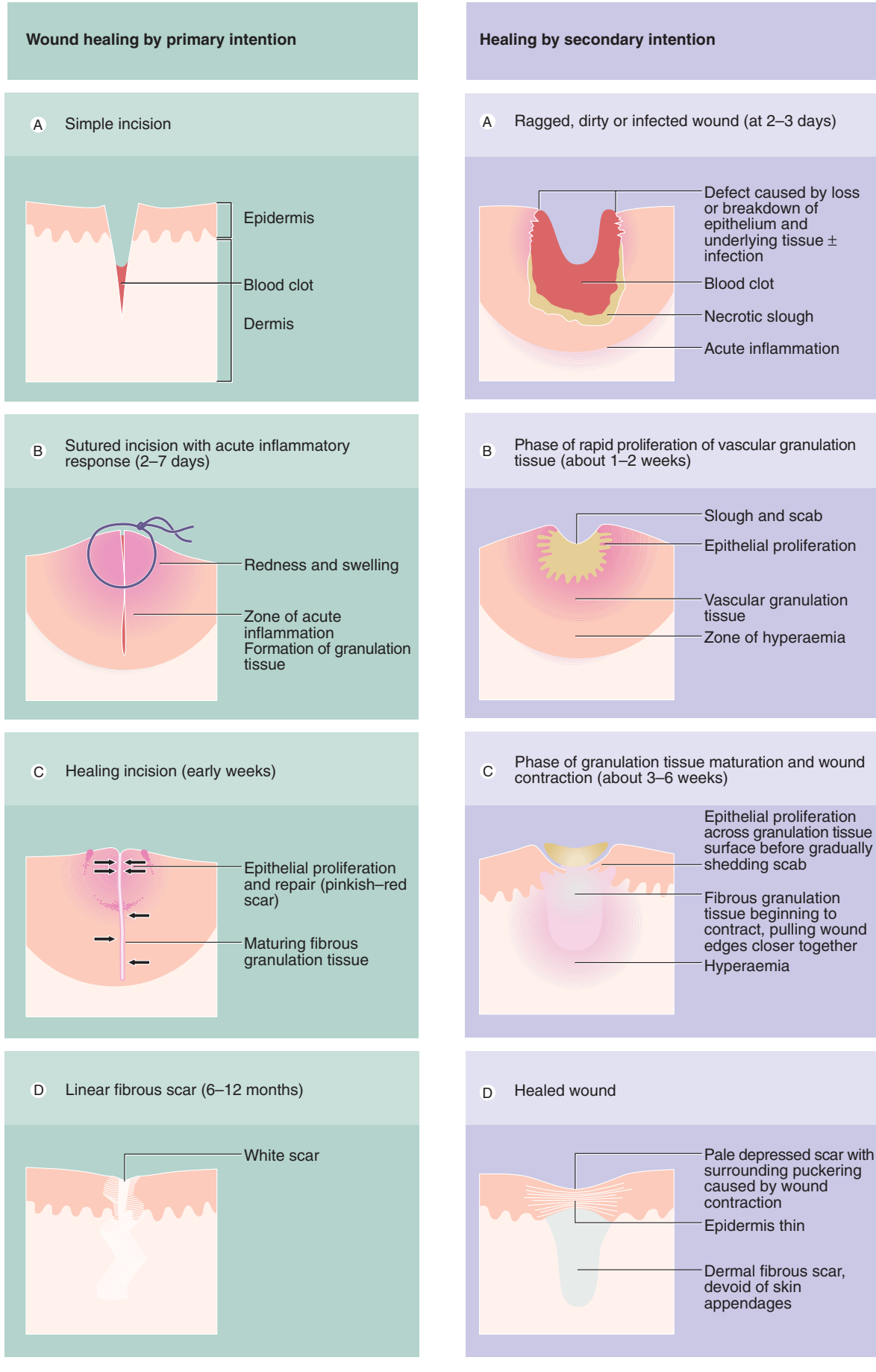
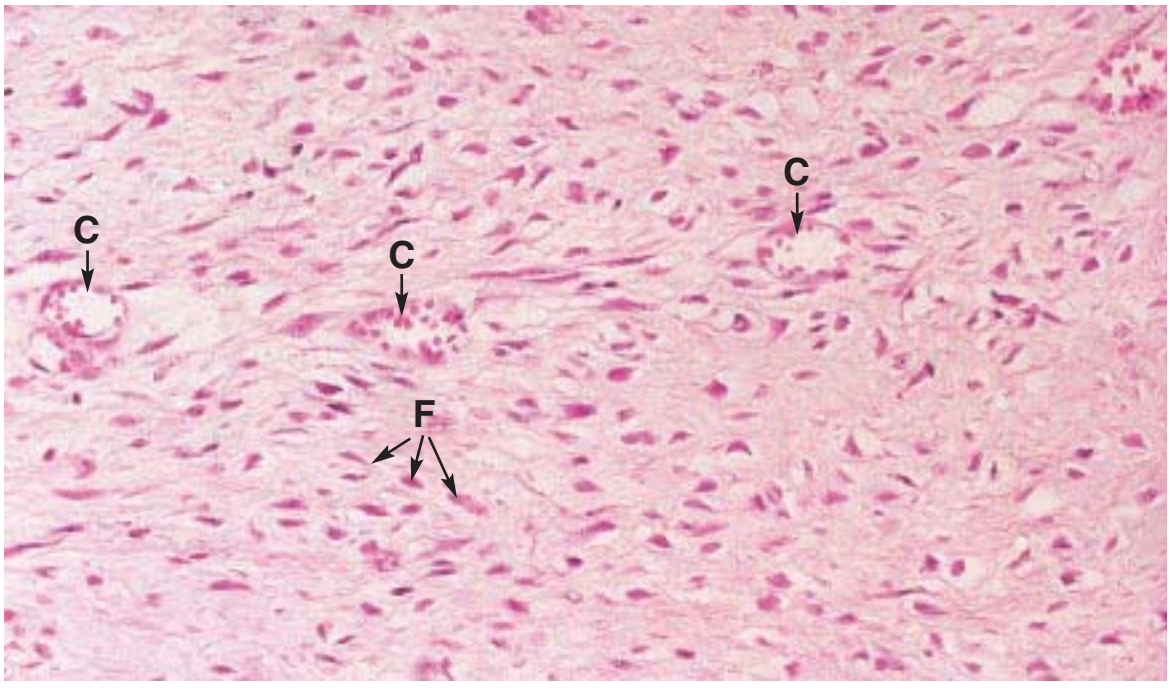


Fig. 2.10 **Wound healing by primary and secondary intention**



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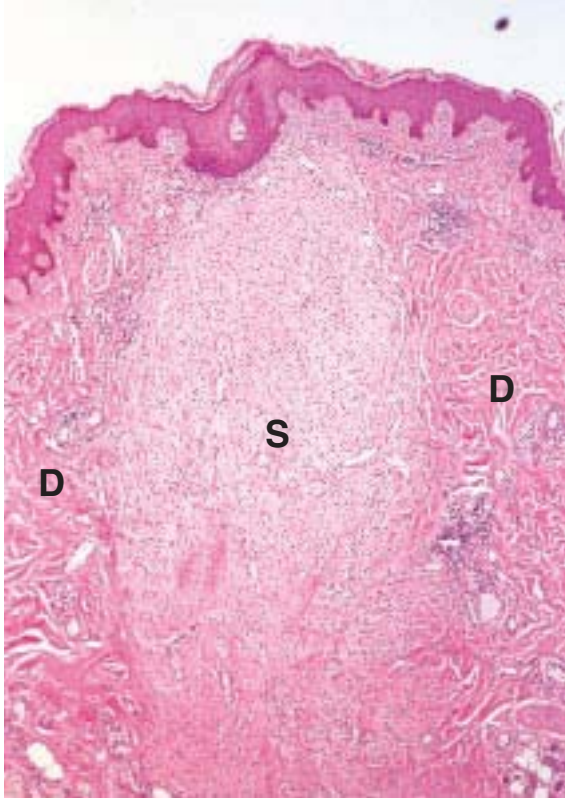
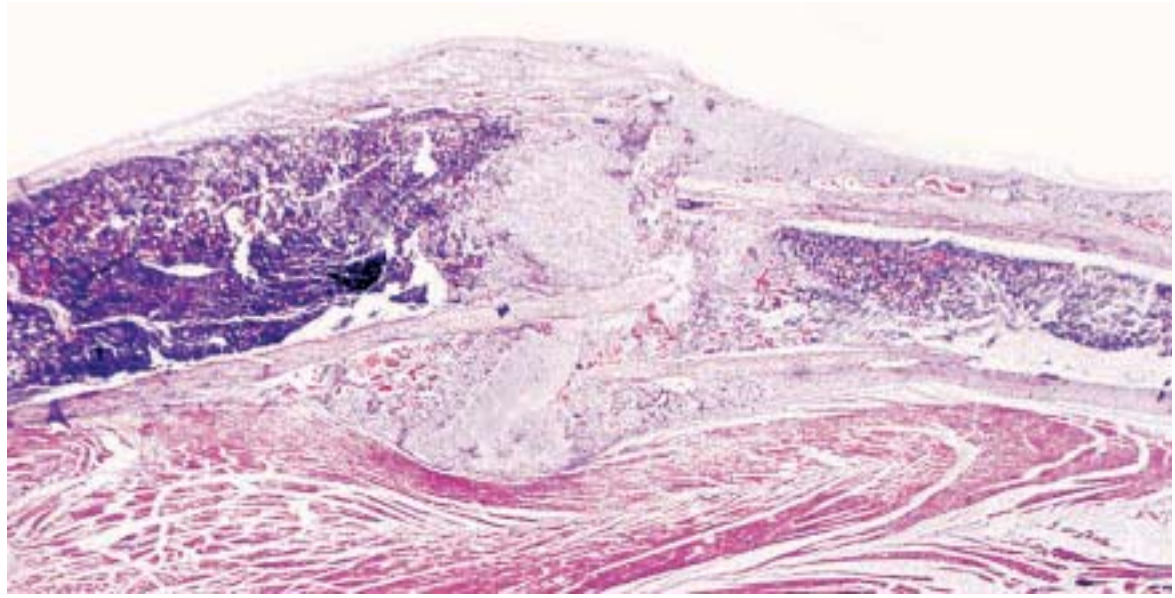


(b)

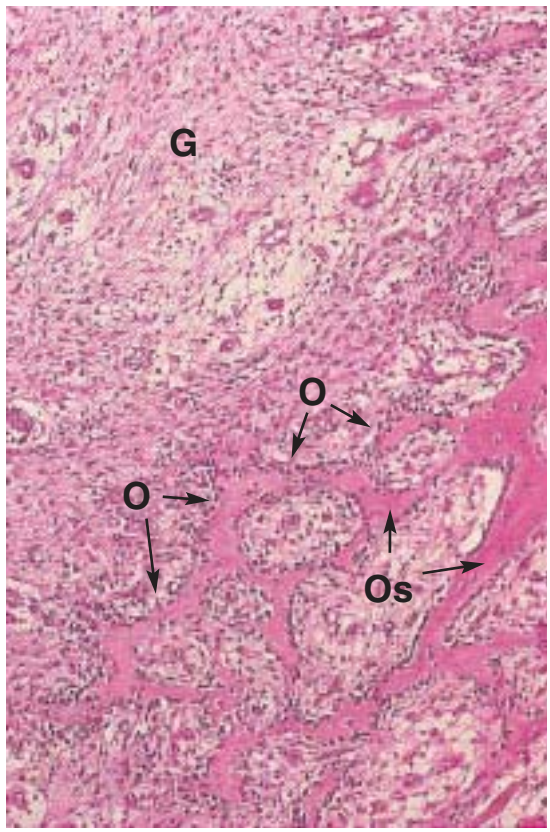
Fig. 2.11 Fibrous scar
(a) Fibrous scar tissue (HP) (b) Skin scar (LP)

The deposition of collagen within fibrous granulation tissue occurs over a period of many weeks. Collagen is remodelled in an appropriate orientation to withstand the tensile stresses placed on the area of repair. With time, the previously plump and metabolically active fibroblasts regress and become relatively inconspicuous as shown in micrograph (a) of a typical area of early fibrous scar. Note the condensed nuclei of inactive fibroblasts **F**. Some capillaries **C** persist, accounting for the red appearance of recent scars.

Micrograph (b) illustrates, at low magnification, a recent area of scarring in the skin after healing of a simple incision for biopsy of a skin tumour. Immature collagenous tissue forms a pale scar **S**, which interrupts the normal pink collagen of the dermis **D** on either side. There are no skin appendages in a skin scar. During the ensuing months and years, the cellularity of the scar diminishes, there is progressive loss of capillary vessels and the scar contracts so that after many years a skin scar may be virtually undetectable macroscopically. Note that healing of skin or mucous membrane involves epithelialisation of the surface by proliferation of epithelium at the edges of the defect (i.e. ***epithelial regeneration***).



(a)



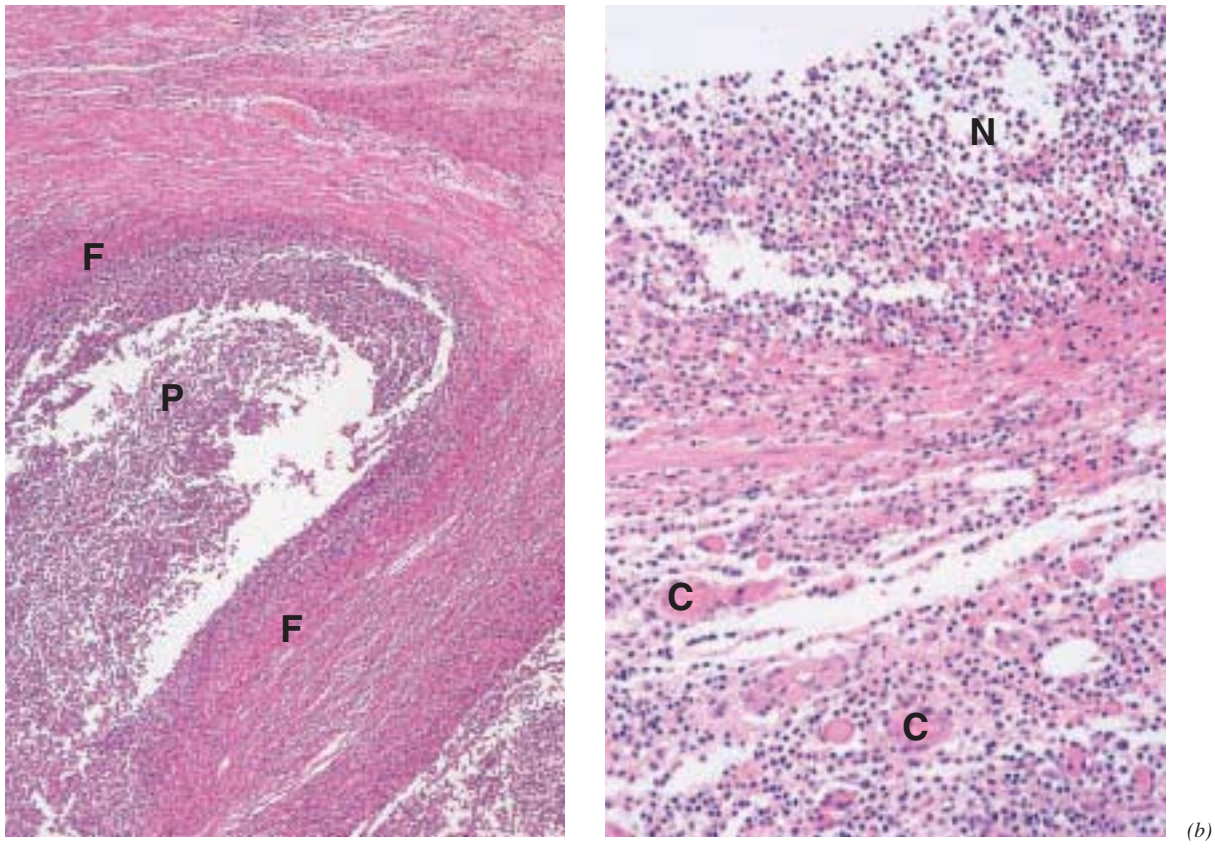
(b)

Fig. 2.12 Specialised repair: healing in bone
(a) LP (b) HP

In most tissues, fibrous scar forms a functionally adequate, albeit unspecialised, replacement for damaged tissues provided sufficient normal tissue remains. In bone, however, the replacement of damaged tissue by fibrous scar is inadequate for restoration of function and so a specialised form of granulation tissue develops where the final product is new bone.

Following fracture, there is usually bleeding in and around the fracture site resulting in a mass of coagulated blood, termed a ***haematoma***. An initial acute inflammatory response is rapidly followed by organisation of the haematoma with formation of granulation tissue in much the same way as described in Figure 2.9. In the case of bone fracture, this granulation tissue is termed ***provisional callus*** **C** and forms around the broken ends of the bone **B** loosely uniting them; this is seen at low magnification in micrograph (a).

In contrast to usual granulation tissue, that of bone contains osteoblasts that produce ***osteoid***, the organic matrix of bone. This is seen in micrograph (b) where typical granulation tissue **G** at the top of the field gives way to osteoblasts **O** which surround pink-staining newly formed osteoid **Os**. Osteoid then becomes mineralised to form the ***bony callus*** between the two fractured ends. This initial bone is haphazardly arranged (known as ***woven bone***) and over the next few months undergoes extensive remodelling by osteoclasts and osteoblasts to form lamellar bone with trabecular architecture best suited to resist local stresses. The end result is restitution of normal bony architecture and function.



(a) (b)

Fig. 2.13 Abscess formation
(a) LP (b) HP

An abscess is a localised collection of pus, which usually develops following extensive tissue damage by one of the *pyogenic bacteria*, such as ***Staphylococcus aureus***. Such organisms excite an inflammatory exudate in which neutrophils predominate. In these circumstances, large numbers of neutrophils die releasing their lysosomal enzymes and undergoing autolysis; the resulting viscous fluid, ***pus***, contains dead and dying neutrophils, necrotic tissue debris and the fluid component of the acute inflammatory exudate with a little fibrin. Pyogenic bacteria often remain viable within the abscess cavity and may cause enlargement of the lesion, which at this stage is described as an ***acute abscess***. At an early stage, expansion of the lesion is limited by the processes of organisation and repair at the margins of the abscess. Thus the abscess may become walled off, isolating the bacteria-containing pus and preventing further spread; an abscess encapsulated by granulation tissue is termed a ***chronic abscess***. On the other hand, if the bacteria are highly virulent and present in large numbers, such attempts at organisation and repair may be overwhelmed, and expansion of the abscess ensues with destruction of surrounding tissue. The coexistence of active tissue damage and attempts at repair are typical of chronic inflammation (see Ch. 3).

Micrograph (a) shows an abscess in the wall of the colon. The centre consists of a collection of pus **P**. At its margin is a pink-staining zone of fibrin **F**. As yet, there is little evidence of organisation at the margins of the abscess; this therefore represents an acute abscess. Micrograph (b) shows the wall and lumen of the abscess at high power, illustrating the neutrophils **N** and tissue debris in the cavity of the abscess, and the capillaries **C** in the inflamed granulation tissue of the wall.

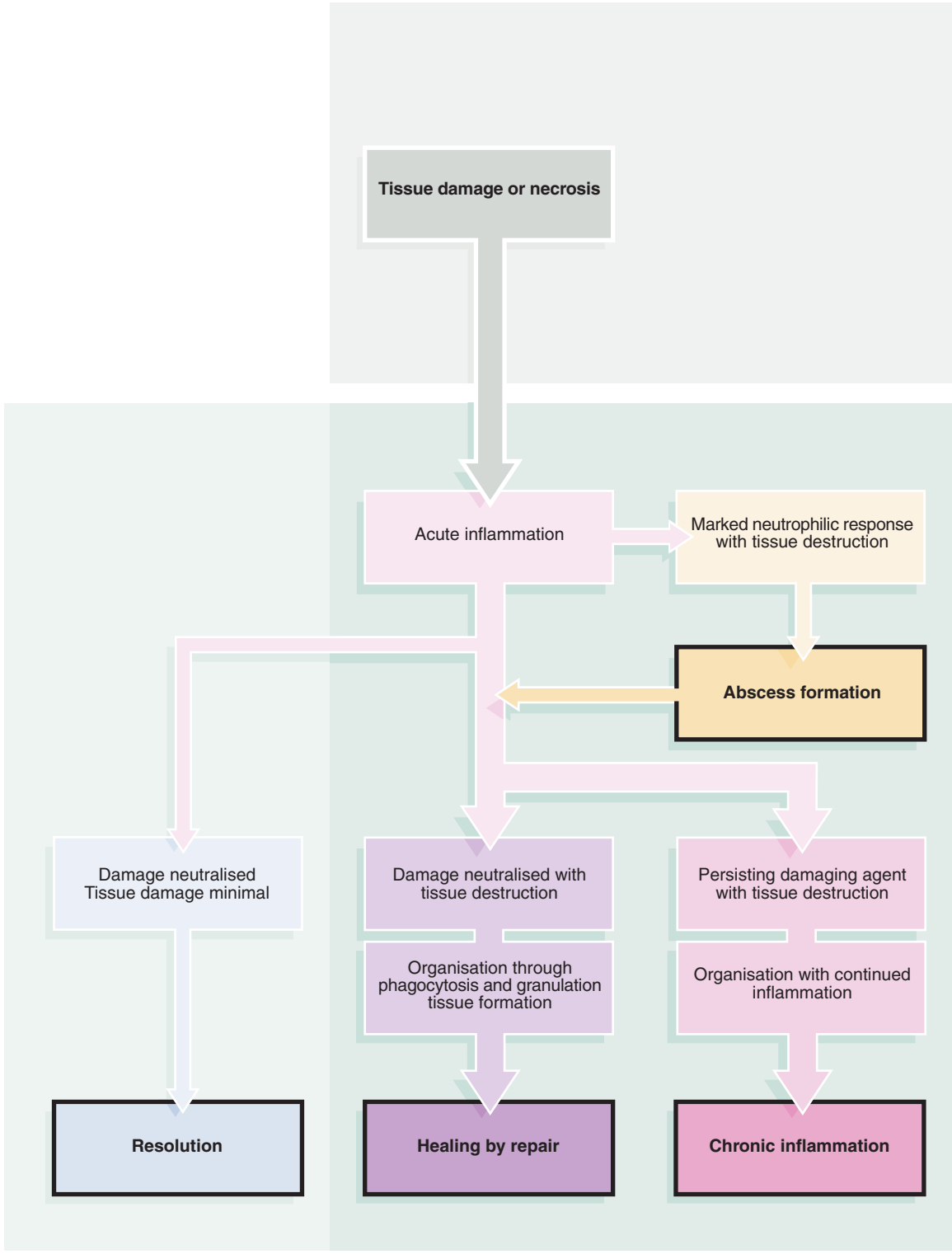


Fig. 2.14 Outcomes of acute inflammation

This flow chart summarises the main outcomes following acute inflammation. Complete resolution is uncommon, the most usual outcomes being either healing by fibrosis (leaving a collagenous scar) or progression to chronic inflammation