The Inflammatory Process

Learning Objectives:
At the end of this course you should be able to:
1. discuss to give a basic, brief, description of the healing process;
2. understand the difference between the intrinsic and extrinsic clotting pathways;
3. understand the role of acute inflammation in the defence of the body;
4. name the main cells involved in the inflammatory response;
5. describe how the characteristics of blood vessels alter to allow the inflammatory process to proceed;
6. understand the implications of inflammation, and it’s potential consequences.

A good definition of the healing process is that it is the substitution of dead cells with viable cells, and can occur either as regeneration or replacement. Regeneration is development of cells of the same type as those damaged, whilst replacement involves the development of a new type of tissue, often causing scarring. Which of these occurs depends upon the type of tissue that is involved.

For example, the majority of cells within the body can be categorized by their ability to regenerate themselves fully or not. The three categories are:
- Labile (renewing) cells - continue to divide throughout life, and any damage is completely repaired by regeneration, eg, skin, mucous membranes, lymphoid tissues.
- Stable cells - do not divide after growth ceases, but can regenerate in response to injury, eg, CT, liver, pancreas.
- Permanent cells - as the name suggests, these cannot replicate, and are often replaced by fibrous tissue, eg, neurones, cardiac tissues.
The process of healing and repair is the same for all tissues, but different stages take different lengths of time, and depend upon the type of injury involved.

The two main types of healing that we see are primary and secondary intention. Primary intention healing occurs usually after a cut or laceration, with close apposition of wound edges. The wound fills with blood and forms a clot, containing fibrin (a thread-like protein which binds the edges of the wound together). The clot dries to form a scab, sealing in the wound and preventing the entry of infection. The inflammatory response induces vasodilation, increasing the numbers of cells and mediators in the area, increasing blood vessel permeability, leading to the development of oedema. Neutrophils move in and get rid of dead tissues and bacteria. As the neutrophils die off they accumulate as slough. Fibroblasts from the surrounding tissues then enter the clot, and produce immature collagen. Angiogenesis occurs, and granulation tissue develops. This eventually contracts and matures, forming a healed area. In secondary healing the process and events are the same, however the edges of the wound cannot be opposed, often because of some tissue loss, therefore the process takes longer.
There is also a situation known as tertiary healing, but this is specific to healing which occurs in relation to tissue and skin grafting.

The actual events of both types of healing are the same –

- Vascular response
- Inflammation
- Proliferation
- Remodeling

In some texts, the vascular response is often combined with the inflammatory response, and so depending upon the source, healing is said to occur in either three or four stages. Generally, these can all be seen in either type of healing, and the whole process can take up to two years to complete. Additionally, different phases of healing can be occurring in the same wound at the same time, depending on the size and type of the wound, but there is a general pattern of their onset in relation to each other, illustrated by the diagram opposite:
The Vascular response.

The formation of a fibrin clot at the site of an injury to the wall of a normal blood vessel is an essential part of the process to stop blood loss after vascular injury. The reactions that lead to fibrin clot formation are commonly described as a cascade, in which the product of each step is an enzyme or cofactor needed for following reactions to proceed efficiently.

The entire clotting cascade can be divided into three portions - the extrinsic pathway, the intrinsic pathway, and the common pathway. The extrinsic pathway begins with the release of tissue factor at the site of vascular injury and leads to the activation of factor X. This is fairly rapid, occurring usually within 15 seconds of injury. The intrinsic pathway provides an alternative mechanism for activation of factor X, starting from the activation of factor XII. This process takes a little longer, up to around 5 minutes. The common pathway consists of the steps linking the activation of factor X to the formation of a multimeric, cross-linked fibrin clot. Each of these pathways includes not only a cascade of events that generate the catalytic activities needed for clot formation, but also numerous positive and negative regulatory events.
**Extrinsic pathway** - Factor VII, the protease that initiates the normal blood clotting cascade, circulates in the blood in both its inactive (factor VII) and its activated (factor VIIa) forms. No clotting occurs because neither form of the protein has any catalytic activity when free in solution. Blood clotting is normally initiated when tissue factor (TF), an intrinsic plasma membrane protein, is exposed to the blood by injury to the wall of a blood vessel. TF is then able to bind factor VIIa from plasma, and possibly also factor VII, to form complexes capable of catalyzing the conversion of factor X, from plasma, into its activated form, factor Xa. Factor Xa catalyzes the conversion of additional factor VII molecules to their activated form, increasing the amount of tissue factor:factor VIIa complex available at the site of injury, accelerating the generation of factor Xa, and allowing the activation of factor IXa as well. At this point the intrinsic pathway, as an independent source of activated factor X, is thought to become critical for the continuation of clot formation.

**Intrinsic pathway** - The intrinsic pathway of blood clotting connects interactions among kininogen (K, HK), prekallikrein (PK), and factor XII to the activation of clotting factor X by a series of reactions that is independent of the extrinsic pathway. It is thus essential for the prolongation of the clotting cascade: while the reactions of the extrinsic pathway appear to be sufficient to initiate clot formation, those of the intrinsic pathway are required to maintain it.

**Common pathway** - The common pathway consists of the cascade of activation events leading from the formation of activated factor X to the formation of active thrombin, the cleavage of fibrinogen by thrombin, and the formation of cleaved fibrin into a stable multimeric, cross-linked complex. Thrombin also efficiently catalyzes the activation of several factors required earlier in the clotting cascade, thus acting in effect as a positive regulator of clotting. At the same time, thrombin activates protein C, which in turn catalyzes the inactivation of several of these upstream factors, thereby limiting the clotting process. Thrombin can also be trapped in a stable, inactive complex with antithrombin-3, a circulating blood protein. The relationships between these positive and negative modulators is critical to the normal regulation of clotting, facilitating the rapid
formation of a protective clot at the site of injury, while limiting and physically confining the process.

KEY LEARNING POINTS.

1. Haemostasis starts immediately after injury, limiting blood loss.
2. Platelet degranulation follows, as well as activation of Factor XII (Hagemann factor). This results in activation of clotting cascades and thrombin generation. This will lead to clot formation, or haemostasis.
3. Intrinsic and extrinsic clotting mechanisms lead to the formation of a fibrin clot
The Inflammatory Phase.

Inflammation is the local physiological response to tissue injury. It is not, in itself, a disease, but is usually a manifestation of disease. Inflammation may have beneficial effects such as the destruction of invading micro-organisms and the walling-off of an abscess cavity to prevent spread of infection. However, it may also produce disease; for example, an abscess in the brain would act as a space-occupying lesion compressing vital surrounding structures, or fibrosis resulting from chronic inflammation may distort tissues and permanently alter their function.

Inflammation is usually classified according to its time course as:

- acute inflammation - the initial and often transient series of tissue reactions to injury
- chronic inflammation - the subsequent and often prolonged tissue reactions following the initial response.

The two main types of inflammation are also characterised by differences in the cell types taking part in the inflammatory response.

**Acute Inflammation**

Acute inflammation is the initial tissue reaction to a wide range of injuries or insults and may last from a few hours to a few days. The acute inflammatory response is similar whatever the causative agent.

The principal causes of acute inflammation are:

- microbial infections, e.g. pyogenic bacteria, viruses
- hypersensitivity reactions, e.g. parasites, tubercle bacilli
- physical agents, e.g. trauma, ionising irradiation, heat, cold
- chemicals, e.g. corrosives, acids, alkalis, reducing agents, bacterial toxins
- tissue necrosis, e.g. ischaemic infarction.
**Microbial infections** - One of the commonest causes of inflammation is microbial infection. Viruses lead to death of individual cells by intracellular multiplication. Bacteria release specific exotoxins (chemicals synthesised by them which specifically initiate inflammation) or endotoxins (which are associated with their cell walls). Additionally, some organisms cause immunologically-mediated inflammation through hypersensitivity reactions.

**Hypersensitivity reactions** - A hypersensitivity reaction occurs when an altered state of immunological responsiveness causes inappropriate or excessive immune reaction which damages the tissues. The types of reaction are classified as Types I, II, III, or IV, but all have cellular or chemical mediators similar to those involved in inflammation.

**Physical agents** - Tissue damage leading to inflammation may occur through physical trauma, ultraviolet or other ionising radiation, burns, or excessive cooling ('frostbite').

**Irritant and corrosive chemicals** - Corrosive chemicals (acids, alkalis, oxidising agents) provoke inflammation through gross tissue damage. However, infecting agents may release specific chemical irritants which lead directly to inflammation.

**Tissue necrosis** - Death of tissues from lack of oxygen or nutrients resulting from inadequate blood flow is a potent inflammatory stimulus. The edge of a recent infarct often shows an acute inflammatory response.

**Clinical appearance of acute inflammation.**

These were originally described by Celsus (30 BC-38AD) using the Latin words rubor, calor, tumor, and dolor. Loss of function is also characteristic, and is referred to as laeso functio.

**Redness(rubor)** – an acutely inflamed tissue appears red, for example sunburn, cellulitis due to bacterial infection or acute conjunctivitis. This is due to dilation of small blood vessels within the damaged tissues.
Heat (calor) - increase in temperature is seen only in peripheral parts of the body, such as the skin. It is due to increased blood flow (hyperaemia) through the region, resulting in vascular dilatation and the delivery of warm blood to the area. Systemic fever, which results from some of the chemical mediators of inflammation, also contributes to the local temperature.

Swelling (tumor) - swelling results from oedema - the accumulation of fluid in the extravascular space as part of the fluid exudate, and to a much lesser extent, from the physical mass of the inflammatory cells migrating into the area.

Pain (dolor) - pain is one of the best-known features of acute inflammation. It results partly from the stretching and distortion of tissues due to inflammatory oedema and, in particular, from pus under pressure in an abscess cavity. Some of the chemical mediators of acute inflammation, including bradykinin, the prostaglandins and serotonin, are known to induce pain.

Loss of function - Loss of function, was added by Virchow (1821-1902) to the list of features drawn up by Celsus. Movement of an inflamed area is consciously inhibited by pain, whilst swelling may physically immobilize the tissues.

Early stages of acute inflammation
In the early stages, oedema, fibrin and neutrophil polymorphs accumulate in the extracellular spaces of the damaged tissue. The presence of the cellular component, the neutrophil, is essential for a histological diagnosis of acute inflammation. These cells begin to appear in the wound rapidly after damage has occurred, usually achieving their maximum population within 48 hours, phagocytosing bacteria. Neutrophils have a very short life span, numbers begin to decline after around 72 hours, particularly if there is no infection.
The acute inflammatory response involves three processes:
1. changes in vessel diameter and, consequently, flow
2. increased vascular permeability and formation of the fluid exudate
3. formation of the cellular exudate - emigration of the neutrophil polymorphs into the extravascular space.

**Changes in vessel diameter.**
The microcirculation consists of the network of small capillaries lying between arterioles, which have a thick muscular wall, and thin-walled venules. Capillaries have no smooth muscle in their walls to control their diameter, and are so narrow that red blood cells must pass through them in single file. The smooth muscle of arteriolar walls forms pre-capillary sphincters which regulate blood flow through the capillary bed. Flow through the capillaries is intermittent, and some form preferential channels for flow while others are usually shut down. In blood vessels larger than capillaries, blood cells flow mainly in the centre of the lumen (axial flow), while the area near the vessel wall carries only plasma (plasmatic zone). This feature of normal blood flow keeps blood cells away from the vessel wall. Changes in the microcirculation occur as a physiological response; for example, there is hyperaemia in exercising muscle and active endocrine glands. The changes following injury which make up the vascular component of the acute inflammatory reaction were described by Lewis in 1927 as 'the triple response to injury': a flush, a flare and a wheal, i.e. if a blunt instrument is drawn firmly across the skin, the following sequential changes take place:
a momentary white line follows the stroke: this is due to arteriolar vasoconstriction, the smooth muscle of arterioles contracting as a direct response to injury. This is followed by:

1. The flush: a dull red line follows due to capillary dilatation.
2. The flare: a red, irregular, surrounding zone then develops, due to arteriolar dilatation. Both nervous and chemical factors are involved in these vascular changes.
3. The wheal: a zone of oedema develops due to exudation into the extravascular space.
The initial phase of arteriolar constriction is transient, and probably of little importance in inflammation. The subsequent phase of vasodilation (active hyperaemia) may last from 15 minutes to several hours, depending upon the severity the injury. As blood flow begins to slow again, blood cells begin to flow nearer to the vessel wall, in the plasmatic zone rather than the axial stream. This allows 'pavementing' of leukocytes (their adhesion to the vascular epithelium) to occur, which is the first step in leukocyte emigration into the extravascular space. The slowing of blood flow which follows the phase of hyperaemia is due to increased vascular permeability, allowing plasma to escape into the tissues while blood cells are retained within the vessels. The blood viscosity is therefore increased.

**Increased vascular permeability**

Small blood vessels are lined by a single layer of endothelial cells. In some tissues, these form a complete layer of uniform thickness around the vessel wall, while in other tissues there are areas of endothelial cell thinning, known as fenestrations. The walls of small blood vessels act as a microfilter, allowing the passage of water and solutes but blocking that of large molecules and cells. Oxygen, carbon dioxide and some nutrients transfer across the wall by diffusion, but the main transfer of fluid and solutes is by ultrafiltration. The high colloid osmotic pressure inside the vessel, due to the presence of plasma proteins, encourages fluid return to the vascular compartment. Under normal circumstances, high hydrostatic pressure at the arteriolar end of capillaries forces fluid out into the extravascular space, but this fluid returns into the capillaries at their venous end, where hydrostatic pressure is low. In acute inflammation, however, not only is capillary hydrostatic pressure increased, but there is also escape of plasma proteins into the extravascular space, increasing the osmotic pressure there. Consequently, much more fluid leaves the vessels than is returned to them. The net escape of protein-rich fluid is called exudation; hence, the fluid is called the fluid exudate.
Formation of the cellular exudate

The accumulation of neutrophil polymorphs (neutrophils) within the extracellular space is the diagnostic histological feature of acute inflammation. There are a number of steps to this process:

1. Margination of neutrophils - In the normal circulation, cells are confined to the central (axial) stream in blood vessels, and do not flow in the peripheral (plasmatic) zone near to the endothelium. However, loss of intravascular fluid and increase in plasma viscosity with slowing of flow at the site of acute inflammation allow neutrophils to flow in this plasmatic zone.
2. Adhesion of neutrophils - The adhesion of neutrophils to the vascular endothelium which occurs at sites of acute inflammation is termed 'pavementing' of neutrophils. Neutrophils randomly contact the endothelium in normal tissues, but do not adhere to it. However, at sites of injury, pavementing occurs early in the acute inflammatory response and appears to be a specific process occurring independently of the eventual slowing of blood flow. Increased leukocyte adhesion results from interaction between adhesion molecules on leukocyte and endothelial surfaces. Leukocyte surface adhesion molecule expression is increased by complement factors, leukotrienes, and tumour necrosis factor (TNF).

As the neutrophil rolls along the blood-vessel wall, the L-selectin on its surface binds to carbohydrate structures such as Sialyl-Lewis^x on the adhesion molecules on the vascular endothelium, and its progress is eventually halted. As the neutrophil becomes activated, it replaces L-selectin with other cell-surface adhesion molecules, such as integrins. These molecules bind E-selectin, which is present on the blood-vessel wall as a result of the influence of inflammatory mediators such as bacterial lipopolysaccharides and the cytokines interleukin-1 and TNF-alpha. The activated neutrophil then enters the tissues, where it is attracted to the infection site by a number of chemoattractants. The neutrophil can then phagocytose and destroy the C3b-coated bacteria.

3. Neutrophil emigration - Leukocytes migrate by active amoeboid movement through the walls of venules and small veins, but do not commonly exit from capillaries. Electron microscopy shows that neutrophil and eosinophil polymorphs and macrophages can insert
pseudopodia between endothelial cells, migrate through the gap so created between the endothelial cells, and then on through the basal lamina into the vessel wall. This process is known as diapedesis. The defect appears to be self-sealing, and the endothelial cells are not damaged by this process.

4. Red cells may also escape from vessels, but in this case the process is passive and depends on hydrostatic pressure forcing the red cells out. The presence of large numbers of red cells in the extravascular space implies severe vascular injury, such as a tear in the vessel wall.

**Chemical mediators of acute inflammation**

The spread of the acute inflammatory response following injury to a small area of tissue suggests that chemical substances are released from injured tissues, spreading outwards into uninjured areas. These chemicals, called endogenous chemical mediators, cause vasodilatation, emigration of neutrophils, chemotaxis, and increased vascular permeability.

Histamine is the best-known chemical mediator in acute inflammation. It causes vascular dilatation and the immediate transient phase of increased vascular permeability. It is stored in mast cells, basophils and eosinophil leukocytes, and platelets. Histamine released from these sites is stimulated by complement factors, and by lysosomal proteins released from neutrophils, including cationic proteins, which may increase vascular permeability, and neutral proteases, which may activate complement.

Prostaglandins are a group of long-chain fatty acids derived from arachidonic acid and synthesised by many cell types. Some prostaglandins potentiate the increase in vascular permeability caused by other compounds. Others include platelet aggregation. Part of the anti-inflammatory activity of drugs such as aspirin and the non-steroidal anti-inflammatory drugs is attributable to inhibition of one of the enzymes involved in prostaglandin synthesis.
Leukotrienes are also synthesised from arachidonic acid, especially in neutrophils, and appear to have vasoactive properties.

5-HT (serotonin) is present in high concentration in mast cells and platelets. It is a potent vasoconstrictor.

Cytokines are a group of proteins whose molecular weights vary between 5 to 500 kilodaltons. They exert a wide range of biological functions via their specific receptors on target cells or proteins. They are produced by multi-cellular origins, and act on a variety of cells. Cytokine is a broad term that covers the following molecules: growth factors, interleukins, tumour necrosis factors, and interferons.

**Effects of acute inflammation**

Acute inflammation has local and systemic effects, both of which may be harmful or beneficial. The local effects are usually clearly beneficial, for example the destruction of invading micro-organisms; but at other times they appear to serve no obvious function, or may even be positively harmful.

Beneficial effects:

Both the fluid and cellular exudates may have useful effects. Beneficial effects of the fluid exudate are:

- Dilution of toxins, such as those produced by bacteria, allows them to be carried away in lymphatics.
- Entry of antibodies, due to increased vascular permeability into the extravascular space, where they may lead either to lysis of micro-organisms, through the participation of complement, or to their phagocytosis by opsonisation. Antibodies are also important in neutralisation of toxins.
- Transport of drugs such as antibiotics to the site where bacteria are multiplying.
- Fibrin formation from exuded fibrinogen may impede the movement of microorganisms, trapping them and so facilitating phagocytosis.
- Delivery of nutrients and oxygen, essential for cells such as neutrophils which have high metabolic activity, is aided by increased fluid flow through the area.
- Stimulation of immune response by drainage of this fluid exudate into the lymphatics allows particulate and soluble antigens to reach the local lymph nodes where they may stimulate the immune response.

The role of neutrophils in the cellular exudate has already been mentioned earlier. They have a life-span of only 1-3 days and must be constantly replaced. Most die locally, but some leave the site via the lymphatics. Blood monocytes also arrive at the site and, on leaving the blood vessels, transform into macrophages, becoming more metabolically active, motile and phagocytic. Phagocytosis of micro-organisms is enhanced by opsonisation by antibodies or by complement. In most acute inflammatory reactions, macrophages play a lesser role in phagocytosis compared with that of neutrophils. They appear late in the response and are usually responsible for clearing away tissue debris and damaged cells.

Harmful effects :
- The release of lysosomal enzymes by inflammatory cells may also have harmful effects:
  - Digestion of normal tissues - Enzymes such as collagenases and proteases may digest normal tissues, resulting in their destruction. This may result particularly in vascular damage.
  - Swelling - The swelling of acutely inflamed tissues may be harmful by increasing pressure on surrounding tissues, or resulting in a blockage of a vessel or duct.
  - Inappropriate inflammatory response - Sometimes, acute inflammatory responses appear inappropriate, such as those which occur in type I hypersensitivity reactions (e.g. hay fever) where the provoking environmental antigen (e.g. pollen) otherwise poses no threat to the individual. Such allergic inflammatory responses may be life-threatening, eg, asthma.
Consequences of acute inflammation.

The events occurring after acute inflammation depend upon the type of tissue involved and the amount of tissue destruction, which depend in turn upon the nature of the injurious agent.

**Resolution** - The term resolution means the complete restoration of the tissues to normal after an episode of acute inflammation. The conditions which favour resolution are:

- minimal cell death and tissue damage
- occurrence in an organ or tissue which has regenerative capacity (e.g. the liver) rather than in one which cannot regenerate (e.g. the central nervous system)
- rapid destruction of the causal agent (e.g. phagocytosis of bacteria)
- rapid removal of fluid and debris by good local vascular drainage.
**Suppuration** - Suppuration is the formation of pus, a mixture of living, dying and dead neutrophils and bacteria, cellular debris and sometimes globules of lipid. The causative stimulus must be fairly persistent and is virtually always an infective agent, usually pyogenic bacteria (e.g. Staphylococcus aureus, Streptococcus pyogenes, Neisseria species or coliform organisms). Once pus begins to accumulate in a tissue, it becomes surrounded by a 'pyogenic membrane' consisting of sprouting capillaries, neutrophils and occasionally fibroblasts. Such a collection of pus is called an abscess, and bacteria within the abscess cavity are relatively inaccessible to antibodies and to antibiotic drugs.

An abscess (e.g., a boil) usually 'points' then bursts; the abscess cavity collapses and is removed by organisation and fibrosis, leaving a small scar. Sometimes, surgical incision and drainage a necessary to eliminate the abscess. Deep-seated abscesses sometimes discharge their pus along a sinus tract (an abnormal connection, lined by granulation tissue, between the abscess and the skin or a mucosal surface). If this results in an abnormal passage connecting two mucosal surfaces or one mucosal surface to the skin surface, it is referred to as a fistula. Sinuses occur particularly when foreign body materials are present, which are indigestible by macrophages and which favour continuing suppuration. The only treatment for this type of condition is surgical elimination of the foreign body material.

**Organisation** - Organisation of tissues is their replacement by granulation tissue. The circumstances favouring this outcome are when:

- large amounts of fibrin are formed, which cannot be removed completely by fibrinolytic enzymes from the plasma or from neutrophil polymorphs
- substantial volumes of tissue become necrotic or if the dead tissue (e.g., fibrous tissue) is not easily digested
- exudate and debris cannot be removed or discharged.

During organisation, new capillaries grow into the inert material (inflammatory exudate), macrophages migrate into the zone and fibroblasts proliferate, resulting in fibrosis.
**Progression to chronic inflammation**

If the agent causing acute inflammation is not removed, the acute inflammation may progress to the chronic stage. In addition to organisation of the tissue as just described, the character of the cellular exudate changes, with lymphocytes, plasma cells and macrophages (sometimes including multinucleate giant cells) replacing the neutrophil polymorphs. Sometimes chronic inflammation occurs as a primary event, there being no preceding period of acute inflammation.

**Systemic effects of inflammation**

Apart from the local features of acute and chronic inflammation described previously, an inflammatory episode also produces systemic effects.

*Pyrexia* - Polymorphs and macrophages produce compounds known as endogenous pyrogens which act on the hypothalamus to set the thermoregulatory mechanisms at a higher temperature. Release of endogenous pyrogen is stimulated by phagocytosis, endotoxins and immune complexes.

*Constitutional symptoms* - Constitutional symptoms include malaise, anorexia and nausea.

*Weight loss* - Weight loss, due to negative nitrogen balance, is common when there is extensive chronic inflammation. For this reason, tuberculosis used to be called ‘consumption’.

*Reactive hyperplasia of the reticulo-endothelial system* - Local or systemic lymph node enlargement commonly accompanies inflammation, while splenomegaly is found in certain specific infections (e.g. malaria, infectious mononucleosis).

*Haematological changes –*

a. *Increased erythrocyte sedimentation rate.* An increased erythrocyte sedimentation rate is a non-specific finding in many types of inflammation.
b. Leukocytosis. Neutrophilia occurs in pyogenic infections and tissue destruction; eosinophilia in allergic disorders and parasitic infection; lymphocytosis in chronic infection (e.g. tuberculosis), many viral infections and in whooping cough; and monocytosis occurs in infectious mononucleosis and certain bacterial infections (e.g. tuberculosis, typhoid).

c. Anaemia. This may result from blood loss in the inflammatory exudate (e.g. in ulcerative colitis), haemolysis (due to bacterial toxins), and 'the anaemia of chronic disorders' due to toxic depression of the bone marrow.

Amyloidosis - Longstanding chronic inflammation (for example, in rheumatoid arthritis, tuberculosis and bronchiectasis), by elevating serum amyloid A protein (SAA), may cause amyloid to be deposited in various tissues resulting in secondary (reactive) amyloidosis.

Chronic Inflammation

The word 'chronic' applied to any process implies that the process has extended over a long period of time. This is usually the case in chronic inflammation, but here the term 'chronic' takes on a much more specific meaning, in that the type of cellular reaction differs from that seen in acute inflammation. Chronic inflammation may be defined as an inflammatory process in which lymphocytes, plasma cells and macrophages predominate, and which is usually accompanied by the formation of granulation tissue, resulting in fibrosis. Chronic inflammation is usually primary, but does occasionally follow acute inflammation.

The commonest appearances of chronic inflammation are:

- chronic ulcer, such as a chronic peptic ulcer of the stomach with breach of the mucosa, a base lined by granulation tissue and with fibrous tissue extending through the muscle layers of the wall
- chronic abscess cavity, for example osteomyelitis
- thickening of the wall of a hollow structure by fibrous tissue in the presence of a chronic inflammatory cell infiltrate
- granulomatous inflammation, perhaps with caseous necrosis as in chronic fibrocaseous tuberculosis of the lung
- fibrosis, which may become the most prominent feature of the chronic inflammatory reaction when most of the chronic inflammatory cell infiltrate has subsided.

KEY LEARNING POINTS.

1. The acute inflammatory response involves changes to vessel permeability, changes in vessel diameter, and the formation of cellular exudate.
2. The accumulation of neutrophils within the extracellular space is the diagnostic histological feature of acute inflammation.
3. Important chemical mediators in the phase include histamine, prostaglandins, serotonin, leukotrienes, and cytokines.