

Underwood: Chapter 8: Inflammation

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 microorganisms and the walling-off of an abscess cavity, thus preventing spread of infection. Equally, it may produce disease.

Inflammation is usually classified according to its time course:

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

Acute inflammation

- Initial reaction of tissue to injury
- Vascular phase: dilatation and increased permeability
- Exudative phase: fluid and cells escape from permeable venules
- Neutrophil polymorph is the characteristic cell
- Outcome may be resolution, suppuration (e.g. abscess), organisation, or progression to chronic inflammation

Acute inflammation is the initial tissue reaction to a wide range of injurious agents; it may last from a few hours to a few days. The process is usually described by the suffix '-itis', preceded by the name of the organ or tissues involved. Thus, acute inflammation of the meninges is called meningitis. The acute inflammatory response is similar whatever the causative agent.

Cause of acute inflammation

Microbial infections

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. Parasitic infections and tuberculous inflammation are instances when hypersensitivity is important.

Hypersensitivity reactions

A hypersensitivity reaction occurs when an altered state of immunological responsiveness causes an inappropriate or excessive immune reaction which damages the tissues.

Physical agents

Irritant and corrosive chemicals

Tissue necrosis

Essential macroscopic appearances of acute inflammation

The essential physical characteristics of acute inflammation were formulated by Celsus (30 BC - 38 AD) using the Latin words *rubor*, *calor*, *tumor* and *dolor*. Loss of function is also characteristic (*functio laesa*).

Redness (*rubor*)

An acutely inflamed tissue appears red, for example skin affected by sunburn, cellulitis due to bacterial infection or acute conjunctivitis. This is due to dilatation of small blood vessels within the damaged area.

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*)

For the patient, pain is one of the best-known features of acute inflammation. It results partly from the stretching and distortion of tissue 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 (*functio laesa*)

Loss of function, a well-known consequence of inflammation, was added by Virchow (1821-1902) to the list of features drawn up by Celsus. Movement of an inflamed area is consciously and reflexly inhibited by pain, while severe swelling may physically immobilise the tissues.

Early stages of acute inflammation

In the early stages, oedema fluid, fibrin and neutrophil polymorphs accumulate in the extracellular spaces of the damaged tissue. *The presence of the cellular component, the neutrophil polymorph, is essential for a histological diagnosis of acute inflammation.* The acute inflammatory response involves three processes:

- changes in vessel calibre, and, consequently, flow
- increased vascular permeability and formation of the fluid exudate
- formation of the cellular exudate - emigration of the neutrophil polymorphs into the extravascular space

Changes in vessel calibre

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 calibre,* 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.* 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.
- The flush: a dull red line follows due to capillary dilatation.
- The flare: a red, irregular, surrounding zone then develops, due to arteriolar dilatation. Both nervous and chemical factors are involved in these vascular changes.
- The wheal: a zone of oedema develops due to fluid exudation into the extravascular space.

The initial phase of arteriolar constriction is transient, and probably of little importance in acute inflammation. The subsequent phase of vasodilatation (active hyperaemia) last from

15 minutes to several hours, depending upon the severity of the injury. There is experimental evidence that blood flow to the injured area may increase up to ten-fold.

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 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, as described by Starling. The high colloid osmotic pressure inside the vessel, due to plasma proteins, favours 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 colloid 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*.

Features of the fluid exudate

The increased vascular permeability means that large molecules, such as protein, can escape from vessels. Hence, the exudate fluid has a high protein content of up to 50 g/l. The proteins present include immunoglobulins, which may be important in the destruction of invading micro-organisms, and coagulation factors, including fibrinogen, which result in fibrin deposition on contact with the extravascular tissues. Hence, acutely inflamed organ surfaces are commonly covered by fibrin: the *fibrinous exudate*. There is a considerable turnover of the inflammatory exudate; it is constantly drained away by local lymphatic channels to be replaced by new exudate.

Ultrastructural basis of increased vascular permeability

This was originally determined using an experimental model in which histamine, one of the chemical mediators of increased vascular permeability, was injected under the skin. This caused transient leakage of plasma proteins into the extravascular space. Electron microscopic examination of venules and small veins during this period showed that gaps of 0.1-0.4 microm in diameter had appeared between endothelial cells. These gaps allowed the

leakage of injected particles, such as carbon, into the tissues. *The endothelial cells are not damaged during this process.* They contain contractile proteins such as actin, which, when stimulated by the chemical mediators of acute inflammation, cause contraction of the endothelial cells, pulling open the transient pores. *The leakage induced by chemical mediators, such as histamine, is confined to venules and small veins.* Although fluid is lost by ultrafiltration from capillaries, there is no evidence that they too become more permeable in acute inflammation.

Certain other stimuli, e.g. heat, cold, UV light and X-rays, bacterial toxins and corrosive chemical, cause delayed prolonged leakage. In these circumstances, there is direct injury to endothelial cells in several types of vessels within the damaged area.

The relative importance of chemical mediators and of direct vascular injury in causing increased vascular permeability varies according to the type of tissue. For example, vessels in the CNS are relatively insensitive to the chemical mediators, while those in the skin, conjunctiva and bronchial mucosa are exquisitely sensitive to agents such as histamine.

Formation of the cellular exudate

The accumulation of *neutrophil polymorphs* within the extracellular space is the diagnostic histological feature of acute inflammation.

Margination of neutrophils

Pavementing 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 a specific process occurring independently of the eventual slowing of blood flow. *The phenomenon is seen only in venules.* Its mechanism remains a mystery, since no ultrastructural changes have been detected in the endothelial cells to which the leukocyte adhere.

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. The defect appears to be self-sealing, and the endothelial cells are not damaged by this process.

Diapedesis

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 process is called diapedesis, and

the presence of large numbers of red cells in the extravascular space implies severe vascular injury, such as a tear in the vessel wall.

Later stages of acute inflammation

Chemotaxis of neutrophils

Neutrophil polymorphs are attracted towards certain chemical substances in solution - a process called *chemotaxis*. *Compounds which appear chemotactic for neutrophils in vitro include certain complement components, lymphokines and products produced by neutrophils themselves. Neutrophils may possibly arrive at sites of injury by random movement, and then be trapped there by immobilising factors (a process analogous to the trapping of macrophages at sites of delayed-type hypersensitivity by migration inhibitory factor).*

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.

Chemical mediators released from cells

Histamine. It causes vascular dilatation and the immediate transient phase of increased vascular permeability. *It is stored in mast cells, basophil and eosinophil leukocytes, and platelets. Histamine release from these sites (for example, mast cell degranulation) is stimulated by complement components C3a and C5a, and by lysosomal proteins released from neutrophils.*

Lysosomal compounds. These are released from neutrophils and include *cationic proteins*, which may increase vascular permeability, and *neutral proteases*, which may activate complement.

Prostaglandins. These 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 (prostaglandin I₂ is inhibitory while prostaglandin A₂ is stimulatory)*. Part of the antiinflammatory 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. These are also synthesised from arachidonic acid, especially in neutrophils, and appear to have vasoactive properties. *SRS-A (slow reacting substance of anaphylaxis)*, involved in type I hypersensitivity, is a mixture of leukotrienes.

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

Lymphokines. This family of chemical messengers released by lymphocytes have a major role in type IV hypersensitivity but may also have vasoactive or chemotactic properties.

Plasma factors

The plasma contains four enzymatic cascade systems - *complement*, the *kinins*, the *coagulation factors* and the *fibrinolytic system* - which are inter-related and produce various inflammatory mediators.

Complement system. The complement system is a cascade system of enzymatic proteins. It can be activated during the acute inflammatory reaction in various ways:

- *In tissue necrosis, enzymes capable of activating complement are released from dying cells.*

During infection, the formation of antigen-antibody complexes can activate complement via the classical pathway, while the endotoxins of Gram-negative bacteria activate complement via the alternative pathway.

- *Products of the kinin, coagulation and fibrinolytic systems can activate complement.*

The products of complement activation most important in acute inflammation include:

- *C5a: chemotactic for neutrophils; increases vascular permeability; releases histamine from mast cells.*

- *C3a: similar properties to those of C5a, but less active.*

- *C567: chemotactic for neutrophils.*

- *C56789: cytolytic activity.*

- *C4b, 2a, 3b: opsonisation of bacteria (facilitates phagocytosis by macrophages).*

Kinin system. The kinins are peptides of 9-11 amino acids; the most important vascular permeability factor is *bradykinin*. The kinin system is activated by *coagulation factor XII (Hageman)*. Bradykinin is also a chemical mediator of the pain which is a cardinal feature of acute inflammation.

Coagulation system. It is responsible for the conversion of soluble fibrinogen into fibrin, a major component of the acute inflammatory exudate.

Coagulation factor XII (Hageman), once activated by contact with extracellular materials such as basal lamina, and various proteolytic enzymes of bacterial origin, can activate the coagulation, kinin and fibrinolytic systems.

Fibrinolytic systems. Plasmin is responsible for the lysis of fibrin into fibrin degradation products, which may have local effects on vascular permeability.

Role of the lymphatics

Terminal lymphatics are blind-ended, endothelium-lined tubes present in most tissues in similar numbers to capillaries. The terminal lymphatics drain into collecting lymphatics which have valves and so propel lymph passively, aided by contraction of neighbouring muscles, to the lymph nodes. The basal lamina of lymphatic endothelium is incomplete, and the junctions between the cells are simpler and less robust than those between capillary endothelial cells. Hence, gaps tend to open up passively between the lymphatic endothelial cells, allowing large protein molecules to enter.

In acute inflammation, the lymphatic channels become dilated as they drain away the oedema fluid of the inflammatory exudate. This drainage tends to limit the extent of oedema in the tissues. The ability of lymphatics to carry large molecules and some particulate matter is important in the immune response to infecting agents; antigens are carried to the regional lymph nodes for recognition by lymphocytes.

Role of the neutrophil polymorph

The neutrophil polymorph is the characteristic cell of the acute inflammatory infiltrate.

Movement

Contraction of cytoplasmic microtubules and gel/sol changes in cytoplasmic fluidity bring about amoeboid movement. *These active mechanism are dependent upon calcium ions and are controlled by intracellular concentrations of cyclic nucleotides.* The movement shows a directional response (chemotaxis) to the various chemicals.

Adhesion to micro-organisms

Micro-organisms are *opsonised*, or rendered more amenable to phagocytosis (from the Greek word meaning 'to prepare for the table'), either by immunoglobulins or by complement components. Bacterial polysaccharides activate complement via the alternative pathway, generating component C3b which has opsonising properties. In addition, if antibody binds to bacterial antigens, this can activate complement via the classical pathway, also generating C3b. In the immune individual, the binding of immunoglobulins to micro-organisms by their Fab components leaves the Fc component exposed. Neutrophils have surface receptors for the Fc fragment of immunoglobulins, and consequently bind to the micro-organisms prior to ingestion.

Phagocytosis

The process whereby cells (such as neutrophil polymorphs and macrophages) ingest solid particles is termed phagocytosis. The first step in phagocytosis is adhesion of the particle to be phagocytosed to the cell surface. This is facilitated by opsonisation. The phagocyte then

ingests the attached particle by sending out pseudopodia around it. These meet and fuse so that the particle lies in a phagocytic vacuole (also called a phagosome) bounded by cell membrane. Lysosomes, membrane-bound packets containing the toxic compounds described below, then fuse with phagosomes to form phagolysosomes. It is within these that intracellular killing of micro-organisms occurs.

Intracellular killing of micro-organisms

Neutrophil polymorphs are highly specialised cells, containing noxious microbicidal agents, some of which are similar to household bleach. The microbicidal agents may be classified as:

- those which are oxygen-dependent
- those which are oxygen-independent

Oxygen-dependent mechanisms. The neutrophils produce hydrogen peroxide which reacts with myeloperoxidase in the cytoplasmic granules in the presence of halide, such as Cl ion, to produce a potent microbicidal agent. Other products of oxygen reduction also contribute to the killing, such as peroxide anions, hydroxyl radicals and singlet oxygen.

Oxygen-independent mechanisms. These include lysozyme (muramidase), lactoferrin which chelates iron required for bacterial growth, cationic proteins, and the low pH inside phagocytic vacuoles.

Release of lysosomal products

Release of lysosomal products from the cell damages local tissues by proteolysis by enzymes such as elastase and collagenase, activates coagulation factor XII, and attracts other leukocytes into the area. Some of the compounds released increase vascular permeability, while others are pyrogens, producing systemic fever by acting on the hypothalamus.

Special macroscopic appearances of acute inflammation

The cardinal signs of acute inflammation are modified according to the tissue involved and the type of agent provoking the inflammation. Several descriptive terms are used for the appearances.

Serous inflammation

In serous inflammation, there is abundant protein-rich fluid exudate with a relatively low cellular content. Examples include inflammation of the serous cavities, such as peritonitis, and inflammation of a synovial joint, acute synovitis. Vascular dilatation may be apparent to the naked eye, the serous surfaces appearing injected, i.e. having dilated, blood-laden vessels on the surface, (like the appearance of the conjunctive in 'blood-shot' eyes).

Catarrhal inflammation

When mucus hypersecretion accompanies acute inflammation of a mucous membrane, the appearance is described as catarrhal. The common cold is a good example.

Fibrinous inflammation

When the inflammatory exudate contains plentiful fibrinogen, this polymerises into a thick fibrin coating. This is often seen in acute pericarditis and gives the parietal and visceral pericardium a 'bread and butter' appearance.

Haemorrhagic inflammation

Haemorrhagic inflammation indicates severe vascular injury or depletion of coagulation factors. This occurs in acute pancreatitis due to proteolytic destruction of vascular walls, and in meningococcal septicaemia due to disseminated intravascular coagulation.

Suppurative (purulent) inflammation

The terms 'suppurative' and 'purulent' denote the production of pus, which consists of dying and degenerate neutrophils, infecting organisms and liquefied tissues. The pus may become walled-off by granulation tissue or fibrous tissue to produce an abscess (a localised collection of pus in a tissue). If a hollow viscus fills with pus, this is called an empyema, for example, empyema of the gall bladder.

Membranous inflammation

In acute membranous inflammation, an epithelium becomes coated by fibrin, desquamated epithelial cells and inflammatory cells. An example is the grey membrane seen in pharyngitis or laryngitis due to *Corynebacterium diphtheriae*.

Pseudomembranous inflammation

The term 'pseudomembranous' describes superficial mucosal ulceration with an overlying slough of disrupted mucosa, fibrin, mucus and inflammatory cells. This is seen in pseudomembranous colitis due to *Clostridium difficile* colonisation of the bowel, usually following broad-spectrum antibiotic treatment.

Necrotising (gangrenous) inflammation

High tissue pressure due to oedema may lead to vascular occlusion and thrombosis, which may result in widespread septic necrosis of the organ. The combination of necrosis and bacterial putrefaction is gangrene.

Effects of acute inflammation

The systemic effects of acute inflammation are discussed later. 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 as follows:

- *Dilution of toxins.* This allows them to be carried away in lymphatics.
- *Entry of antibodies.* Increased vascular permeability allows antibodies to enter 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.
- *Drug transport.* The fluid carries with it therapeutic drugs such as antibiotics to the site where bacteria are multiplying.
- *Fibrin formation.* Fibrin formation from exuded fibrinogen may impede the movement of micro-organisms, trapping them and so facilitating phagocytosis.
- *Delivery of nutrients and oxygen.* 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.* The 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 discussed. 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 neutrophil polymorphs. They appear late in the response and are usually responsible for clearing away tissue debris and damaged cells.

Both neutrophils and macrophages may discharge their lysosomal enzymes into the extracellular fluid by exocytosis, or the entire cell contents may be released when the cells die. Release of these enzymes assists in the *digestion of the inflammatory exudate*.

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, for example in type III hypersensitivity reactions and in some types of glomerulonephritis.

- *Swelling.* The swelling of acutely inflamed tissues may be harmful: for example, the swelling of the epiglottis in acute epiglottitis in children due to *Haemophilus influenzae* infection may obstruct the airway, resulting in death. Inflammatory swelling is especially serious when it occurs in an enclosed space such as the cranial cavity. Thus, acute meningitis or a cerebral abscess may raise intracranial pressure to the point where blood flow into the brain is impaired, resulting in ischaemic damage, or may force the cerebral hemispheres against the tentorial orifice and the cerebellum into the foramen magnum (pressure coning).

- *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, for example extrinsic asthma.

Sequelae of acute inflammation

The sequelae of 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 CNS)*
- *rapid destruction of the causal agent (e.g. phagocytosis of bacteria)*
- *rapid removal of fluid and debris by good local vascular drainage.*

A good example of an acute inflammatory condition which usually resolves completely is acute lobar pneumonia. The alveoli become filled with acute inflammatory exudate containing fibrin, bacteria and neutrophil polymorphs. The alveolar walls are thin and have many capillaries (for gas exchange) and lymphatic channels. The sequence of events leading to resolution is usually:

- phagocytosis of bacteria (i.e., pneumococci) by neutrophils and intracellular killing
- fibrinolysis
- phagocytosis of debris, especially by macrophages, and carriage through lymphatics to the hilar lymph nodes
- disappearance of vascular dilatation.

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 (i.e., *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 occasional 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 (thus, for example, acute osteomyelitis, an abscess in the bone marrow cavity, is notoriously difficult to treat).

Abscess

An abscess (for example, a boil) usually 'points', then bursts; the abscess cavity collapses and is obliterated by organisation and fibrosis, leaving a small scar. Sometimes, surgical incision and drainage is necessary to eliminate the abscess.

If an abscess forms inside a hollow viscus (i.e., the gall bladder) the mucosal layers of the outflow tract of the viscus may become fused together by fibrin, resulting in an empyema.

Such 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 fibrous walls of long-standing abscesses may become complicated by *dystrophic calcification*.

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 (i.e., 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*. A good example of this is seen in the pleural space following acute lobar pneumonia. Resolution usually occurs in the lung parenchyma, but very extensive fibrinous exudate fills the pleural cavity. The fibrin is not easily removed and consequently capillaries grow into the fibrin, accompanied by macrophages and fibroblasts (the exudate becomes 'organised'). Eventually, fibrous adhesions occur between the parietal and visceral pleura.

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 just described, the character of the cellular exudate changes, with lymphocytes, plasma cells, and macrophages (sometimes including multinucleate giant cells) replacing the neutrophil polymorphs.

Systemic effects of inflammation

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

Malaise, anorexia, nausea.

Negative nitrogen balance

Weight loss 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

Increased erythrocyte sedimentation rate.

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).

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

- *Lymphocytes, plasma cells and macrophages predominate*
- *Usually primary, but may follow acute inflammation*
- *Granulomatous inflammation is a specific type of chronic inflammation*
- *A granuloma is an aggregate of epithelioid histiocytes*
- *May be complicated by secondary (reactive) amyloidosis*

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 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.

Causes of chronic inflammation

Chronic inflammation developing from acute inflammation

Most cases of acute inflammation do not develop into the chronic form, but resolve completely. The commonest variety of acute inflammation to progress to chronic inflammation is the suppurative type. If the pus forms an abscess cavity which is deep-seated, and drainage is delayed or inadequate, then by the time that drainage occurs the abscess will have developed thick walls composed of granulation and fibrous tissues. The rigid walls of the

abscess cavity therefore fail to come together after drainage, and the stagnating pus within the cavity becomes organised by the ingrowth of granulation tissue, eventually to be replaced by a fibrous scar.

Another feature which favours progression to chronic inflammation is the presence of indigestible material. This may be keratin from a ruptured epidermal cyst, or fragments of necrotic bone as in the sequestrum of chronic osteomyelitis. These materials are relatively inert, and are resistant to the action of lysosomal enzymes. The most indigestible forms of material are inert foreign body materials: some types of surgical suture, wood, metal or glass.

Foreign bodies have in common the tendency to provoke a special type of chronic inflammation called 'granulomatous inflammation', and to cause macrophages to form multinucleate giant cells called 'foreign body giant cells'.

Primary chronic inflammation

In most cases of chronic inflammation, the inflammatory response has all the histological features of chronic inflammation from the onset, and there is no initial phase of acute inflammation.

Transplant Rejection

Cellular rejection of transplants involves chronic inflammatory cell infiltration.

Macroscopic appearances of chronic inflammation

- *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, empyema thoracis

- *thickening of the wall of a hollow viscus* by fibrous tissue in the presence of a chronic inflammatory cell infiltrate, for example Crohn's disease, chronic cholecystitis

- *granulomatous inflammation*, perhaps with caseous necrosis as in chronic fibrocereous 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. This is commonly seen in chronic cholecystitis, 'hour-glass contracture' of the stomach, where fibrosis distorts the gastric wall and may even lead to acquired pyloric stenosis, and in the strictures which characterise Crohn's disease.

Microscopic Features of Chronic Inflammation

The cellular infiltrate consists characteristically of lymphocytes, plasma cells and macrophages. A few eosinophil polymorphs may be present, but neutrophil polymorphs are

scarce. Some of the macrophages may form multinucleate giant cells. Exudation of fluid is not a prominent feature, but there may be production of new fibrous tissue from granulation tissue. There may be evidence of continuing destruction of tissue at the same time as tissue regeneration and repair. Tissue necrosis may be a prominent feature, especially in granulomatous conditions such as tuberculosis.

Cellular Cooperation in Chronic Inflammation

B-lymphocytes, on contact with antigen, become progressively transformed into plasma cells which are cells specially adapted for the production of antibodies. On contact with antigen, T-lymphocytes produce a range of soluble factors called lymphokines, which have a number of important activities.

- *Recruitment of macrophages into the area.* It is thought that macrophages are recruited into the area mainly via factors such as migration inhibition factor (MIF), which trap macrophages in the tissue. Macrophage activation factors (MAF) stimulate macrophage phagocytosis and killing of bacteria.

- *Production of inflammatory mediators.* T-lymphocytes produce a number of inflammatory mediators, including chemotactic factors for neutrophils, and factors which increase vascular permeability.

- *Recruitment of other lymphocytes.* Mitogenic factors stimulate other lymphocytes to divide. 'Transfer factor' confers on other lymphocytes the ability to mount cell-mediated immune responses to a variety of antigens. T-lymphocytes also cooperate with B-lymphocytes, assisting them in recognising antigens.

Destruction of Target Cells

Factors, such as perforins, are produced which destroy other cells by damaging their cell membranes.

Interferon Production

Interferons have non-specific antiviral properties, and are synthesised by T-lymphocytes and by macrophages.

Macrophages in Chronic Inflammation

Macrophages are relatively large cells, up to 30 microm in diameter, which move by amoeboid motion through the tissues. They respond to certain chemotactic stimuli (possibly lymphokines and antigen-antibody complexes) and have considerable phagocytic capabilities for the ingestion of micro-organisms and cell debris. When neutrophil polymorphs ingest micro-organisms, they usually bring about their own destruction and thus have a limited life-span of up to about three days. Macrophages can ingest a wider range of materials than can polymorphs and, being long-lived, they can harbour viable organisms if they are not able to kill them by their lysosomal enzymes. Examples of organisms which can survive inside macrophages include mycobacteria, such as *Mycobacterium tuberculosis* and *Mycobacterium*

leprae, and organisms such as *Histoplasma capsulatum*. When macrophages participate in the delayed-type hypersensitivity response to these types of organism, they often die in the process, contributing to the large areas of necrosis by release of their lysosomal enzymes.

Macrophages in inflamed tissues are derived from blood monocytes which have migrated out of vessels and have become transformed in the tissues. They are thus part of the *mononuclear phagocyte system (MPS)*. This system is in turn part of the *reticulo-endothelial system* which refers not only to the phagocytic cells, but also to interdigitating reticulum cells of lymph nodes and the endothelial cells in lymphoid organs.

The MPS is now known to include macrophages, fixed tissue histiocytes in many organs and, probably, the osteoclasts of bone. All are derived from monocytes which in turn are derived from a haemopoietic stem cell in the bone marrow.

The 'activation' of macrophages as they migrate into an area of inflammation involves an increase in size, protein synthesis, mobility, phagocytic activity and content of lysosomal enzymes. Cells have a roughened cell membrane bearing filopodia, while the cytoplasm contains numerous dense bodies - phagolysosomes (formed by the fusion of lysosomes with phagocytic vacuoles).

Specialised Forms of Macrophages and Granulomatous Infection

A *granuloma* is an aggregate of epithelioid histiocytes.

Epithelioid histiocytes

Named for their vague histological resemblance to epithelial cells, epithelioid histiocytes have large vesicular nuclei, plentiful eosinophilic cytoplasm and are often rather elongated. They tend to be arranged in clusters. They have little phagocytic activity, but appear to be adapted to a secretory function. One of the products is angiotensin converting enzyme. Measurement of the activity of this enzyme in the blood can act as a marker for systemic granulomatous disease, such as sarcoidosis.

The appearance of granulomata may be augmented by the presence of caseous necrosis (as in tuberculosis) or by the conversion of some of the histiocytes into multinucleate giant cells. A common feature of many of the stimuli which induce granulomatous inflammation is indigestibility of particulate matter by macrophages. In *sarcoidosis* there appear to be far-reaching derangements in immune responsiveness favouring granulomatous inflammation.

Histiocytic giant cells

They tend to form where particulate matter which is indigestible by macrophages accumulates, for example inert minerals such as silica, or bacteria such as tubercle bacilli which have cell walls containing mycolic acids and waxes which resist enzymatic digestion. The multinuclear giant cells, which may contain over 100 nuclei, are thought to develop 'by accident' when two or more macrophages attempt simultaneously to engulf the same particle; their cell membranes fuse and the cells unite. The multinucleate giant cells resulting have little phagocytic activity and no known function.

Langhans' giant cells

It has a horse-shoe arrangement of peripheral nuclei at one pole of the cell and are characteristically seen in tuberculosis, although they may be seen in other granulomatous conditions.

Foreign-body giant cells

Those are large cells with nuclei randomly scattered throughout their cytoplasm.

Touton giant cells

These have a central ring of nuclei while the peripheral cytoplasm is clear due to accumulated lipid. They are seen at sites of adipose tissue breakdown and in xanthomata (tumour-like aggregates of lipid-laden macrophages).

Although giant cells are commonly seen in granulomata, they do not constitute a defining feature. Solitary giant cells in the absence of epithelioid histiocytes do not constitute a granuloma.