Congestion and hyperemia are terms that refer to excessive blood within the vascular system (**3.1**) due to the dilation of blood vessels and increased blood flow to tissues. Hyperemia of the sclera and conjunctiva are one of the earliest signs of acute ocular inflammation. These changes may be a sign of either local inflammation or, because of the interdependence of the structures in the eye, inflammation in the cornea or uveal tissues.

Edema is another manifestation of acute inflammation. This is the result of increased vascular permeability and movement of low-protein fluid from within the vascular component to the extravascular tissues. Edema of the cornea results in decreased corneal clarity; therefore, even minor degrees of disruption by edema, that in almost any other tissue would be insignificant and even imperceptible, are significant in the eye[3].

Serous exudate is not uncommon in early inflammation. This exudate consists of serum and plasma proteins that have moved from within the blood vascular system to the extravascular space. This fluid tends to be higher in protein than the transudate seen with edema. (Transudate is fluid low in protein, which is produced primarily by either an increase in hydrostatic pressure or decreased blood osmotic pressure without a change in permeability). Serous effusion from the choroid is an example of a fluid exudate and it causes retinal detachment, which can lead to blindness and photoreceptor degeneration (**3.2**)[1].

Any damage to blood vessels can result in fluid effusion into the globe. Hypertension is an example of vascular damage that is due to a combination of increased blood flow and hypoxia[4]. This leads to damage to the blood vessel (**3.3**), itself resulting in fluid effusion and hemorrhage.

Changes in vessel caliber

The microcirculation consists of the network of small capillaries which lie between arterioles, which have thick muscular walls, and venules, which have thin walls. Capillaries have no smooth muscle in their walls to control their caliber, and are so narrow that red blood cells must pass through them in single file. The smooth muscle of arteriolar walls forms precapillary sphincters that regulate blood flow through the capillary bed. Flow through the capillaries is intermittent; some precapillary sphincters form preferential channels for flow while others are usually shut down.

In blood vessels larger than capillaries, blood cells flow mainly in the center of the lumen (axial flow), while the area near the vessel wall carries only plasma. This feature of normal blood flow keeps blood cells away from the vessel wall.

Following injury, the initial phase of the vascular component is vascular constriction, which is transient and probably of little importance in acute inflammation. The subsequent phase of vasodilation resulting in hyperemia may last from 15 minutes to several hours, depending upon the severity of the injury. Experimental evidence indicates that blood flow to the injured area may increase up to tenfold.

Increased vascular permeability

A single layer of endothelial cells line capillaries. In some tissues these form a blood–tissue barrier, composed of a complete layer of tightly aligned endothelial cells (tight junctions) around the vessel wall. In other tissues there are areas of endothelial cell thinning, known as fenestrations. There are no tight junctions along the anterior border layer of the iris. The blood–eye barrier is at the level of the choroidal vascular endothelium[3]. Thus, any inflammatory cells or fluids that exude from the iris vessels almost immediately enter the aqueous humor. Therefore, any cytokines or growth factors present in the aqueous humor will have free access to the iris stroma. Heavy accumulation of edema or granulocytes is rarely seen in the iris, even when there is massive accumulation within the aqueous humor, due to the absence of tight junctions in the anterior border layer of the iris[3].

The blood vessels within the ciliary processes are freely permeable, and the blood–eye barrier exists at the level of tight junctions between adjacent ciliary epithelial cells. It is thus common to see marked distension of ciliary processes with edema during the early stages of inflammation, as the fluid is able to exude through the vessels but not through the ciliary epithelium[5].

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[6]. The high colloid osmotic pressure inside the vessel, due to plasma proteins, favors fluid return to the vascular compartment.

Increased vascular permeability in acute inflammation

There are two mechanisms for increased permeability of small vessels following tissue damage: toxins and physical agents may cause necrosis of vascular endothelium, leading to abnormal leakage (injury-induced vascular leakage); and chemical mediators of acute inflammation may cause retraction of endothelial cells, leaving intercellular gaps (chemical-mediated vascular leakage).

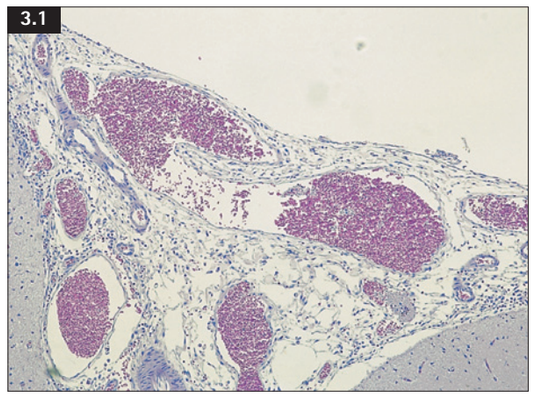
As the vessels become leaky, they permit the passage of water, salts, and some small proteins from the plasma into the damaged area (exudation). One of the main proteins to leak out is the small soluble molecule, fibrinogen. Endothelial cells swell and partially retract so that they no longer form a completely intact internal lining. Expression of adhesion molecules on the capillary endothelium allows white blood cells to adhere and eventually migrate.

Cellular events

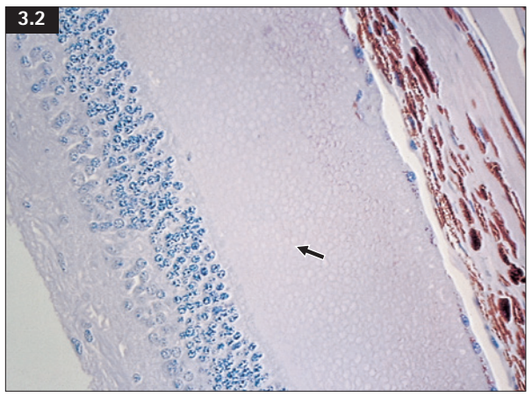
In acute inflammation, the capillary hydrostatic pressure increases and vascular permeability increases, allowing the escape of larger molecules such as plasma proteins into the extravascular space. Consequently, much more fluid leaves the vessels than is returned to them, resulting in the net escape of protein-rich (≤50 g/l) fluid (exudate). The proteins present include immunoglobulins, which may be important in the destruction of invading microorganisms, and coagulation factors (such as fibrinogen), which result in fibrin deposition on contact with the extravascular tissues. Hence, acutely inflamed organ surfaces are commonly covered by fibrinous exudate. There is considerable turnover of the inflammatory exudate.

Circulating neutrophils initially become closely apposed to the endothelium (pavementing), then adhere to the swollen endothelial cells (margination), then actively migrate through the vessel basement membrane (emigration), passing into the area of tissue damage. These events are mediated through expression of ligands on the blood cell surface that interact with adhesion molecules on the endothelium[1, 6]. These leukocyte and endothelial cell adhesion molecules are called selectins and integrins. Cytokines control the expression of the adhesion molecules and thus orchestrate these cellular events. Later, small numbers of blood monocytes (macrophages) migrate in a similar way, as do lymphocytes.

Theoretically, since the cornea is normally an avascular tissue, it cannot undergo inflammation. However, the nomenclature of 'keratitis' is widespread in the clinical literature, even though many of the conditions included under that name are probably not truly inflammatory. Neutrophils can gain access to the cornea from any break in the continuity of the surface epithelium, or by migrating from the limbal blood vessels in response to any pathogens in the corneal stroma. The presence of inflammatory cells within the stroma can result in the development of bystander stromal injury from granulocytic enzymes, and the production of leukocyte-associated growth factors that will stimulate corneal neovascularization and increased inflammatory infiltrate. Deep stromal mycotic keratitis is almost exclusively a disease of horses. The histologic lesion is distinctive: a deep stromal purulent keratitis in which the neutrophils are always karyorrhectic. They are most numerous adjacent to Descemet's membrane, and the fungi are also found in greatest numbers adjacent to, or within, Descemet's membrane. In many cases this is the only location in which they can be found. Because the

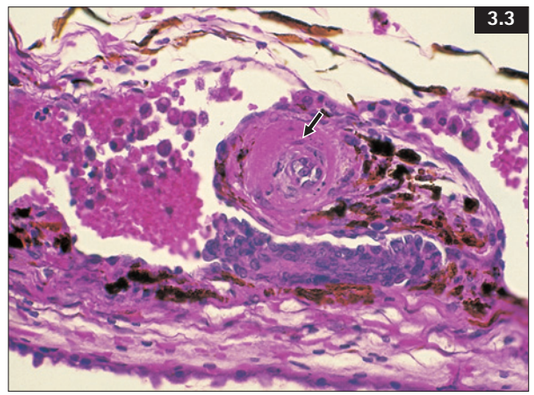


3.1 Histologic section of cerebral blood vessels from a dog. Blood vessels are distended with erythrocytes. The interstitial connective tissue is edematous.



3.2 Histologic section of the subretinal space in the eye of a dog, containing eosinophilic fluid consistent with serous effusion (arrow).

3.3 Choroidal blood vessel from a dog with hypertension. The vessel wall is thickened (arrow) and the surrounding choroid is hemorrhagic.



lesion is chronic and deep, there is frequently healing of the overlying stroma and epithelium, creating a deep-seated stromal 'abscess' (**3.4, 3.5**).

Eosinophilic keratoconjunctivitis is another inflammatory disease of horses[7]. Heavy infiltrations of eosinophils into the conjunctiva and, sometimes, the cornea characterize this disease. The chemotactic agent for the eosinophils is not well understood.

As previously noted, it is unusual to find large amounts of granulocytes outside the blood vessels of the uveal tract in early inflammation, due to the impervious nature of the vasculature. However, significant accumulations of granulocytes are not uncommon in the anterior chamber (hypopyon) or adhered to the endothelium and the posterior aspect of the cornea (keratic precipitates). Blood (hemorrhage) in the anterior chamber is called hyphema (**3.6, 3.7**).

Appearance of acute inflammation

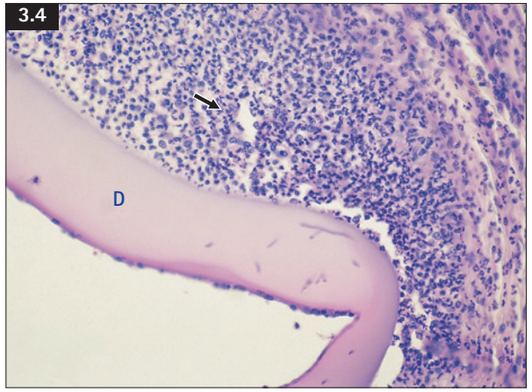
Specific descriptive terms are used to describe the pathologic appearance of acute inflammation.

Serous inflammation

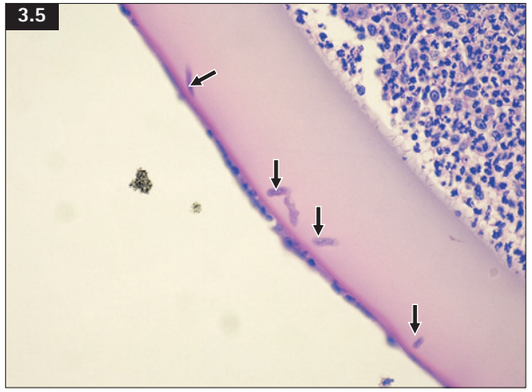
In serous inflammation there is exudation of abundant protein-rich fluid exudate with a relatively low cellular content, for instance in acute conjunctivitis. Vascular dilatation may be apparent to the naked eye, the serous surfaces appearing injected, i.e. having dilated, blood-laden vessels on the surface, as in the conjunctiva in 'bloodshot' eyes.

Catarrhal inflammation

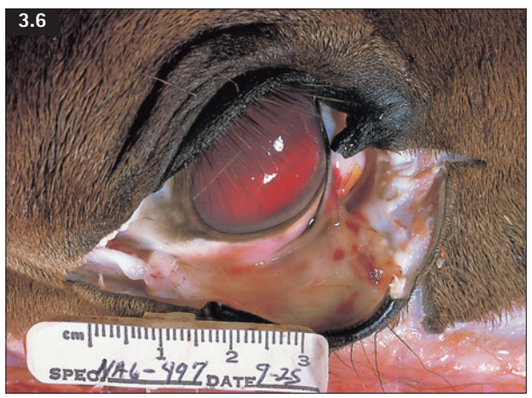
When mucus hypersecretion accompanies acute inflammation of a mucous membrane, the appearance is described as catarrhal. This type of inflammation is usually seen in the acute stage of inflammation in tissue such as the



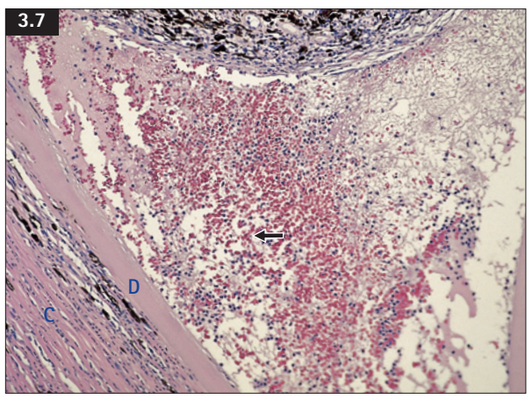
3.4 Histologic section of a cornea from a horse containing a dense accumulation of neutrophils (arrow) consistent with a corneal stromal abscess. (D, Descemet's membrane.) H&E.



3.5 Increased magnification of **3.4** shows the fungal hyphae (arrows) in Descemet's membrane deep to the corneal stromal abscess.



3.6 Hyphema in the anterior chamber of the eye of a horse.



3.7 Photomicrograph of a dog with hyphema showing an accumulation of free erythrocytes (arrow) in the anterior chamber. (D, Descemet's membrane; C, corneal stroma.) H&E.

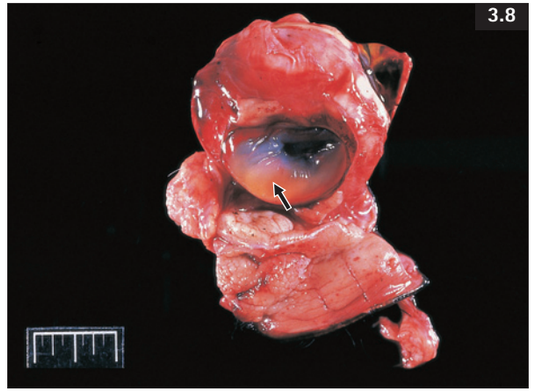
conjunctiva that has goblet (mucus producing) cells. As the disease progresses, other inflammatory exudates may be seen, such as neutrophils (mucopurulent) or fibrin.

Fibrinous inflammation

When the inflammatory exudate contains abundant fibrinogen, fibrin polymerizes into a thick fibrin coating. Exudation of fibrin as well as other proteins frequently occurs in the anterior chamber of the eye.

Suppurative (purulent) inflammation

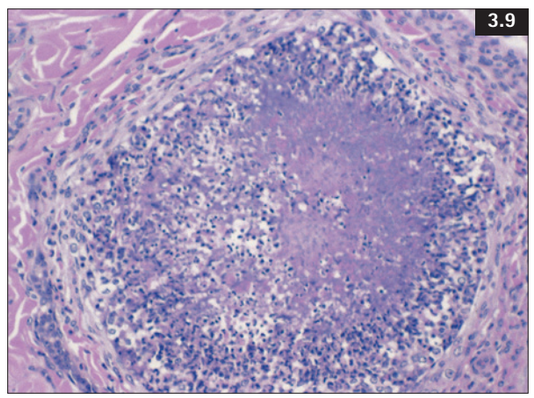
The terms 'suppurative' and 'purulent' denote the production of pus, which consists of dying and degenerate neutrophils, infecting organisms, and liquefied tissues. The pus may become walled-off by granulation tissue or fibrous tissue to produce an abscess (a localized collection of pus in a tissue). This is often seen in cases of canine distemper in which the conjunctiva is covered with thick greenish exudate. Accumulation of pus in the anterior chamber of the eye is termed hypopyon (**3.8**).



3.8 Photograph illustrating hypopyon in the anterior chamber of an equine eye (arrow). This is an example of purulent exudate.

Necrotizing inflammation

The products of inflammation (such as proteolytic enzymes) and vascular occlusion and thrombosis may result in widespread necrosis of the affected organ. The term necrotizing can be used to describe this kind of inflammation (**3.9**). As with other types of inflammation, necrotizing inflammation can occur in conjunction with an influx of neutrophils (necropurulent) or hemorrhage (necrohemorrhagic). In the eye, necrotizing inflammation is seen most often in association with an infectious agent, such as bacteria, fungi, and some viruses[8, 9], and with some poorly defined idiopathic lesions[10].



3.9 Histologic section of equine choroid showing a large focal area of necrosis surrounded by inflammatory cells.

Causes of inflammation

The most common cause of inflammation is microbial infection. These microbes include viruses, bacteria, protozoa, fungi, and parasites. Viruses lead to death of individual cells by intracellular multiplication. Bacteria synthesize and release specific exotoxins, which initiate inflammation, or endotoxins, which are associated with their cell walls. Additionally, some organisms such as parasites and *Mycobacterium* spp. cause immunologically-mediated inflammation through hypersensitivity reactions.

It is important to note here that there is a difference between inflammation and infection. Infectious agents can cause inflammation but not all inflammatory reactions are caused by infectious agents. Examples of noninfectious causes of inflammation are described below.

Hypersensitivity reactions

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

Physical agents

Tissue damage leading to inflammation may occur through physical (perforating or blunt) trauma, ultraviolet or other ionizing radiation, burns, or excessive cooling ('frostbite'). Trauma to the eye can result in a myriad of inflammatory responses; these may include immune-mediated inflammation, such as in lens-induced uveitis, and inflammation as a result of infection, such as in sepsis due to secondary bacterial infection of a ruptured globe.

Irritant and corrosive chemicals

Corrosive chemicals (acids, alkalis, oxidizing agents) provoke inflammation through direct tissue damage. The eye is susceptible and sensitive to damage by a variety of corrosive chemicals, damage which often first manifests as corneal damage.

Tissue necrosis

Death of tissues from lack of oxygen or nutrients resulting from inadequate blood flow (infarction) is a potent inflammatory stimulus. In the cornea, keratomalacia is the specific term used to describe liquefactive necrosis of corneal stroma. This is usually a sequela to bacterial or fungal contamination, and results from a bystander effect of neutrophilic inflammation, as well as other causes.

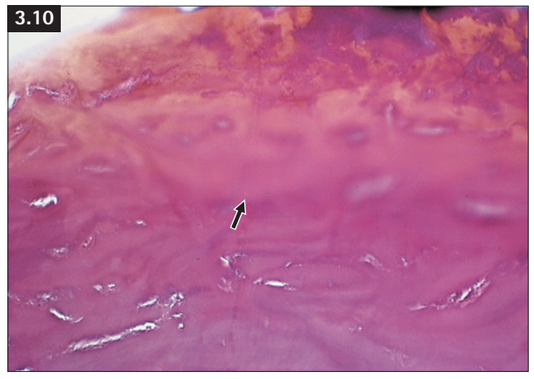
Another form of corneal necrosis is corneal sequestrum (**3.10**). This is devitalization of the corneal stroma, usually secondary to ulceration[11]. The condition is most often seen in cats, although a similar lesion has been described in dogs and horses. In cats, the necrotic stroma acquires a characteristic brown/black discoloration. The dead stroma becomes acellular and amorphous and is usually surrounded by a thin zone of lytic neutrophils. The lesion is slowly extruded through the corneal surface, with gradual turnover of the corneal stroma.

Manifestations of inflammation

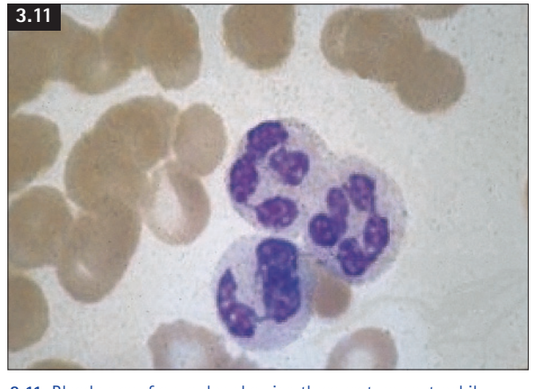
The manifestations of inflammation include cellular and biochemical changes.

Cellular changes

An increased leukocyte count due to an increase in neutrophil count in the peripheral blood often occurs in acute inflammatory responses. The leukocytes respond to chemical attractants (chemotaxins) originating from the site of injury. Leukocytes are released from the bone marrow into the blood in larger numbers than are normally present under the influence of cytokines.



3.10 Histologic section of feline cornea. The corneal stroma is amorphous (arrow) from coagulation necrosis and discolored brown, depicting a corneal sequestrum. H&E.



3.11 Blood smear from a dog showing three mature neutrophils. Note the lack of color in the cytoplasm and the multilobed nucleus.

Therefore, when a blood sample is taken, increased numbers of neutrophils are counted. Sometimes, increased numbers of monocytes can be present in severe or more chronic inflammation.

The major cells in inflammatory responses include: mast cells, neutrophils, eosinophils, macrophages, endothelial cells, and platelets. These cells react to a variety of signals, stimuli, and irritants in order to orchestrate the inflammatory response.

Granulocytes consist of neutrophils, eosinophils, and basophils.

Neutrophils

Neutrophilic leukocytes are also known as polymorphs, segmented cells or segs, and polymorphonuclear cells (**3.11**). In some species, notably guinea pigs, birds, reptiles, and rabbits, the term heterophil is used to describe the functional counterpart. These cells are key cells involved in the earliest events associated with inflammation. There are a large number of neutrophils within the body; for instance, a dog has approximately 10^9/kg body weight. About half of these are moving rapidly along with the circulation. Others are sequestered in vascular eddies or are temporarily lining the vascular walls (the marginal pool). There are also vast numbers of mature and nearly mature neutrophils held in reserve in the bone marrow (the storage pool).

Neutrophils are formed in the bone marrow from granulocytic stem cells, the myeloblasts. The nucleus of a very immature neutrophil is slightly indented; with maturity, it assumes a 'band' shape. As the neutrophil continues to mature, the nucleus becomes hyperindented to take on a multilobed configuration with multiple constrictions.

Even with the vast numbers of neutrophils in the body, there are severe infections in which tissue demand exceeds the vascular supply. The body responds by releasing neutrophils from the storage pool in the bone marrow to increase the number in the circulation. This increase is called a neutrophilic leukocytosis. If the tissue demand for neutrophils persists or even increases, many of the immature forms or 'bands' will be released as well. This is referred to as a 'left shift'.

There are two main types of cytoplasmic granules in neutrophils: azurophilic and neutrophil-specific. Azurophilic (or primary) granules contain myeloperoxidase, lysozyme, defensins, and a variety of neutral proteases. These azurophilic granules are generally denser than the neutrophil-specific granules. Neutrophil-specific, or secondary granules, contain lysozyme, collagenase, plasminogen activator, and histaminase. Both types of granules fuse with phagosomes to form phagolysosomes, where digestion of phagocytized material takes place. If activated, the neutrophil-specific granules may also fuse with the plasma membrane, releasing their damaging enzymes out into the extracellular environment.

Neutrophils have a very short half-life; they probably only survive about 6 hours at a site of inflammation and last less than a few days in blood. Therefore, the pool needs to be continually replenished. Neutrophils leave the blood in response to tissue damage. They migrate rapidly to where they are needed, and emigrate through the wall in response to chemotactic signals. Such signals include bacterial components, a factor of complement C5, fibrin, interleukin-8, and leukotriene B4.

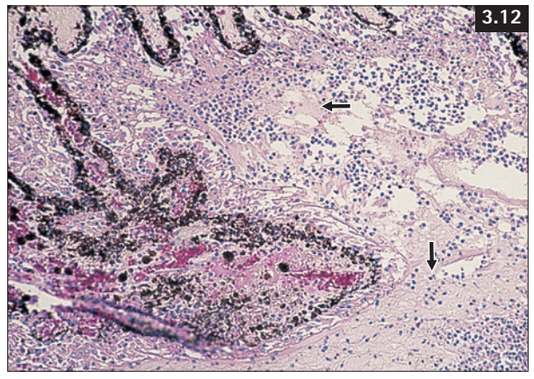
Neutrophils are the most common cell in purulent exudate. In fact, pus is an accumulation of dead neutrophils (**3.12**).

> Most bacteria have very strong chemotactic factors that attract neutrophils. Any accumulation of pus should trigger the suspicion that bacteria are present.

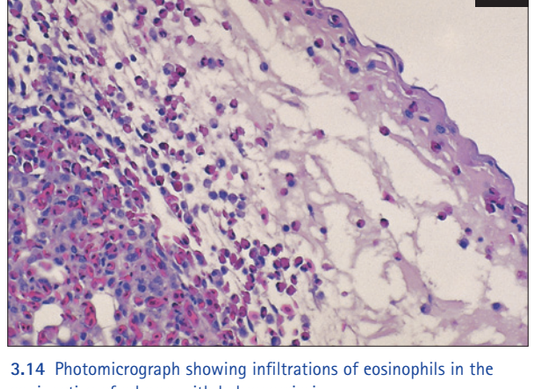
The myeloperoxidase in neutrophils give pus its green color. As neutrophils die in large numbers within inflamed tissues, their contents are released into the extracellular fluids. These contents are also further chemotactic to other neutrophils.

Eosinophils

Eosinophilic granulocytes are so called because of the presence of red-pink (the same color as erythrocytes) cytoplasmic granules when stained with Wright's stain or with hematoxylin and eosin (H&E) (**3.13**). These granules vary in size and shape in the different species, being very large and globular in the horse and quite small and rod-shaped in the cat. The granules contain major basic protein, which is toxic to parasites and causes lysis of mammalian epithelial cells.



3.12 Histologic picture of the hypopyon seen in **3.8**, showing accumulations of neutrophils, cellular debris and necrosis (arrows). H&E.



3.14 Photomicrograph showing infiltrations of eosinophils in the conjunctiva of a horse with habronemiasis.

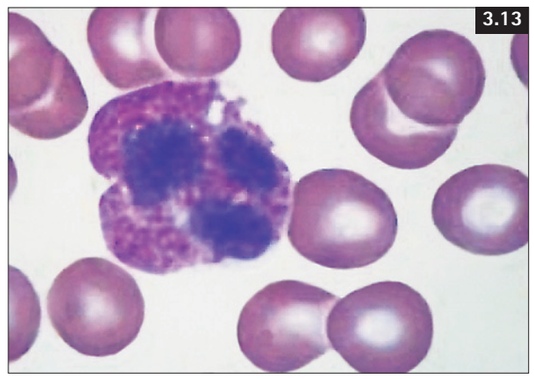
Eosinophils are similar to neutrophils in their maturation and release sequences. Like neutrophils, eosinophils are also end-cells that do not replicate after release. They are more long-lived than neutrophils, persisting up to 8–12 days in tissue.

Eosinophils are most often associated with fungal and parasitic infection, hypersensitivity reactions, which may be allergic or anaphylactic (**3.14**)[12], and some neoplasms[13], including mast cell tumors[14] and some types of lymphoma[15].

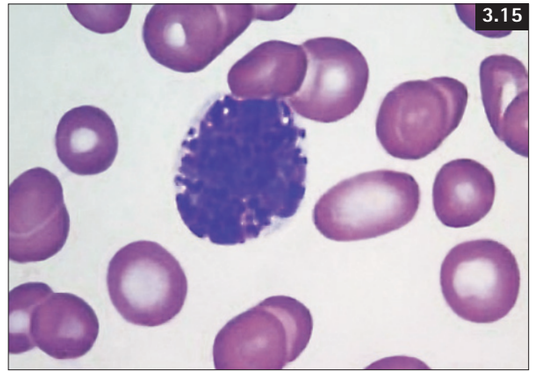
Once eosinophils reach the tissue, they can function in several ways. They can be bacteriocidal, although not as effectively as neutrophils; although eosinophils have high levels of peroxidase, they lack lysozyme. Eosinophils are most effective at killing metazoan parasites, due to major basic protein released from the eosinophil granule, which appears to be enhanced by mast cell products.

Basophils and mast cells

Basophils are the third type of granulocytic leukocyte (**3.15**). Produced in the bone marrow, they occur in the circulation in very low numbers and emigrate into extravascular tissues at sites of inflammation. They have



3.13 Blood smear from a horse showing an eosinophil. Note the eosinophilic granularity of the cytoplasm and the multilobed nucleus.



3.15 Blood smear showing a canine basophil. Note the blue granularity of the cytoplasm that obliterates the nucleus.

a multilobed nucleus and large, globular basophilic granules that can obliterate the nucleus.

Although mast cells are granulated, they are usually not considered granulocytes. These cells are related to basophils but are present in connective and mucosal tissue and only very rarely in the circulation. They are particularly abundant in skin, gastrointestinal mucosa, and respiratory tract, all host–environment interfaces. The nucleus is round to oval and contains a prominent nucleolus. Mast cells possess distinct spherical basophilic to metachromatic cytoplasmic granules.

Neither mast cells nor basophils are end-cells, and both are capable of continued division at the site of inflammation. These cells are not phagocytic and are only sluggishly motile. Their main function is the degranulation of their cytoplasmic contents when stimulated, which releases a number of preformed proinflammatory products contained within the granules. The end result is increased vascular permeability, vasodilation, anticoagulation, tissue destruction, and attraction of eosinophils.

Lymphocytes

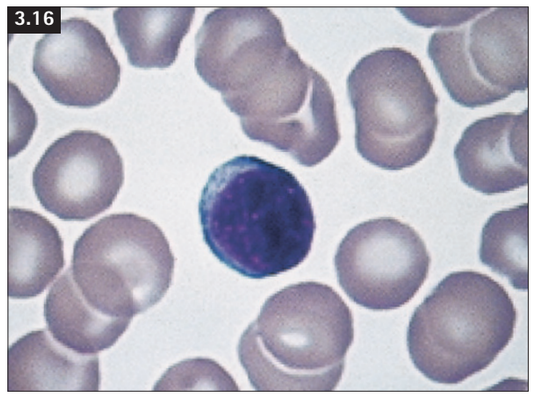
Lymphocytes are small round cells with a round, hyperchromatic nucleus and scant, light blue-staining cytoplasm (**3.16**). Although lymphocytes all appear similar morphologically, they come in two functional varieties, B-cells and T-cells. The B-lymphocytes are committed to making antibodies. They originate in the bone marrow and come to reside in extramedullary lymphoid issues. The precursors of T-lymphocytes migrate from the bone marrow through the thymic cortex to differentiate into mature T-cells. Approximately 80–90% of the cells in the circulation are T-cells, while B-cells are much more sedentary by comparison.

Lymphocytes are maintained in populations of clones that are each specific for a certain antigen. Each lymphocyte clone is preprogrammed to recognize only a single antigen. In an animal there may be lymphocytes capable of responding to 10^8 different antigens, most of which have never been encountered. When challenged with a specific antigen, the population of cells that recognizes the antigen will proliferate in response[16].

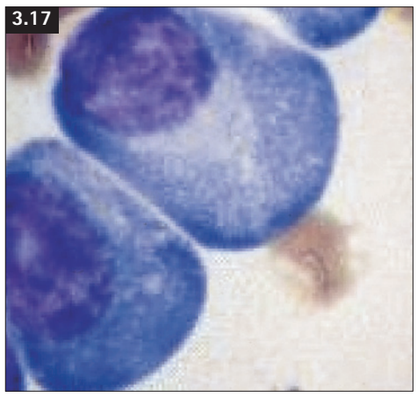
Functionally, lymphocytes can be divided into two broad classes. The primary function of B-cells, as mentioned earlier, is to produce antibodies. B-cells have specific antibody on their surface that serves as a receptor to the homologous specific antigen. When specific antigen is bound to the surface of B-cells they are induced to divide repeatedly, forming a line of memory cells and a line of antibody-producing cells called plasma cells[17]. These plasma cells only live for a few days but they work full-time producing large amounts of immunoglobulin (**3.17**). Plasma cells have a unique appearance. They are smoothly spherical or elliptical with much more cytoplasm than a lymphocyte. The nucleus is usually eccentrically placed and the chromatin often is clumped at the periphery, creating a 'wagon-wheel' appearance. The cytoplasm contains abundant protein-producing machinery such as rough endoplasmic reticulum, and therefore takes on a slightly basophilic tone. In many cells an area of pallor just adjacent to the nucleus can be seen histologically. This represents the cell's packaging machinery, the Golgi apparatus.

T-cells are roughly divided into T-helper cells and T-cytotoxic cells. The helper cells all have a CD4 molecule on the surface, which allows the helper cell to recognize an antigen presented by an antigen-presenting cell (any cell with MHC II surface marker), usually a macrophage. The combination of T-helper cell and macrophage is essential in complexing with a B-cell to allow the production of antibodies. The second type of T-cells is the CD8 group. The CD8 molecule complexes with nonmacrophage-type cells, i.e. cells with MHC I molecules on their surface. When the CD8 molecule aligns with an MHC I expressing cell that also has specific antigen on its surface, the T-cell destroys that cell.

Lymphocytes are drawn into sites of inflammation by a number of factors. Once at the site, they can either cluster around blood vessels or form nodular aggregates. The presence of these nodular aggregates is usually a nonspecific indication of chronic antigenic stimulation. In these cases, plasma cells are quite often also seen.



3.16 Blood smear from a dog containing a lymphocyte. Note the round nucleus and the paucity of cytoplasm.



3.17 Two plasma cells from a dog in a bone marrow aspirate. The cells have eccentrically placed nuclei and abundant basophilic cytoplasm.

Mononuclear phagocytes

Macrophages are professional tissue phagocytes (**3.18**). The word macrophage is used to describe a monocyte that has emigrated from the blood to the tissue. The term histiocyte is also used to describe these cells. There are a number of factors that recruit monocytes to sites of inflammation. Once there, however, they do not divide at the site of inflammation. Compared to neutrophils, they are more long-lived, surviving at an inflammatory site for as long as 1 month. In general, they are also slower to arrive at the site of inflammation, usually taking about 48 hours. They appear as large cells with bean-shaped or oval nuclei with fine, diffusely scattered chromatin. The cytoplasm stains a pale pink and may contain vacuoles or particulate debris of phagocytozed foreign material.

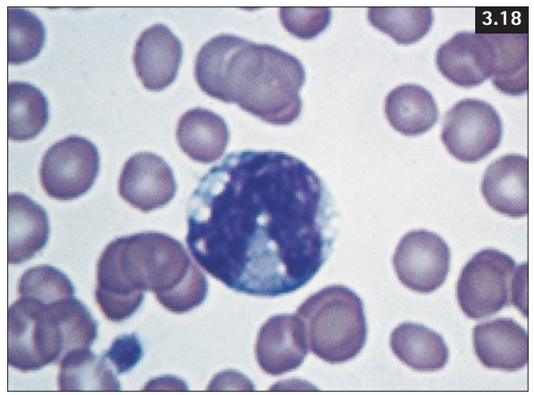
The function of macrophages is primarily phagocytosis and destruction of foreign material[18]. In addition to their phagocytic function, activated macrophages can become glassy, eosinophilic, 'epithelioid' macrophages. These cells produce and secrete a wide variety of biologically active substances. These include: toxic oxygen metabolites, proteases, neutrophil chemotactic factors, nitric oxide, arachidonic acid metabolites, growth factors that promote fibrosis, and angiogenesis factors.

When the inciting cause remains for a long time, macrophages will often fuse to form a multinucleated giant cell. These cells are metabolically active but their phagocytic potential is significantly reduced. Macrophages have been incriminated in proliferative neoplasm-like diseases such as systemic histiocytosis[19].

Chemotaxis of leukocytes

During the early phases of the inflammatory response, the normally inactive endothelium has to be activated to allow adhesion of neutrophils. Normally inactive neutrophils have to be activated to enhance their capacity for phagocytosis, bacterial killing, and generation of inflammatory mediators. Neutrophils have to develop the ability to move actively, from vessels towards the specific area of tissue damage. When leukocytes accumulate, their main function is phagocytosis and microbial killing.

The process whereby cells (such as neutrophils and macrophages) ingest solid particles is termed phagocytosis. The first step in phagocytosis is adhesion of the particle to be phagocytozed to the cell surface. This is facilitated by opsonization. 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 microorganisms occurs.



3.18 Blood smear showing a canine monocyte. The nucleus is horseshoe shaped and the cytoplasm is vacuolated.

Biochemical changes

Inflammation is mediated in large part by soluble substances found in plasma called mediators. Many noncellular mediators of inflammation can be measured clinically. An increase in the concentration of acute-phase proteins in the blood is commonly seen. (These are normally present in small concentrations but increase dramatically in response to acute inflammation.) Produced by the liver, they are induced by circulating cytokines. Specific acute-phase proteins, like fibrinogen, may be measured in blood to monitor inflammatory processes.

The movement of leukocytes from the vessel lumen to the site of tissue damage is by chemotaxis, and is mediated by substances known as chemotactic factors (chemotaxins), which diffuse from the area of tissue damage. All granulocytes and monocytes respond to chemotaxins, and respond to a concentration gradient, moving from an area of lesser concentration of the factor to an area of greater concentration of the factor.

Chemotaxins can be exogenous or endogenous. Most exogenous chemotaxins are bacterial or other microbial products, e.g. endotoxin. Chemotaxins bind to receptors on the surface of leukocytes and activate secondary messenger systems. These messenger systems work by stimulating increased intracytoplasmic calcium. The calcium then interacts with the cytoskeleton with resulting assembly of cytoskeletal specializations involved in motility.

In large part the acute inflammatory response is orchestrated by plasma-derived and cell-derived chemical mediators.

Plasma-derived factors

The plasma contains four major protease cascade systems that contribute to acute inflammation: complement, the kinins, the coagulation factors, and the fibrinolytic systems. These are interrelated and produce various inflammatory mediators.

Complement system: the complement system consists of approximately 20 known proteins and their cleavage products. It can be activated during the acute inflammatory reaction in several ways. With 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