Inflammation (Latin, *inflammatio*) is part of the complex biological response of body tissues to harmful stimuli, such as pathogens, damaged cells, or irritants.[1]

Inflammation is a protective response that involves immune cells, blood vessels, and molecular mediators. The purpose of inflammation is to eliminate the initial cause of cell injury, clear out necrotic cells and tissues damaged from the original insult and the inflammatory process, and to initiate tissue repair.

The classical signs of acute inflammation are pain, heat, redness, swelling, and loss of function. Inflammation is a generic response, and therefore it is considered as a mechanism of innate immunity, as compared to adaptive immunity, which is specific for each pathogen.[2]

Too little inflammation could lead to progressive tissue destruction by the harmful stimulus (e.g. bacteria) and compromise the survival of the organism. In contrast, chronic inflammation may lead to a host of diseases, such as hay fever, periodontitis, atherosclerosis, rheumatoid arthritis, and even cancer (e.g.,gallbladder carcinoma). Inflammation is therefore normally closely regulated by the body.

Inflammation can be classified as either *acute* or *chronic*. *Acute inflammation* is the initial response of the body to harmful stimuli and is achieved by the increased movement of plasma and leukocytes (especially granulocytes) from the blood into the injured tissues. A series of biochemical events propagates and matures the inflammatory response, involving the local vascular system, the immune system, and various cells within the injured tissue. Prolonged inflammation, known as *chronic inflammation*, leads to a progressive shift in the type of cells present at the site of inflammation and is characterized by simultaneous destruction and healing of the tissue from the inflammatory process.

Inflammation is not a synonym for infection. Infection describes the interaction between the action of microbial invasion and the reaction of the body's inflammatory defensive response — the two components are considered together when discussing an infection, and the word is used to imply a microbial invasive cause for the observed inflammatory reaction. Inflammation on the other hand describes purely the body's immunovascular response, whatever the cause may be. But because of how often the two are correlated, words ending in the suffix *-itis* (which refers to inflammation) are sometimes informally described as referring to infection. For example, the word *urethritis* strictly means only "urethral inflammation", but clinicalhealth care providers usually discuss urethritis as a urethral infection because urethral microbial invasion is the most common cause of urethritis.

It is useful to differentiate inflammation and infection as there are many pathological situations where inflammation is not driven by microbial invasion - for example, atherosclerosis, type III hypersensitivity, trauma, ischaemia. There are also pathological situations where microbial invasion does not result in classic inflammatory response—for example, parasitosis, eosinophilia.

Contents

[hide]

Causes[edit]

Physical:

- Burns
- Frostbite

- Physical injury, blunt or penetrating
- Foreign bodies, including splinters, dirt and debris
- Trauma
- Ionizing radiation

Biological:

- Infection by pathogens
- Immune reactions due to hypersensitivity
- Stress

Chemical:

- Chemical irritants
- Toxins
- Alcohol

Psychological:

- Embarrassment
- Excitement

Types[edit]

- Appendicitis
- Bursitis
- Colitis
- Cystitis
- Dermatitis
- Phlebitis
- RSD/CRPS
- Rhinitis
- Tendonitis
- Tonsillitis
- Vasculitis

Comparison between acute and chronic inflammation:

	Acute	Chronic
Causative agent	Bacterial pathogens, injured tissues	Persistent acute inflammation due to non-degradable pathogens, viral

		infection, persistent foreign bodies, or autoimmune reactions
Major cells involved	neutrophils (primarily), basophils (inflammatory response), and eosinophils (response to helminth worms and parasites), mononuclear cells (monocytes, macrophages)	Mononuclear cells (monocytes, macrophages, lymphocytes, plasma cells), fibroblasts
Primary mediators	Vasoactive amines, eicosanoids	IFN-γ and other cytokines, growth factors, reactive oxygen species, hydrolytic enzymes
Onset	Immediate	Delayed
Duration	Few days	Up to many months, or years
Outcomes	Resolution, abscess formation, chronic inflammation	Tissue destruction, fibrosis, necrosis

Cardinal signs[edit]

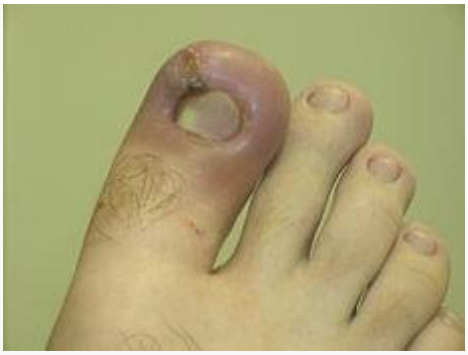
The classic signs and symptoms of acute inflammation:

English	Latin
Redness	*Rubor**
Swelling	*Tumor**
Heat	*Calor**
Pain	*Dolor**
Loss of function	*Functio laesa***

All the above signs may be observed in specific instances, but no single sign must, as a matter of course, be present.[3]

These are the original, or "cardinal signs" of inflammation.[3]*

Functio laesa is an apocryphal notion, as it is not unique to inflammation and is a characteristic of many disease states.[4]**



Infected ingrown toenail showing the characteristic redness and swelling associated with acute inflammation

Acute inflammation is a short-term process, usually appearing within a few minutes or hours and begins to cease upon the removal of the injurious stimulus.[5] It is characterized by five cardinal signs:[6]

An acronym that may be used to remember the key symptoms is "PRISH", for pain, redness, immobility (loss of function), swelling and heat.

The traditional names for signs of inflammation come from Latin:

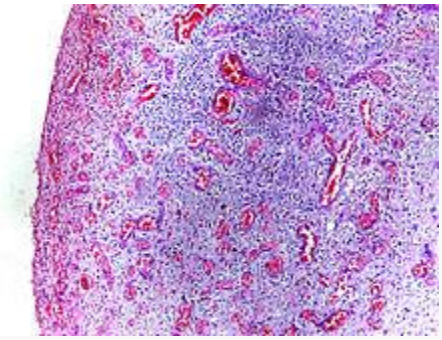
- Dolor (pain)
- Calor (heat)
- Rubor (redness)
- Tumor (swelling)
- Functio laesa (loss of function)[7]

The first four (classical signs) were described by Celsus (ca. 30 BC–38 AD),[8] while *loss of function* was added later by Galen[9] even though the attribution is disputed and the origination of the fifth sign has also been ascribed to Thomas Sydenham[10] and Virchow.[5][6]

Redness and heat are due to increased blood flow at body core temperature to the inflamed site; swelling is caused by accumulation of fluid; pain is due to the release of chemicals such as bradykinin and histamine that stimulate nerve endings. Loss of function has multiple causes.[6]

Acute inflammation of the lung (pneumonia) does not cause pain unless the inflammation involves the parietal pleura, which does have pain-sensitive nerve endings.[6]

Process of acute inflammation[edit]



Micrograph showing granulation tissue. H&E stain.

The process of acute inflammation is initiated by resident immune cells already present in the involved tissue, mainly resident macrophages, dendritic cells, histiocytes, Kupffer cells and mastocytes. These cells present on their surfaces certain receptors named *pattern recognition receptors* (PRRs), which recognise generic molecules that are broadly shared by pathogens but distinguishable from host molecules, collectively referred to as pathogen-associated molecular patterns (PAMPs). At the onset of an infection, burn, or other injuries, these cells undergo activation (one of their PRRs recognize a PAMP) and release inflammatory mediatorsresponsible for the clinical signs of inflammation. Vasodilation and its resulting increased blood flow causes the redness (*rubor*) and increased heat (*calor*). Increased permeability of the blood vessels results in an exudation (leakage) of plasma proteins and fluid into the tissue (edema), which manifests itself as swelling (*tumor*). Some of the released mediators such as bradykinin increase the sensitivity to pain (hyperalgesia, *dolor*). The mediator molecules also alter the blood vessels to permit the migration of leukocytes, mainly neutrophils andmacrophages, outside of the blood vessels (extravasation) into the tissue. The neutrophils migrate along achemotactic gradient created by the local cells to reach the site of injury.[5] The loss of function (*functio laesa*) is probably the result of a neurological reflex in response to pain.

In addition to cell-derived mediators, several acellular biochemical cascade systems consisting of preformed plasma proteins act in parallel to initiate and propagate the inflammatory response. These include thecomplement system activated by bacteria and the coagulation and fibrinolysis systems activated by necrosis, e.g. a burn or a trauma.[5]

The acute inflammatory response requires constant stimulation to be sustained. Inflammatory mediators are short-lived and are quickly degraded in the tissue. Hence, acute inflammation begins to cease once the stimulus has been removed.[5]

Vascular component[edit]

Vasodilation and increased permeability[edit]

As defined, acute inflammation is an immunovascular response to an inflammatory stimulus. This means acute inflammation can be broader divided into a vascular phase that occurs first, followed by

a cellular phase involving immune cells (more specifically myeloid granulocytes in the acute setting). The vascular component of acute inflammation involves the movement of plasma fluid, containing important proteins such as fibrin and immunoglobulins(antibodies), into inflamed tissue.

Upon contact with PAMPs, tissue macrophages and mastocytes release vasoactive amines such as histamine and serotonin, as well as eicosanoidssuch as prostaglandin E2 and leukotriene B4 to remodel the local vasculature. Macrophages and endothelial cells release nitric oxide. These mediators vasodilate and permeabilize the blood vessels, which results in the net distribution of blood plasma from the vessel into the tissue space. The increased collection of fluid into the tissue causes it to swell (edema). This exuded tissue fluid contain various antimicrobial mediators from the plasma such ascomplement, lysozyme, antibodies, which can immediately deal damage to microbes, and opsonise the microbes in preparation for the cellular phase. If the inflammatory stimulus is a lacerating wound, exuded platelets, coagulants, plasmin and kinins can clot the wounded area and provide haemostasisin the first instance. These clotting mediators also provide a structural staging framework at the inflammatory tissue site in the form of a fibrin lattice - as would construction scaffolding at a construction site - for the purpose of aiding phagocytic debridement and wound repair later on. Some of the exuded tissue fluid is also funneled by lymphatics to the regional lymph nodes, flushing bacteria along to start the recognition and attack phase of the adaptive immune system.

Acute inflammation is characterized by marked vascular changes, including vasodilation, increased permeability and increased blood flow, which are induced by the actions of various inflammatory mediators. Vasodilation occurs first at the arteriole level, progressing to the capillary level, and brings about a net increase in the amount of blood present, causing the redness and heat of inflammation. Increased permeability of the vessels results in the movement of plasma into the tissues, with resultant *stasis* due to the increase in the concentration of the cells within blood - a condition characterized by enlarged vessels packed with cells. Stasis allows leukocytes to marginate (move) along the endothelium, a process critical to their recruitment into the tissues. Normal flowing blood prevents this, as the shearing force along the periphery of the vessels moves cells in the blood into the middle of the vessel.

Plasma cascade systems[edit]

- The complement system, when activated, creates a cascade of chemical reactions that promotes opsonization, chemotaxis, and agglutination, and produces the MAC.
- The kinin system generates proteins capable of sustaining vasodilation and other physical inflammatory effects.
- The coagulation system or *clotting cascade*, which forms a protective protein mesh over sites of injury.

- The fibrinolysis system, which acts in opposition to the *coagulation system*, to counterbalance clotting and generate several other inflammatory mediators.

Plasma-derived mediators[edit]

** non-exhaustive list*

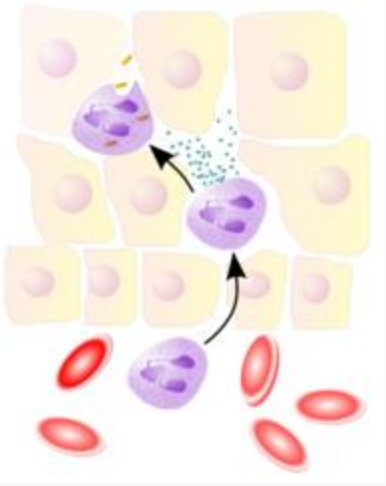
Name	Produced by	Description
Bradykinin	*Kinin system*	A vasoactive protein that is able to induce vasodilation, increase vascular permeability, cause smooth muscle contraction, and induce pain.
C3	*Complement system*	Cleaves to produce *C3a* and *C3b*. C3a stimulates histamine release by mast cells, thereby producing vasodilation. C3b is able to bind to bacterial cell walls and act as an opsonin, which marks the invader as a target for phagocytosis.
C5a	*Complement system*	Stimulates histamine release by mast cells, thereby producing vasodilation. It is also able to act as a chemoattractant to direct cells via chemotaxis to the site of inflammation.
Factor XII(*Hageman Factor*)	*Liver*	A protein that circulates inactively, until activated by collagen, platelets, or exposed basement membranes viaconformational change. When activated, it in turn is able to activate three plasma systems involved in inflammation: the kinin system, fibrinolysis system, and coagulation system.
Membrane attack complex	*Complement system*	A complex of the complement proteins C5b, C6, C7, C8, and multiple units of C9. The combination and activation of this range of complement proteins forms the *membrane attack complex*, which is able to insert into bacterial cell walls and causes cell lysis with ensuing bacterial death.

Plasmin	*Fibrinolysis system*	Able to break down fibrin clots, cleave complement protein C3, and activate Factor XII.
Thrombin	*Coagulation system*	Cleaves the soluble plasma protein fibrinogen to produce insoluble fibrin, which aggregates to form a blood clot. Thrombin can also bind to cells via the PAR1 receptor to trigger several other inflammatory responses, such as production of chemokines and nitric oxide.

Cellular component[edit]

The *cellular component* involves leukocytes, which normally reside in blood and must move into the inflamed tissue via *extravasation* to aid in inflammation. Some act as phagocytes, ingesting bacteria, viruses, and cellular debris. Others release enzymatic granules that damage pathogenic invaders. Leukocytes also release inflammatory mediators that develop and maintain the inflammatory response. In general, acute inflammation is mediated by granulocytes, whereas chronic inflammation is mediated by mononuclear cells such as monocytes and lymphocytes.

Leukocyte extravasation[edit]



Neutrophils migrate from blood vessels to the infected tissue via chemotaxis, where they remove pathogens through phagocytosis and degranulation

Main article: Leukocyte extravasation

Various leukocytes are critically involved in the initiation and maintenance of inflammation. These cells must be able to get to the site of injury from their usual location in the blood, therefore mechanisms exist to recruit and direct leukocytes to the appropriate place. The process of leukocyte

movement from the blood to the tissues through the blood vessels is known as *extravasation*, and can be divided up into a number of broad steps:

1. **Leukocyte margination and endothelial adhesion:** Activated tissue macrophages release cytokines such as IL-1 and TNFα, which bind to their respective G protein-coupled receptors on the endothelial wall. Signal transduction induces the immediate expression of P-selectin on endothelial cell surfaces. This receptor binds weakly to carbohydrate ligands on leukocyte surfaces and causes them to "roll" along the endothelial surface as bonds are made and broken. Cytokines from injured cells induce the expression of E-selectin on endothelial cells, which functions similarly to P-selectin. Cytokines also induce the expression of integrinligands such as ICAM-1 and VCAM-1 on endothelial cells, which further slow leukocytes down. These weakly bound leukocytes are free to detach if not activated by chemokines produced in injured tissue. Activation increases the affinity of bound integrin receptors for ICAM-1 and VCAM-1 on the endothelial cell surface, firmly binding the leukocytes to the endothelium.
2. **Migration across the endothelium, known as *transmigration,* via the process of diapedesis:**Chemokine gradients stimulate the adhered leukocytes to move between endothelial cells and pass the basement membrane into the tissues.
3. **Movement of leukocytes within the tissue via chemotaxis:** Leukocytes reaching the tissue interstitium bind to extracellular matrix proteins via expressed integrins and CD44 to prevent their loss from the site. Chemoattractants cause the leukocytes to move along a chemotactic gradient towards the source of inflammation.

Phagocytosis[edit]

Main article: Phagocyte

Extravasated neutrophils in the cellular phase come into contact with microbes at the inflamed tissue. Phagocytes express cell-surface endocytic pattern recognition receptors (PRRs) that have affinity and efficacy against non-specific microbe-associated molecular patterns (PAMPs). Most PAMPs that bind to endocytic PRRs and initiate phagocytosis are cell wall components, including complex carbohydrates such as mannans and β-glucans,lipopolysaccharides (LPS), peptidoglycans, and surface proteins. Endocytic PRRs on phagocytes reflect these molecular patterns, with C-type lectinreceptors binding to mannans and β-glucans, and scavenger receptors binding to LPS.

Upon endocytic PRR binding, actin-myosin cytoskeletal rearrangement adjacent to the plasma membrane occurs in a way that endocytoses the plasma membrane containing the PRR-PAMP complex, and the microbe. Phosphatidylinositol and Vps34-Vps15-Beclin1 signalling pathways have been implicated to traffic the endocytosed phagosome to intracellular lysosomes, where fusion of the phagosome and the lysosome produces a phagolysosome. The reactive oxygen

species, superoxides and hypochlorite bleach within the phagolysosomes then kill microbes inside the phagocyte.

Phagocytic efficacy can be enhanced by opsonization. Plasma derived complement C3b and antibodies that exude into the inflamed tissue during the vascular phase bind to and coat the microbial antigens. As well as endocytic PRRs, phagocytes also express opsonin receptors Fc receptor andcomplement receptor 1 (CR1), which bind to antibodies and C3b, respectively. The co-stimulation of endocytic PRR and opsonin receptor increases the efficacy of the phagocytic process, enhancing the lysosomal elimination of the infective agent.

Cell-derived mediators[edit]

** non-exhaustive list*

Name	Type	Source	Description
Lysosome granules	*Enzymes*	Granulocytes	These cells contain a large variety of enzymes that perform a number of functions. Granules can be classified as either *specific* or *azurophilic* depending upon the contents, and are able to break down a number of substances, some of which may be plasma-derived proteins that allow these enzymes to act as inflammatory mediators.
Histamine	*Vasoactiveamine*	Mast cells, basophils, platelets	Stored in preformed granules, histamine is released in response to a number of stimuli. It causesarteriole dilation and increased venous permeability.
IFN-γ	*Cytokine*	T-cells, NK cells	Antiviral, immunoregulatory, and anti-tumour properties. This interferon was originally called macrophage-

			activating factor, and is especially important in the maintenance of chronic inflammation.
IL-8	*Chemokine*	Primarilymacrophages	Activation and chemoattraction of neutrophils, with a weak effect on monocytes and eosinophils.
Leukotriene B4	*Eicosanoid*	Leukocytes	Able to mediate leukocyte adhesion and activation, allowing them to bind to the endothelium and migrate across it. In neutrophils, it is also a potent chemoattractant, and is able to induce the formation of reactive oxygen species and the release of lysosomal enzymes by these cells.
Nitric oxide	*Soluble gas*	Macrophages, endothelial cells, some neurons	Potent vasodilator, relaxes smooth muscle, reduces platelet aggregation, aids in leukocyte recruitment, direct antimicrobial activity in high concentrations.
Prostaglandins	*Eicosanoid*	Mast cells	A group of lipids that can cause vasodilation, fever, and pain.
TNF-α and IL-1	*Cytokines*	Primarily macrophages	Both affect a wide variety of cells to induce many similar inflammatory reactions: fever, production of cytokines, endothelial gene regulation, chemotaxis, leukocyte adherence, activation of fibroblasts. Responsible for the systemic effects of inflammation, such as loss of

			appetite and increased heart rate. TNF-α inhibits osteoblast differentiation.

Morphologic patterns[edit]

Specific patterns of acute and chronic inflammation are seen during particular situations that arise in the body, such as when inflammation occurs on anepithelial surface, or pyogenic bacteria are involved.

- **Granulomatous inflammation:** Characterised by the formation of granulomas, they are the result of a limited but diverse number of diseases, which include among others tuberculosis, leprosy, sarcoidosis, and syphilis.
- **Fibrinous inflammation:** Inflammation resulting in a large increase in vascular permeability allows fibrin to pass through the blood vessels. If an appropriate *procoagulative* stimulus is present, such as cancer cells,[5] a fibrinous exudate is deposited. This is commonly seen in serous cavities, where the conversion of fibrinous exudate into a scar can occur between serous membranes, limiting their function. The deposit sometimes forms a pseudomembrane sheet. During inflammation of the intestine (Pseudomembranous colitis), pseudomembranous tubes can be formed.
- **Purulent inflammation:** Inflammation resulting in large amount of pus, which consists of neutrophils, dead cells, and fluid. Infection by pyogenic bacteria such as staphylococci is characteristic of this kind of inflammation. Large, localised collections of pus enclosed by surrounding tissues are called abscesses.
- **Serous inflammation:** Characterised by the copious effusion of non-viscous serous fluid, commonly produced by mesothelial cells of serous membranes, but may be derived from blood plasma. Skin blisters exemplify this pattern of inflammation.
- **Ulcerative inflammation:** Inflammation occurring near an epithelium can result in the necrotic loss of tissue from the surface, exposing lower layers. The subsequent excavation in the epithelium is known as an ulcer.

Cytokines are crucial for fighting off infections and in other immune responses.[17] However, they can become dysregulated and pathological ininflammation, trauma, and sepsis.[17]

Adverse effects of cytokines have been linked to many disease states and conditions ranging from schizophrenia, major depression[18] and Alzheimer's disease[19] to cancer.[20] Normal tissue

integrity is preserved by feedback interactions between diverse cell types mediated by adhesion molecules and secreted cytokines; disruption of normal feedback mechanisms in cancer, threatens tissue integrity.[21] Over-secretion of cytokines can trigger a dangerous syndrome known as a cytokine storm; this may have been the cause of severe adverse events during a clinical trial of TGN1412. Cytokine storms also were the main cause of death in the 1918 "Spanish Flu" pandemic. Deaths were weighted more heavily towards people with healthy immune systems, due to its ability to produce stronger immune responses, likely increasing cytokine levels. Another important example of cytokine storm is seen in acute pancreatitis. Cytokines are integral and implicated in all angles of the cascade resulting in the systemic inflammatory response syndrome and multi organ failure associated with this intra-abdominal catastrophe.[22]