

Inflammation

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Toes inflamed by [chilblains](#)

Inflammation ([Latin](#), *īnflammō*, "I ignite, set alight") is part of the complex biological response of [vascular](#) tissues to harmful stimuli, such as [pathogens](#), damaged cells, or irritants.^[1]

Inflammation is a protective attempt by the organism to remove the injurious stimuli and to initiate the healing process. Inflammation is not a synonym for [infection](#), even in cases where inflammation is caused by infection. Although infection is caused by a microorganism, inflammation is one of the responses of the organism to the pathogen. However, inflammation is a stereotyped response, and therefore it is considered as a mechanism of [innate immunity](#), as compared to [adaptive immunity](#), which is specific for each pathogen.^[2]

Without inflammation, wounds and infections would never heal.^[*citation needed*] Similarly, progressive destruction of the tissue would compromise the survival of the organism. However, chronic inflammation can also lead to a host of diseases, such as [hay fever](#), [periodontitis](#), [atherosclerosis](#), [rheumatoid arthritis](#), and even cancer (e.g., [gallbladder carcinoma](#)). It is for that reason that inflammation is 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 cascade 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.

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[\[edit\]](#) Causes

- [Burns](#)
- Chemical [irritants](#)
- [Frostbite](#)
- [Toxins](#)
- [Infection](#) by [pathogens](#)

- [Physical injury](#), blunt or penetrating
- Immune reactions due to [hypersensitivity](#)
- [Ionizing radiation](#)
- Foreign bodies, including splinters, dirt and debris
- Stress
- Trauma
- Alcohol

[edit] Types

- [Appendicitis](#)
- [Bursitis](#)
- [Colitis](#)
- [Cystitis](#)
- [Dermatitis](#)
- [Meningitis](#)
- [Phlebitis](#)
- [Rhinitis](#)
- [Tendonitis](#)
- [Tonsillitis](#)
- [Vasculitis](#)

Comparison between acute and chronic inflammation:

	Acute	Chronic
<i>Causative agent</i>	Bacterial Pathogens, injured tissues	Persistent acute inflammation due to non-degradable pathogens, viral infection, persistent foreign bodies, or autoimmune reactions
<i>Major cells involved</i>	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
<i>Primary mediators</i>	Vasoactive amines, eicosanoids	IFN-γ and other cytokines, growth factors, reactive oxygen species, hydrolytic enzymes
<i>Onset</i>	Immediate	Delayed
<i>Duration</i>	Few days	Up to many months, or years
<i>Outcomes</i>	Resolution, abscess formation, chronic inflammation	Tissue destruction, fibrosis, necrosis

[edit] Cardinal signs

The classic signs and symptoms of acute inflammation:

All the above signs may be observed in specific instances, but no single sign is always present.

English: Redness, Swelling, Heat, Pain

Latin: *Rubor*, *Tumor*, *Calor*, *Dolor*

These are the original, or "cardinal signs"



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 ceasing upon the removal of the injurious stimulus.^[5] It is characterized by five cardinal signs.^[6]

The acronym that may be used for this 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]}

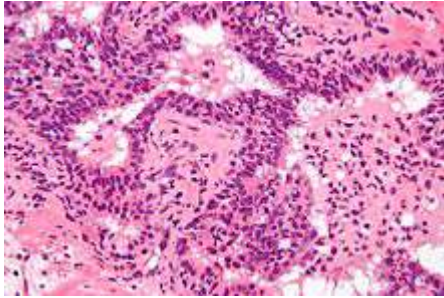
Redness and heat are due to increased blood flow at body core temperature to the inflamed site; swelling is caused by accumulation of fluid; [pain](#) is due to release of chemicals that stimulate nerve endings. Loss of function has multiple causes.^[6]


These five signs appear when acute inflammation occurs on the body's surface, whereas acute inflammation of internal organs may not result in the full set. Pain only happens where the appropriate sensory nerve endings exist in the inflamed area—e.g., 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]

[[edit](#)] Process of acute inflammation

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]**}



 [Micrograph](#) showing acute inflammation of the [prostate gland](#) with the characteristic [neutrophilic infiltrate](#). [H&E stain](#).

The process of acute inflammation is initiated by cells already present in all tissues, mainly resident [macrophages](#), [dendritic cells](#), histiocytes, Kupffer cells and [mastocytes](#). These cells present on their surfaces certain receptors named [pattern recognition receptors](#) (PRRs), which recognize 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 mediators](#) responsible 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](#), outside of the blood vessels (extravasation) into the tissue. The neutrophils migrate along a [chemotactic](#) 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 the [complement 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 have short half lives and are quickly degraded in the tissue. Hence, acute inflammation ceases once the stimulus has been removed.^[5]

[edit] Exudative component

The [exudative component](#) involves the movement of [plasma fluid](#), containing important [proteins](#) such as [fibrin](#) and [immunoglobulins](#) ([antibodies](#)), into inflamed tissue. This movement is achieved via the chemically induced dilation and increased permeability of [blood vessels](#), which results in a net loss of [blood plasma](#). The increased collection of fluid into the tissue causes it to swell ([edema](#)). This extravasated fluid is funneled by [lymphatics](#) to the regional lymph nodes, flushing bacteria along to start the recognition and attack phase of the [adaptive immune system](#).

[\[edit\]](#) Vascular changes

Acute inflammation is characterized by marked vascular changes, including [vasodilation](#), increased permeability and the slowing of 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.

[\[edit\]](#) Plasma cascade systems

- 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.

[\[edit\]](#) Plasma derived mediators

* *non-exhaustive list*

Name	Produced by	Description
Bradykinin	Kinin system	A vasoactive protein which is able to induce vasodilation, increase vascular permeability, cause smooth muscle contraction, and induce pain.
C3	Complement system	Cleaves to produce <i>C3a</i> and <i>C3b</i> . <i>C3a</i> stimulates histamine release by mast cells, thereby producing vasodilation. <i>C3b</i> 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 (<i>Hageman Factor</i>)	Liver	A protein which circulates inactively, until activated by collagen, platelets, or exposed basement membranes via conformational 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	Complement	A complex of the complement proteins C5b , C6 , C7 , C8 , and

attack complex

system

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 death.

Plasmin

Fibrinolysis system

Able to break down fibrin clots, cleave complement protein C3, and activate Factor XII.

Thrombin

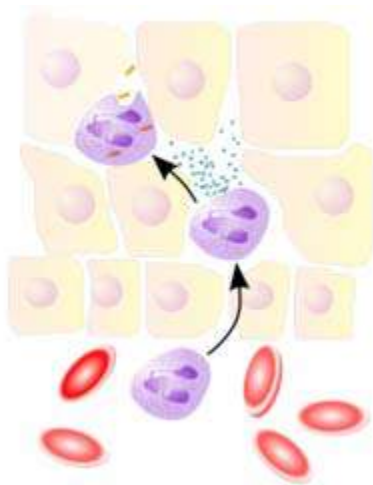
Coagulation system

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](#).

[edit] Cellular component

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](#) which damage pathogenic invaders. Leukocytes also release inflammatory mediators which develop and maintain the inflammatory response. Generally speaking, acute inflammation is mediated by [granulocytes](#), while chronic inflammation is mediated by mononuclear cells such as [monocytes](#) and [lymphocytes](#).

[edit] Leukocyte extravasation



Neutrophils migrate from blood vessels to the inflamed 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 localisation and recruitment to the endothelium local to the site of inflammation – involving margination and adhesion to the endothelial cells:**
Recruitment of leukocytes is [receptor](#)-mediated. The products of inflammation, such as [histamine](#), promote 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 [immunoglobulin](#) ligands 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 immunoglobulin ligands 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.

[\[edit\]](#) Cell derived mediators

* *non-exhaustive list*

Name	Type	Source	Description
Lysosome granules	Enzymes	Granulocytes	These cells contain a large variety of enzymes which perform a number of functions. Granules can be classified as either <i>specific</i> or <i>azurophilic</i> depending upon the contents, and are able to break down a number of substances, some of which may be plasma-derived proteins which allow these enzymes to act as inflammatory mediators.
Histamine	<i>Vasoactive</i> amine	Mast cells, basophils, platelets	Stored in preformed granules, histamine is released in response to a number of stimuli. It causes arteriole 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.

<u>IL-8</u>	<u>Chemokine</u>	Primarily <u>macrophages</u>	Activation and chemoattraction of neutrophils, with a weak effect on monocytes and eosinophils. 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 lysosome enzymes by these cells.
<u>Leukotriene B4</u>	<u>Eicosanoid</u>	Leukocytes	Potent vasodilator, relaxes smooth muscle, reduces platelet aggregation, aids in leukocyte recruitment, direct antimicrobial activity in high concentrations.
<u>Nitric oxide</u>	<u>Soluble gas</u>	Macrophages, endothelial cells, some neurons	A group of lipids which can cause vasodilation, fever, and pain. 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 <u>fibroblasts</u> . Responsible for the systemic effects of inflammation, such as loss of appetite and increased heart rate.
<u>TNF-α and IL-1</u>	<u>Cytokines</u>	Primarily macrophages	

[\[edit\]](#) Morphologic patterns

Specific patterns of acute and chronic inflammation are seen during particular situations that arise in the body, such as when inflammation occurs on an [epithelial](#) 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.
- **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](#).

[edit] Inflammatory disorders

Inflammatory abnormalities are a large group of disorders which underlie a vast variety of human diseases. The immune system is often involved with inflammatory disorders, demonstrated in both [allergic reactions](#) and some [myopathies](#), with many [immune system disorders](#) resulting in abnormal inflammation. Non-immune diseases with etiological origins in inflammatory processes include cancer, [atherosclerosis](#), and [ischaemic heart disease](#).^[5]

A large variety of proteins are involved in inflammation, and any one of them is open to a genetic mutation which impairs or otherwise dysregulates the normal function and expression of that protein.

Examples of disorders associated with inflammation include:

- [Acne vulgaris](#)
- [Asthma](#)
- [Autoimmune diseases](#)
- [Celiac disease](#)
- [Chronic prostatitis](#)
- [Glomerulonephritis](#)
- [Hypersensitivities](#)
- [Inflammatory bowel diseases](#)
- [Pelvic inflammatory disease](#)
- [Reperfusion injury](#)
- [Rheumatoid arthritis](#)
- [Sarcoidosis](#)
- [Transplant rejection](#)
- [Vasculitis](#)
- Interstitial cystitis

[edit] Atherosclerosis

Main article: [Atherosclerosis](#)

Atherosclerosis, formerly considered a bland lipid storage disease, actually involves an ongoing inflammatory response. Recent advances in basic science have established a fundamental role for inflammation in mediating all stages of this disease from initiation through progression and, ultimately, the thrombotic complications of atherosclerosis. These new findings provide important links between risk factors and the mechanisms of atherogenesis. Clinical studies have shown that this emerging biology of inflammation in atherosclerosis applies directly to human patients. Elevation in markers of inflammation predicts outcomes of patients with acute coronary syndromes, independently of myocardial damage. In addition, low-grade chronic inflammation,

as indicated by levels of the inflammatory marker C-reactive protein, prospectively defines risk of atherosclerotic complications, thus adding to prognostic information provided by traditional risk factors. Moreover, certain treatments that reduce coronary risk also limit inflammation. In the case of lipid lowering with statins, this anti-inflammatory effect does not appear to correlate with reduction in low-density lipoprotein levels. These new insights into inflammation in atherosclerosis not only increase our understanding of this disease, but also have practical clinical applications in risk stratification and targeting of therapy for this scourge of growing worldwide importance. [Clinical Cardiology: New Frontiers \(Inflammation and Atherosclerosis\)](#)

[\[edit\]](#) Allergies

An allergic reaction, formally known as [type 1 hypersensitivity](#), is the result of an inappropriate immune response triggering inflammation. A common example is [hay fever](#), which is caused by a hypersensitive response by skin [mast cells](#) to [allergens](#). Pre-sensitised mast cells respond by [degranulating](#), releasing [vasoactive](#) chemicals such as histamine. These chemicals propagate an excessive inflammatory response characterised by blood vessel dilation, production of pro-inflammatory molecules, cytokine release, and recruitment of leukocytes.^[5] Severe inflammatory response may mature into a systemic response known as [anaphylaxis](#).

Other [hypersensitivity](#) reactions ([type 2](#) and [type 3](#)) are mediated by antibody reactions and induce inflammation by attracting leukocytes which damage surrounding tissue.^[5]

[\[edit\]](#) Myopathies

Inflammatory myopathies are caused by the immune system inappropriately attacking components of muscle, leading to signs of muscle inflammation. They may occur in conjunction with other immune disorders, such as [systemic sclerosis](#), and include [dermatomyositis](#), [polymyositis](#), and [inclusion body myositis](#).^[5]

[\[edit\]](#) Leukocyte defects

Due to the central role of leukocytes in the development and propagation of inflammation, defects in leukocyte function often result in a decreased capacity for inflammatory defense with subsequent vulnerability to infection.^[5] Dysfunctional leukocytes may be unable to correctly bind to blood vessels due to surface receptor mutations, digest bacteria ([Chediak-Higashi syndrome](#)), or produce [microbicides](#) ([chronic granulomatous disease](#)). Additionally, diseases affecting the [bone marrow](#) may result in abnormal or few leukocytes.

[\[edit\]](#) Pharmacological

Certain drugs or exogenic chemical compounds are known to affect inflammation. [Vitamin A](#) deficiency causes an increase in inflammatory responses,^[11] and [anti-inflammatory](#) drugs work specifically by inhibiting normal inflammatory components. Certain illicit drugs such as cocaine and ecstasy may exert some of their detrimental effects by activating transcription factors intimately involved with inflammation (e.g. NF-κB).^{[12][13]}

[edit] Cancer

Inflammation orchestrates the microenvironment around tumours, contributing to proliferation, survival and migration. Cancer cells use [selectins](#), [chemokines](#) and their receptors for invasion, migration and metastasis.^[14] On the other hand, many cells of the immune system contribute to [cancer immunology](#), suppressing cancer.

[edit] Resolution of inflammation

The inflammatory response must be actively terminated when no longer needed to prevent unnecessary "bystander" damage to tissues.^[5] Failure to do so results in chronic inflammation, and cellular destruction. Resolution of inflammation occurs by different mechanisms in different tissues. Mechanisms which serve to terminate inflammation include:^{[5][15]}

- Short [half-life](#) of [inflammatory mediators](#) *in vivo*.
- Production and release of [Transforming growth factor \(TGF\) beta](#) from [macrophages](#)^{[16][17][18]}
- Production and release of [Interleukin 10](#) (IL-10)^[19]
- Production of anti-inflammatory [lipoxins](#)^[20]
- Downregulation of pro-inflammatory molecules, such as [leukotrienes](#).
- Upregulation of anti-inflammatory molecules such as the [Interleukin 1 receptor antagonist](#) or the soluble [tumor necrosis factor receptor](#) (TNFR)
- [Apoptosis](#) of pro-inflammatory cells^[21]
- Desensitization of receptors.
- Increased survival of cells in regions of inflammation due to their interaction with the [extracellular matrix](#) (ECM)^{[22][23]}
- Downregulation of receptor activity by high concentrations of [ligands](#)
- Cleavage of [chemokines](#) by [matrix metalloproteinases](#) (MMPs) might lead to production of anti-inflammatory factors.^[24]
- Production of [resolvins](#), [protectins](#) or [maresins](#).

“ Acute inflammation normally resolves by mechanisms that have remained somewhat elusive. Emerging evidence now suggests that an active, coordinated program of resolution initiates in the first few hours after an inflammatory response begins. After entering tissues, [granulocytes](#) promote the switch of [arachidonic acid](#)-derived [prostaglandins](#) and [leukotrienes](#) to lipoxins, which initiate the termination sequence. [Neutrophil](#) recruitment thus ceases and programmed death by [apoptosis](#) is engaged. These events coincide with the biosynthesis, from [omega-3 polyunsaturated fatty acids](#), of [resolvins](#) and [protectins](#), which critically shorten the period of neutrophil infiltration by initiating apoptosis. Consequently, apoptotic neutrophils undergo [phagocytosis](#) by [macrophages](#), leading to neutrophil clearance and release of anti-inflammatory and reparative [cytokines](#) such as transforming growth factor- β 1. The anti-inflammatory program ends with the departure of macrophages through the [lymphatics](#).^[25] ”

—Charles Serhan

[\[edit\]](#) Systemic effects

An [infectious organism](#) can escape the confines of the immediate tissue via the [circulatory system](#) or [lymphatic system](#), where it may spread to other parts of the body. If an organism is not contained by the actions of acute inflammation it may gain access to the lymphatic system via nearby [lymph vessels](#). An infection of the lymph vessels is known as [lymphangitis](#), and infection of a lymph node is known as [lymphadenitis](#). A pathogen can gain access to the bloodstream through lymphatic drainage into the circulatory system.

When inflammation overwhelms the host, [systemic inflammatory response syndrome](#) is diagnosed. When it is due to [infection](#), the term [sepsis](#) is applied, with the terms [bacteremia](#) being applied specifically for bacterial sepsis and [viremia](#) specifically to viral sepsis. [Vasodilation](#) and organ dysfunction are serious problems associated with widespread infection that may lead to [septic shock](#) and death.

[\[edit\]](#) Acute-phase proteins

Inflammation also induces high systemic levels of [acute-phase proteins](#). In acute inflammation, these proteins prove beneficial, however in chronic inflammation they can contribute to [amyloidosis](#).^[5] These proteins include [C-reactive protein](#), [serum amyloid A](#), and [serum amyloid P](#), which cause a range of systemic effects including^[5]:

- [Fever](#)
- Increased [blood pressure](#)
- Decreased [sweating](#)
- [Malaise](#)
- [Loss of appetite](#)
- [Somnolence](#)

[\[edit\]](#) Leukocyte numbers

Inflammation often affects the numbers of leukocytes present in the body:

- [Leukocytosis](#) is often seen during inflammation induced by infection, where it results in a large increase in the amount of leukocytes in the blood, especially immature cells. Leukocyte numbers usually increase to between 15 000 and 20 000 cells per microliter, but extreme cases can see it approach 100 000 cells per microliter.^[5] Bacterial infection usually results in an increase of [neutrophils](#), creating [neutrophilia](#), whereas diseases such as [asthma](#), [hay fever](#), and parasite infestation result in an increase in [eosinophils](#), creating [eosinophilia](#).^[5]
- [Leukopenia](#) can be induced by certain infections and diseases, including viral infection, [Rickettsia](#) infection, some [protozoa](#), [tuberculosis](#), and some [cancers](#).^[5]

[\[edit\]](#) Systemic inflammation and obesity

With the discovery of [interleukins](#) (IL), the concept of [systemic inflammation](#) developed. Although the processes involved are identical to tissue inflammation, systemic inflammation is not confined to a particular tissue but involves the [endothelium](#) and other organ systems.

Chronic inflammation is widely observed in obesity.^[26] The [obese](#) commonly have many elevated markers of inflammation, including^{[27][28]}:

- [IL-6 \(Interleukin-6\)](#)^{[29][30]}
- [IL-8 \(Interleukin-8\)](#)
- [IL-18 \(Interleukin-18\)](#)^{[29][30]}
- [TNF- \$\alpha\$ \(Tumor necrosis factor-alpha\)](#)^{[29][30]}
- [CRP \(C-reactive protein\)](#)^{[29][30]}
- [Insulin](#)^{[29][30]}
- [Blood glucose](#)^{[29][30]}
- [Leptin](#)^{[29][30]}

Low-grade chronic inflammation is characterized by a two- to threefold increase in the systemic concentrations of cytokines such as TNF- α , IL-6, and CRP.^[31] Waist circumference correlates significantly with systemic inflammatory response.^[32] A predominant factor in this correlation is due to the autoimmune response triggered by adiposity, whereby immune cells may mistake fatty deposits for intruders. The body attacks fat similar to bacteria and fungi. When expanded fat cells leak or break open, macrophages mobilize to clean up and embed into the adipose tissue. Then macrophages release inflammatory chemicals, including TNF- α and (IL-6). TNF's primary role is to regulate the immune cells and induce inflammation. White blood cells then assist by releasing more [cytokines](#). This link between adiposity and inflammation has been shown to produce 10-35% of IL-6 in a resting individual, and this production increases with increasing adiposity.^[33]

During clinical studies, inflammatory-related molecule levels were reduced and increased levels of anti-inflammatory molecules were seen within four weeks after patients began a very low calorie diet.^[34] The association of systemic inflammation with [insulin resistance](#) and [atherosclerosis](#) is the subject of intense research.^[35]

In the obese mouse models, inflammation and [macrophage](#)-specific genes are upregulated in white adipose tissue (WAT). There were also signs of dramatic increase in circulating [insulin](#) level, adipocyte lipolysis and formation of multinucleate [giant cells](#).^[36] The fat-derived protein called [angiopoietin](#)-like protein 2 (Angptl2) elevates in fat tissues. Higher than normal Angptl2 level in fat tissues develop inflammation as well as insulin and leptin resistance. Stored fat secretes [Leptin](#) to signal satiety. Leptin resistance plays a role in the process where appetite overrules the message of satiety. Angptl2 then starts an inflammatory cascade causing blood vessels to remodel and attract macrophages. Angptl2 is an adipocyte-derived inflammatory mediator linking obesity to systemic insulin resistance.^[citation needed] It is possible that, as an inflammatory marker, [leptin responds specifically to adipose-derived inflammatory cytokines](#).

[C-reactive protein](#) (CRP) is generated at a higher level in obese people. It raises when there is inflammation throughout the body. Mild elevation in CRP increase risk of heart attacks, strokes, high blood pressure, muscle weakness and fragility. ^[citation needed]

[\[edit\]](#) Systemic inflammation and overeating

[Hyperglycemia](#) induces IL-6 production from endothelial cells and macrophages. ^[37] Meals high in [saturated fat](#), as well as meals high in [calories](#) have been associated with increases in inflammatory markers. ^{[38][39]} While the inflammatory responses are acute and arise in response to [overeating](#), the response may become chronic if the overeating is chronic.

[\[edit\]](#) Outcomes



Scars present on the skin, evidence of fibrosis and healing of a wound

The outcome in a particular circumstance will be determined by the tissue in which the injury has occurred and the injurious agent that is causing it. Here are the possible outcomes to inflammation. ^[5]

1. **Resolution**

The complete restoration of the inflamed tissue back to a normal status. Inflammatory measures such as vasodilation, chemical production, and leukocyte infiltration cease, and damaged [parenchymal](#) cells regenerate. In situations where limited or short lived inflammation has occurred this is usually the outcome.

2. **Fibrosis**

Large amounts of tissue destruction, or damage in tissues unable to regenerate, can not be regenerated completely by the body. Fibrous [scarring](#) occurs in these areas of damage, forming a scar composed primarily of [collagen](#). The scar will not contain any specialized structures, such as [parenchymal](#) cells, hence functional impairment may occur.

3. **Abscess Formation**

A cavity is formed containing pus, an opaque liquid containing dead white blood cells and bacteria with general debris from destroyed cells.

4. **Chronic inflammation**

In acute inflammation, if the injurious agent persists then chronic inflammation will

ensue. This process, marked by inflammation lasting many days, months or even years, may lead to the formation of a [chronic wound](#). Chronic inflammation is characterised by the dominating presence of macrophages in the injured tissue. These cells are powerful defensive agents of the body, but the [toxins](#) they release (including [reactive oxygen species](#)) are injurious to the organism's own tissues as well as invading agents. Consequently, chronic inflammation is almost always accompanied by tissue destruction.

[\[edit\]](#) Examples

Inflammation is usually indicated by adding the suffix "[-itis](#)", as shown below. However, some conditions such as [asthma](#) and [pneumonia](#) do not follow this convention. More examples are available at [list of types of inflammation](#).



Acute [appendicitis](#)



Acute [dermatitis](#)



Acute infective [meningitis](#)



Acute [tonsillitis](#)

[\[edit\]](#) Exercise and Inflammation

[\[edit\]](#) Exercise-induced acute inflammation

Acute inflammation of the [muscle cells](#), as understood in exercise physiology,^[40] can result after [induced eccentric](#) and [concentric](#) muscle training. Participation in eccentric training and conditioning, including resistance training and activities that emphasize eccentric lengthening of the [muscle](#) including downhill running on a moderate to high incline can result in considerable soreness within 24 to 48 hours, even though [blood lactate](#) levels, previously thought to cause muscle soreness, were much higher with level running. This [delayed onset muscle soreness](#) (DOMS) results from structural damage to the contractile filaments and [z-disks](#), which has been noted especially in marathon runners whose muscle fibers revealed [remarkable damage](#) to the muscle fibers after both training and marathon competition. The onset and timing of this [gradient damage](#) to the muscle parallels the degree of muscle soreness experienced by the runners.

Z-disks are the point of contact for the contractile proteins. They provide structural support for the transmission of force when the muscle fibers are activated to shorten. However, in marathon runners and those who subscribe to the overload principle to enhance their muscles, show moderate Z-disk streaming and major disruption of the thick and thin filaments in parallel groups of sarcomeres as a result of the force of eccentric actions or stretching of the tightened muscle fibers.

This disruption of the muscle fibers triggers white blood cells to increase following the induced muscle soreness, leading to the inflammatory response observation from the induced muscle soreness. Elevations in plasma enzymes, myoglobinemia, and abnormal muscle histology and ultrastructure are concluded to be associated with the inflammatory response. High tension in the contractile-elastic system of muscle results in structural damage to the muscle fiber and plasmalemma and its epimysium, perimysium, and/or endomysium. The mysium damage disrupts calcium homeostasis in the injured fiber and fiber bundles, resulting in necrosis that peaks about 48 hours after exercise. The products of the macrophage activity and intracellular contents (such as histamines, kinins, and K⁺) accumulate outside the cells. These substances then stimulate the free nerve endings in the muscle; a process that appears accentuated by eccentric exercise, in which large forces are distributed over a relatively small cross-sectional area of the muscle.

[\[edit\]](#) Post-inflammatory muscle growth and repair

There is a known relationship between inflammation and muscle growth.^[41] For instance, high doses of anti-inflammatory medicines (e.g., [NSAIDs](#)) are able to blunt muscle growth.^{[42][43]}

It has been further theorized that the acute localized inflammatory responses to muscular contraction during exercise, as described above, are a necessary precursor to muscle growth.^[44] As a response to muscular contractions, the acute inflammatory response initiates the breakdown and removal of damaged muscle tissue.^[45] Muscles can synthesize cytokines in response to contractions,^{[46][47][48]} such that the cytokines [Interleukin-1 beta \(IL-1 \$\beta\$ \)](#), TNF- α , and IL-6 are expressed in skeletal muscle up to 5 days after exercise.^[45]

In particular, the increase in levels of IL-6 can reach up to one hundred times that of resting levels.^[48] Depending on volume, intensity, and other training factors, the IL-6 increase associated with training initiates about 4 hours after resistance training and remains elevated for up to 24 hours.^{[49][50][51]}

These acute increases in cytokines, as a response to muscle contractions, help initiate the process of muscle repair and growth by activating [satellite cells](#) within the inflamed muscle. Satellite cells are crucial for skeletal muscle adaptation to exercise.^[52] They contribute to hypertrophy by providing new myonuclei and repair damaged segments of mature myofibers for successful regeneration following injury- or exercise-induced muscle damage;^{[53][54][55]} high-level [powerlifters](#) can have up to 100% more satellite cells than untrained controls.^{[56][57]}

A rapid and transient localization of the IL-6 receptor and increased IL-6 expression occurs in satellite cells following contractions.^[49] IL-6 has been shown to mediate hypertrophic muscle growth both *in vitro* and *in vivo*.^[52] Unaccustomed exercise can increase IL-6 by up to sixfold at 5 hours post-exercise and threefold 8 days after exercise.^[58] Also telling is the fact that NSAIDs can decrease satellite cell response to exercise,^[42] thereby reducing exercise-induced protein synthesis.^[43]

The increase in cytokines after resistance exercise coincides with the decrease in levels of [myostatin](#), a protein that inhibits muscle differentiation and growth.^[51] The cytokine response to resistance exercise and moderate-intensity running occur differently, with the latter causing a more prolonged response, especially at the 12-24 hour mark.^[51]

[\[edit\]](#) **Chronic inflammation and muscle loss**

Both chronic and extreme inflammation are associated with disruptions of anabolic signals initiating muscle growth. Chronic inflammation has been implicated as part of the cause of the [muscle loss that occurs with aging](#).^{[41][59]} Increased protein levels of myostatin have been described in patients with diseases characterized by chronic low-grade inflammation.^[60] Increased levels of TNF- α can suppress the AKT/mTOR pathway, a crucial pathway for regulating skeletal muscle hypertrophy,^[61] thereby increasing muscle [catabolism](#).^{[62][63][64]} Cytokines may [antagonize](#) the [anabolic](#) effects of [Insulin-like growth factor 1 \(IGF-1\)](#).^{[65][66]} In the case of [sepsis](#), an extreme whole body inflammatory state, the synthesis of both [myofibrillar](#) and [sarcoplasmic](#) proteins are inhibited, with the inhibition taking place preferentially in [fast-twitch muscle fibers](#).^{[65][67]} Sepsis is also able to prevent [leucine](#) from stimulating muscle protein synthesis.^[46] In animal models, when inflammation is created, [mTOR](#) loses its ability to be stimulated by muscle growth.^[68]

[\[edit\]](#) **Exercise as a treatment for inflammation**

Regular physical activity is reported to decrease markers of inflammation^[quantify],^{[69][70][71]} although the correlation is imperfect and seems to reveal differing results contingent upon training intensity. For instance, while baseline measurements of circulating inflammatory markers do not seem to differ greatly between healthy trained and untrained adults,^{[72][73]} long-term chronic training may help reduce chronic low-grade inflammation.^[74] On the other hand,

levels of inflammatory markers (IL-6) remained elevated longer into the recovery period following an acute bout of exercise in patients with inflammatory diseases, relative to the recovery of healthy controls.^[74] It may well be that low-intensity training can reduce resting pro-inflammatory markers (CRP, IL-6), while moderate-intensity training has milder and less-established anti-inflammatory benefits.^{[72][75][76][77]} There is a strong relationship between exhaustive exercise and chronic low-grade inflammation.^[78] Marathon running may enhance IL-6 levels as much as 100 times over normal and increases total leukocyte count and neutrophil mobilization.^[78] As such, individuals pursuing exercise as a means to treat the other factors behind chronic inflammation may wish to balance their exercise protocol with bouts of low-intensity training, while striving to avoid chronic over-exertion.

[\[edit\]](#) Signal-to-noise theory

Given that localized acute inflammation is a necessary component for muscle growth, and that chronic low-grade inflammation is associated with a disruption of anabolic signals initiating muscle growth, it has been theorized that a [signal-to-noise](#) model may best describe the relationship between inflammation and muscle growth.^[79] By keeping the "noise" of chronic inflammation to a minimum, the localized acute inflammatory response signals a stronger anabolic response than could be achieved with higher levels of chronic inflammation.

[\[edit\]](#) See also



Wikimedia Commons has media related to: [Inflammation](#)

- [Anaphylatoxin](#)
- [Anti-inflammatories](#)
- [Essential fatty acid interactions](#)
- [Healing](#)
- [Interleukin](#)
- [Lipoxin](#)
- [Substance P](#)

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