

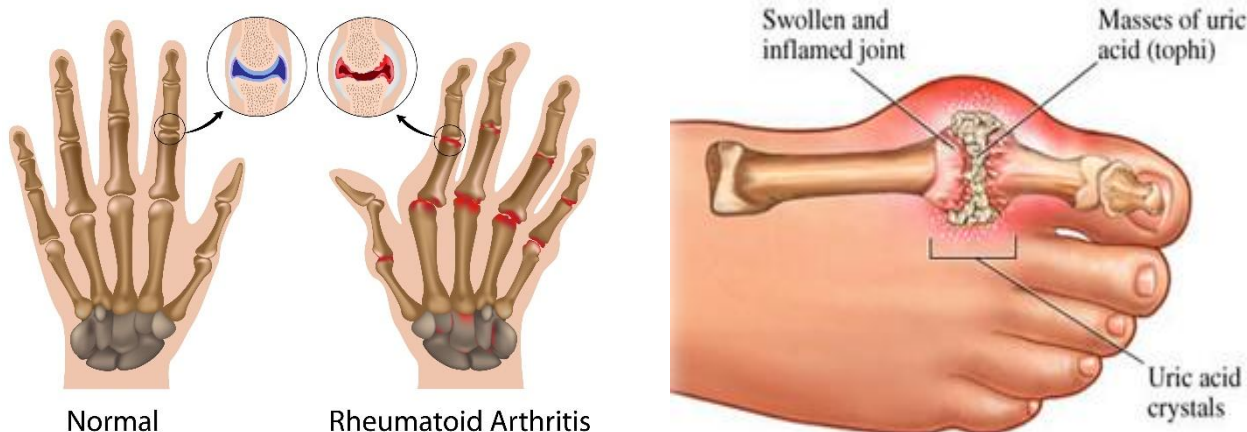
INFLAMMATION

Inflammation is the body's attempt at self-protection; the aim being to remove harmful stimuli, including damaged cells, irritants, or pathogens - and begin the healing process.

Inflammation is the immune system's response to infection and injury and has been implicated in the pathogenesis of arthritis, cancer, and stroke, as well as in neurodegenerative and cardiovascular disease. Inflammation is an intrinsically beneficial event that leads to removal of offending factors and restoration of tissue structure and physiological function. The acute phase of inflammation is characterized by the rapid influx of blood granulocytes, typically neutrophils, followed swiftly by monocytes that mature into inflammatory macrophages that subsequently proliferate and thereby affect the functions of resident tissue macrophages. This process causes the cardinal signs of acute inflammation: rubor (redness), calor (heat), tumor (swelling), and dolor (pain). Once the initiating noxious stimulus is removed via phagocytosis, the inflammatory reaction can decrease and resolve. During the resolution of inflammation, granulocytes are eliminated, and macrophages and lymphocytes return to normal preinflammatory numbers and phenotypes. The usual outcome of the acute inflammatory program is successful resolution and repair of tissue damage, rather than persistence and dysfunction of the inflammatory response, which can lead to scarring and loss of organ function. It may be anticipated, therefore, that failure of acute inflammation to resolve may predispose to autoimmunity, chronic dysplastic inflammation, and excessive tissue damage.

Prostaglandins (PGs) play a key role in the generation of the inflammatory response. Their biosynthesis is significantly increased in inflamed tissue, and they contribute to the development of the cardinal signs of acute inflammation. Although the proinflammatory properties of individual PGs during the acute inflammatory response are well established, their role in the resolution of inflammation is more controversial. In this review, we discuss the biosynthesis of and response to PGs and the pharmacology of their blockade in orchestrating the inflammatory response, with particular regard to cardiovascular disease.

When something harmful or irritating affects a part of our body, there is a biological response to try to remove it, the signs and symptoms of inflammation, specifically acute inflammation, show that the body is trying to heal itself. Inflammation does not mean infection, even when an infection causes inflammation. Infection is caused by a bacterium, virus or fungus, while inflammation is the body's response to it.



The word **inflammation** comes from the Latin "*inflammo*", meaning "*I set alight, I ignite*".

Inflammation is part of the body's immune response. Initially, it is beneficial when, for example, your knee sustains a blow and tissues need care and protection. However,

sometimes inflammation can cause further inflammation; it can become self-perpetuating. More inflammation is created in response to the existing inflammation.

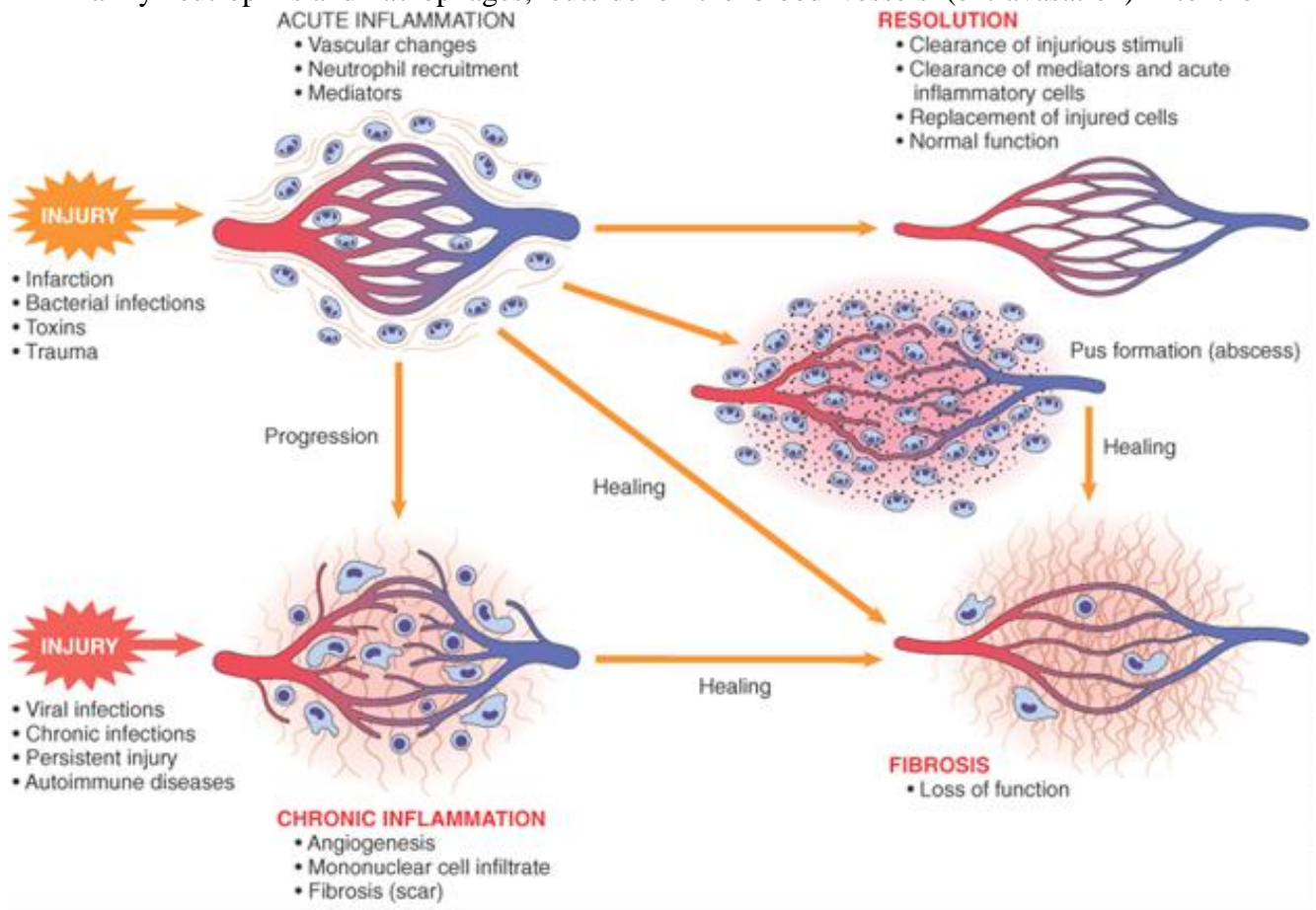
Key points about inflammation.

1. Inflammation is the body's attempt at self-protection to remove harmful stimuli and begin the healing process.
2. Inflammation is part of the body's immune response.
3. The first stage of inflammation is often called irritation, which then becomes inflammation - the immediate healing process.
4. Inflammation is followed by suppuration (discharging of **pus**). Then there is the granulation stage, the formation in wounds of tiny, rounded masses of tissue during healing.
5. Acute inflammation - starts rapidly (rapid onset) and quickly becomes severe.
6. Chronic inflammation - this means long-term inflammation, which can last for several months and even years.
7. Our infections, wounds and any damage to tissue would never heal without inflammation - tissue would become more and more damaged and the body, or any organism, would eventually perish.
8. Chronic inflammation can eventually cause several diseases and conditions, including some cancers, rheumatoid, **atherosclerosis**, **periodontitis**, and **hay fever**.
9. Although scientists know that inflammation plays a key role in **heart disease** and several other illnesses, what drives inflammation in the first place is still a mystery.
10. It should be remembered that inflammation is part of the healing process. Sometimes reducing inflammation is necessary, but not always

PROCESS OF ACUTE INFLAMMATION

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 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*).

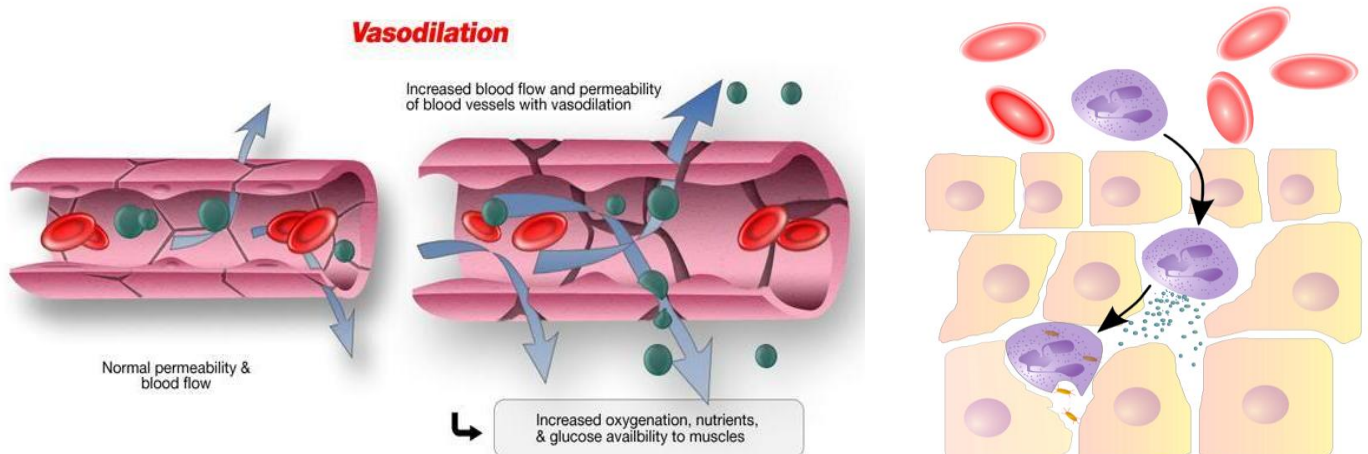
The mediator molecules also alter the blood vessels to permit the migration of leukocytes, mainly neutrophils and macrophages, outside of the blood vessels (extravasation) into the



tissue. The neutrophils migrate along a chemotactic gradient created by the local cells to reach the site of injury. The loss of function (*functiolaesa*) is probably the result of a neurological reflex in response to pain. In addition to cell-derived mediators, several cellular 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

(1) Vasodilation and Increased Permeability

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,



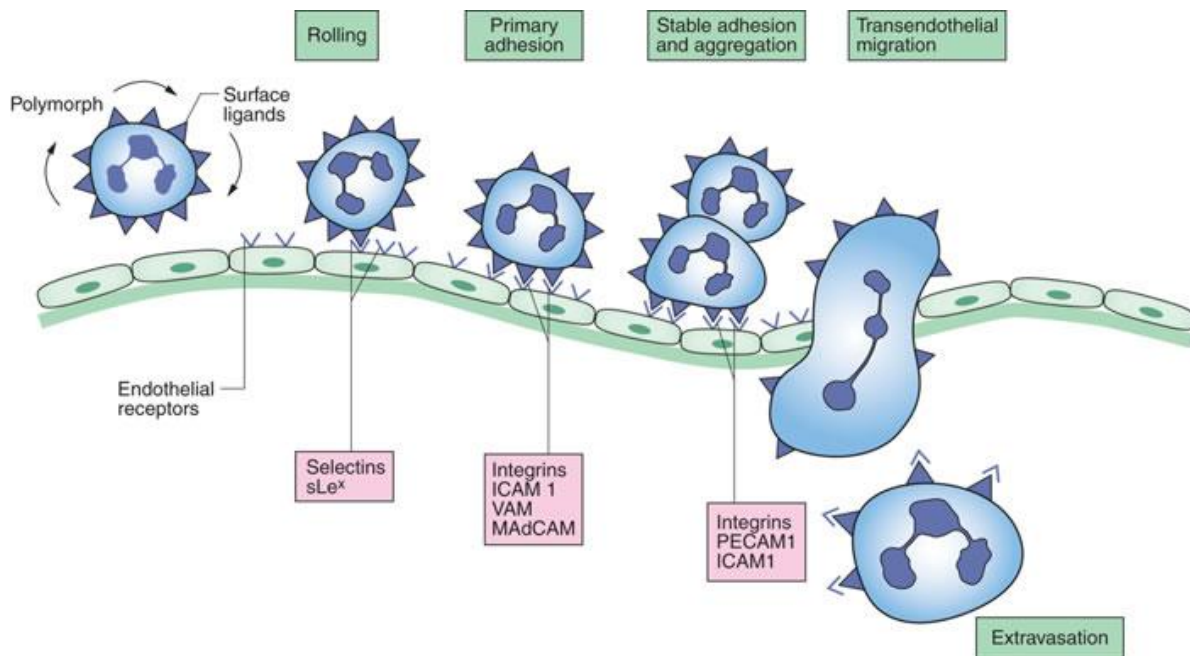
followed by a cellular phase involving immune cells (more specifically myeloid granulocytes in the acute setting). The vascular component of acute inflammation involves the movement of plasma fluid, containing important proteins such as fibrin and immunoglobulin (antibodies), into inflamed tissue. Upon contact with PAMPs, tissue macrophages and mastocytes release vasoactive amines such as histamine and serotonin, as well as eicosanoids such as prostaglandin E₂ and leukotriene B₄ to remodel the local vasculature. Macrophages and endothelial cells release nitric oxide. These mediators vasodilate and permeabilise 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 contains various antimicrobial mediators from the plasma such as complement, 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 haemostasis in 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.

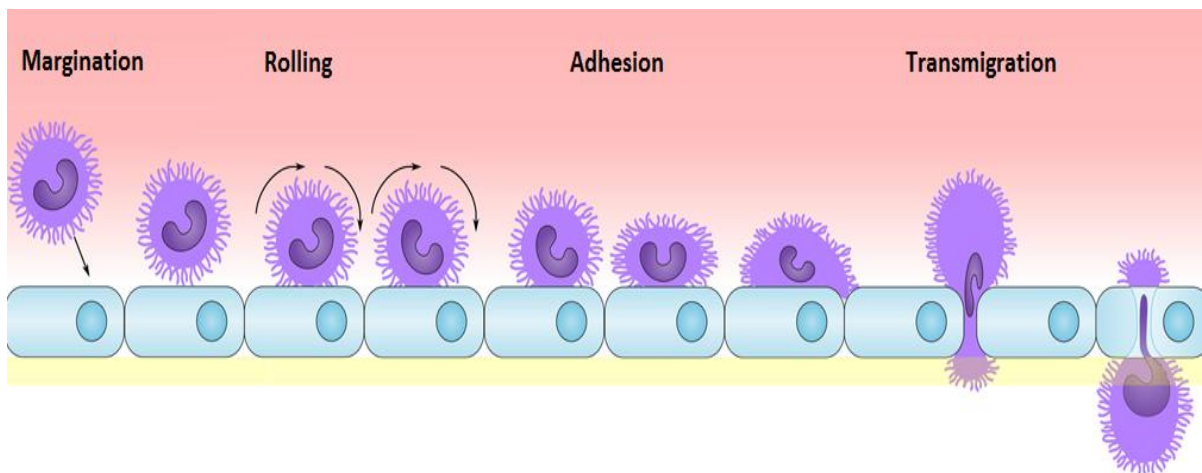
(2) Cellular component

Leukocyte extravasation

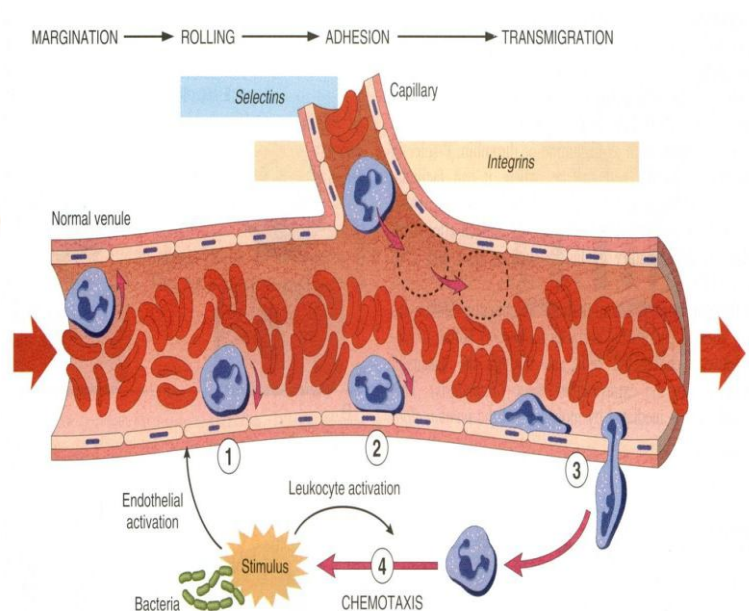
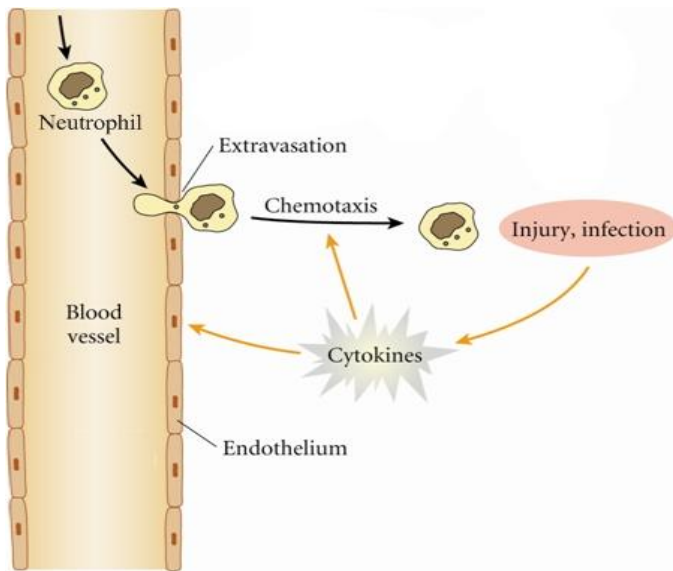
Various leukocytes are critically involved in the initiation and maintenance of inflammation. These cells must be able to get to the site of injury from their usual location in the blood, therefore mechanisms exist to recruit and direct leukocytes to the appropriate place. The process of leukocyte movement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

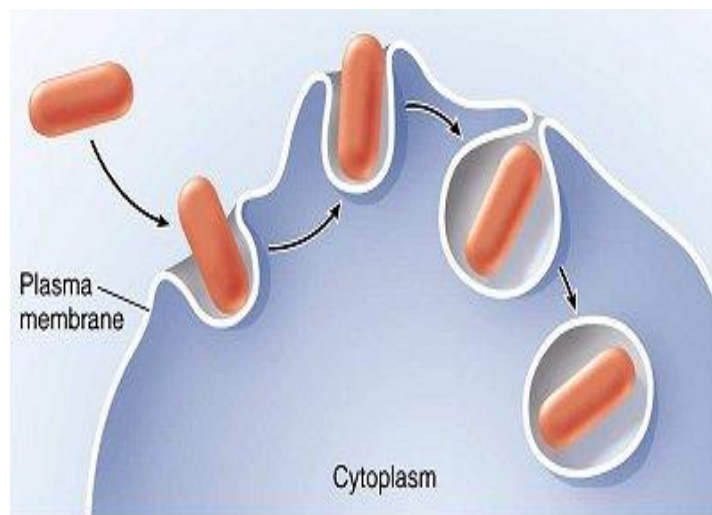
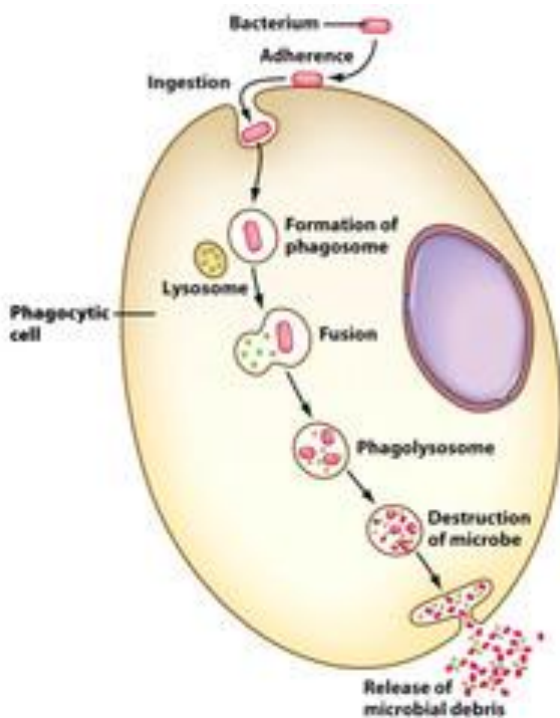


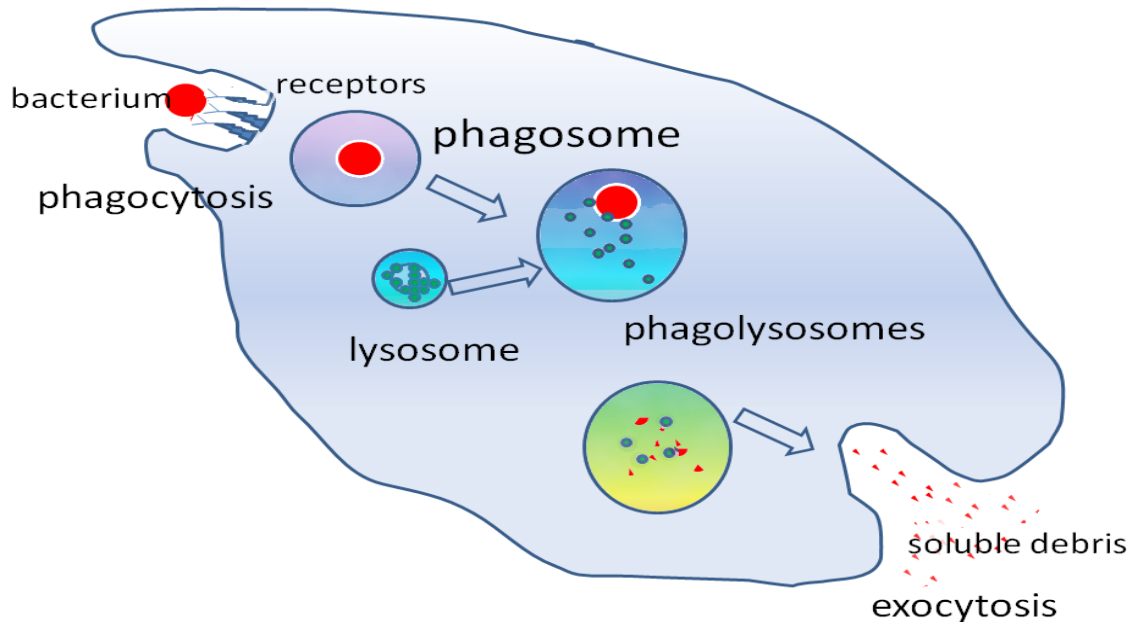
2. **Movement of leukocytes within the tissue via chemotaxis:** Leukocytes reaching the tissue interstitium bind to extracellular matrix proteins via expressed integrins and CD44 to prevent their loss from the site. Chemo attractants cause the leukocytes to move along a chemotactic gradient towards the source of inflammation.



(3) Phagocytosis

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 lectin receptors 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 opsonisation. 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 and complement 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.

Difference between chronic inflammation and acute inflammation

Acute inflammation - starts rapidly (rapid onset) and quickly becomes severe. Signs and symptoms are only present for a few days, but in some cases may persist for a few weeks.

Examples of diseases, conditions, and situations which can result in acute inflammation include:

1. Acute **bronchitis**
2. Infected **ingrown toenail**
3. **Sore throat** from a cold or **flu**
4. A scratch/cut on the skin
5. Exercise (especially intense training)
6. Acute **appendicitis**
7. Acute dermatitis
8. Acute **tonsillitis**
9. Acute infective **meningitis**
10. Acute **sinusitis**

Chronic inflammation - this means long-term inflammation, which can last for several months and even years. It can result from:

1. Failure to eliminate whatever was causing an acute inflammation
2. An autoimmune response to a self antigen - the immune system attacks healthy tissue, mistaking it (them) for harmful pathogens
3. A chronic irritant of low intensity that persists.

Examples of diseases and conditions with chronic inflammation include:

1. **Asthma**
2. Chronic **peptic ulcer**
3. **Tuberculosis**
4. Rheumatoid arthritis
5. Chronic periodontitis
6. Ulcerative colitis and **Crohn's disease**
7. Chronic sinusitis
8. Chronic active **hepatitis** (there are many more).

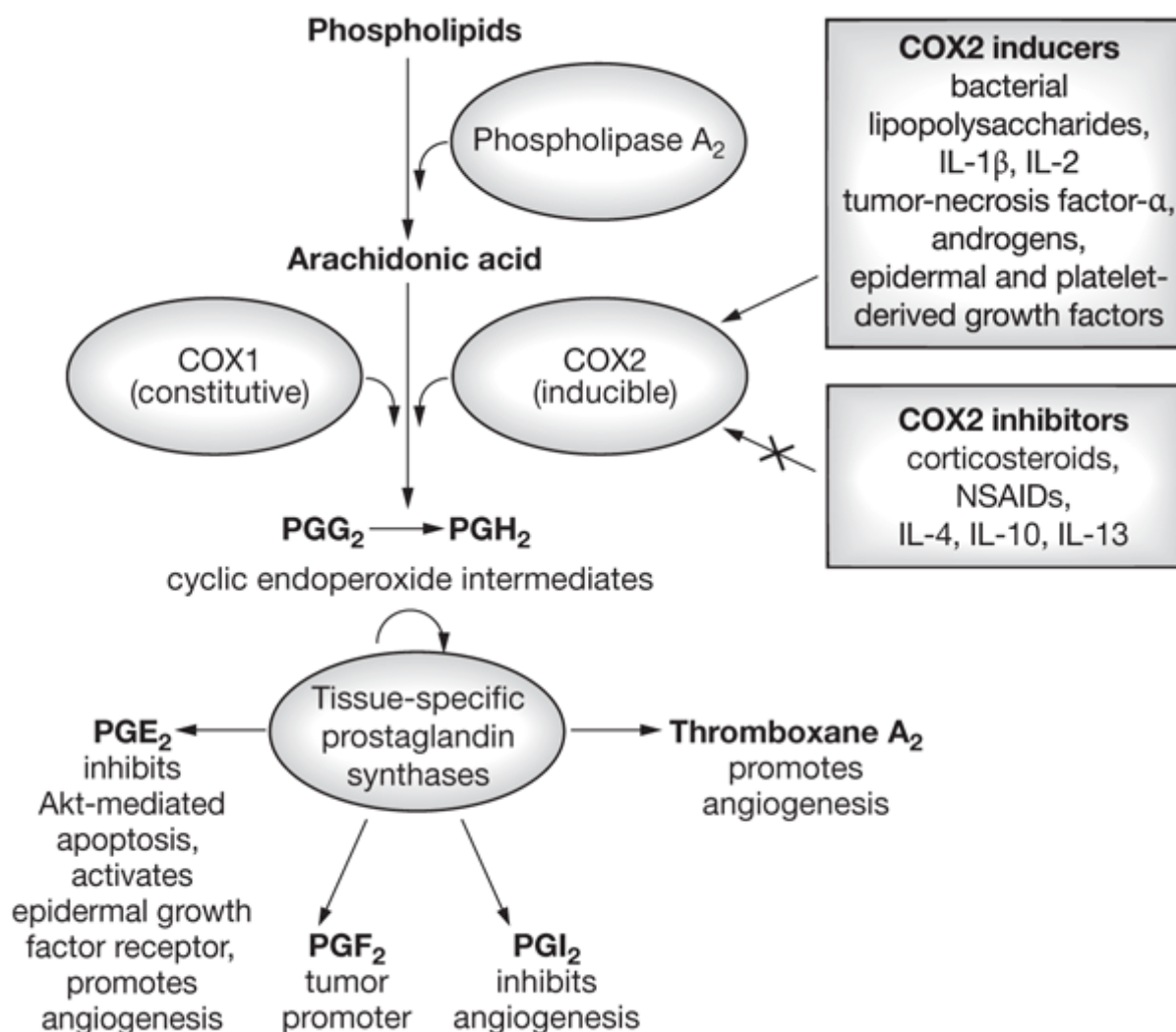
The five cardinal signs of acute inflammation - "PRISH"

1. **Pain** - the inflamed area is likely to be painful, especially when touched. Chemicals that stimulate nerve endings are released, making the area much more sensitive.
2. **Redness** - this is because the capillaries are filled up with more blood than usual
3. **Immobility** - there may be some loss of function
4. **Swelling** - caused by an accumulation of fluid
5. **Heat** - as with the reason for the redness, more blood in the affected area makes it feel hot to the touch.

Anti-inflammatory medications

NSAIDs (non-steroidal anti-inflammatory drugs) are taken to alleviate pain caused by inflammation. They counteract the COX (cyclooxygenase) enzyme, which synthesizes prostaglandins which create inflammation. If prostaglandin synthesis can be blocked, pain is either eliminated or reduced. Examples of NSAIDs include naproxen, ibuprofen and **aspirin**.

People should not use NSAIDs long-term without being under the supervision of a doctor, because there is a risk of stomach ulcers, and even severe and life-threatening hemorrhage. NSAIDs may also worsen asthma symptoms and cause kidney damage. NSAID medications, with the exception of aspirin, can also increase the risk of stroke and myocardial infarction (**heart attack**).



(1) **Acetaminophen** (paracetamol, Tylenol) can reduce pain associated with inflammatory conditions, but have no anti-inflammatory effects. They may be ideal for those wishing to treat just the pain, while allowing the inflammation to run its course.

(2) **Corticosteroids** - these are a class of steroid hormones naturally produced in the cortex (outer portion) of the adrenal gland. They are synthesized in laboratories and added to medications.

Corticosteroids, such as cortisol are anti-inflammatory; they prevent phospholipid release, which undermines eosinophil action and a number of other mechanisms involved in inflammation.

There are two sets of corticosteroids:

1. **Glucocorticoids**, which are produced as a reaction to stress, and are also involved in metabolizing fats, proteins and **carbohydrates**. Synthetic glucocorticoids are prescribed for inflammation of the joints (arthritis), temporal **arteritis** dermatitis, inflammatory bowel disease, systemic lupus, hepatitis, asthma, allergic reactions, and sarcoidosis. Creams and ointments (topical formulations) may be prescribed for inflammation of the skin, eyes, lungs, bowels and nose.
2. **Mineralocorticoids**, which regulate our salt and water balance. Medications with mineral corticoids are used for the treatment of cerebral salt wasting, and to replace missing aldosterone (a hormone) for patients with adrenal insufficiency