8 Inflammation

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8.1 Acute Inflammation

Acute inflammation is viewed as the body's physiological response to all factors that are destructive to cells. The goal of this response is to isolate and destroy these factors and eliminate them along with any associated dead tissue. Acute inflammation is commonly a self-limiting process that ends with restoration of normal conditions (*restitutio ad integrum*), particularly in the skin. By contrast, acute inflammation of internal organs is often a very severe condition, as in encephalitis, meningitis, appendicitis, etc. However, even in the case of the skin, restoration of normal conditions, from a functional and morphological perspective, is by no means the rule. Above and beyond this, certain life-threatening anaphylactic reactions, e.g poisonous insect toxins, are acute inflammatory processes.

The noxious substances[1] that stimulate an acute inflammatory response from the body are summarized in Fig. 8.1. Figure 8.2 illustrates the cascade of mutually dependent events that lead to the local symptoms described by Celsus[2]: *calor* (overheating), *rubor* (redness), *dolor* (pain), and *tumor* (swelling) – in other words, edema.[3] In this context, it is worth noting that "tumor" here is equated with an insufficiency of localized lymphatic vessels! This condition occurs despite the formation of new lymph vessels set in motion by some inflammatory processes (It should be noted that acute inflammation is also accompanied by general symptoms such as fever, leukocytosis, accelerated rates of erythrocyte sedimentation, production of C-reactive protein through the liver, etc.).

In the previous discussion of shear force in Chapter 4, we saw that when shear force is normal and regular, pro-inflammatory adhesion molecules, which cause leukocytes to adhere to the endothelia, are weakly expressed by endothelial cells, while anti-inflammatory molecules are strongly expressed. If the shear force declines, then shear stress arises and the situation is reversed: production of pro-inflammatory genetic prod-

[1] Latin nocere = "to damage"

[2] Roman physician (30 b.c. – 38 a.d.)

[3] Virchow (1821 – 1902) added the symptom "Functio laesa"

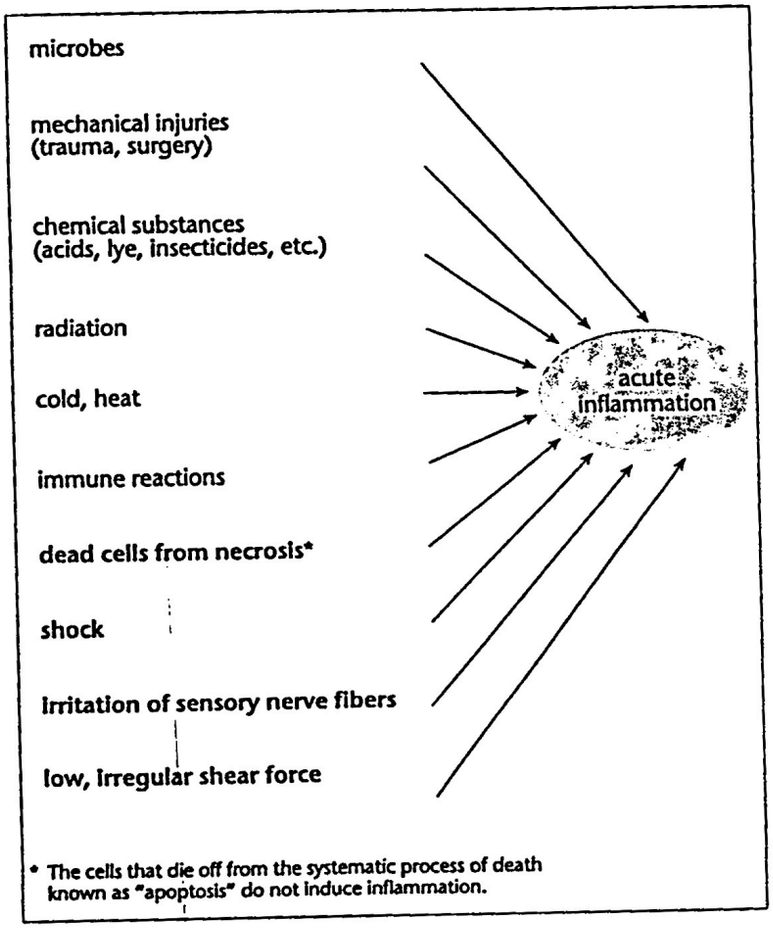

Fig. 8.1
Causes of acute infection [M 150]

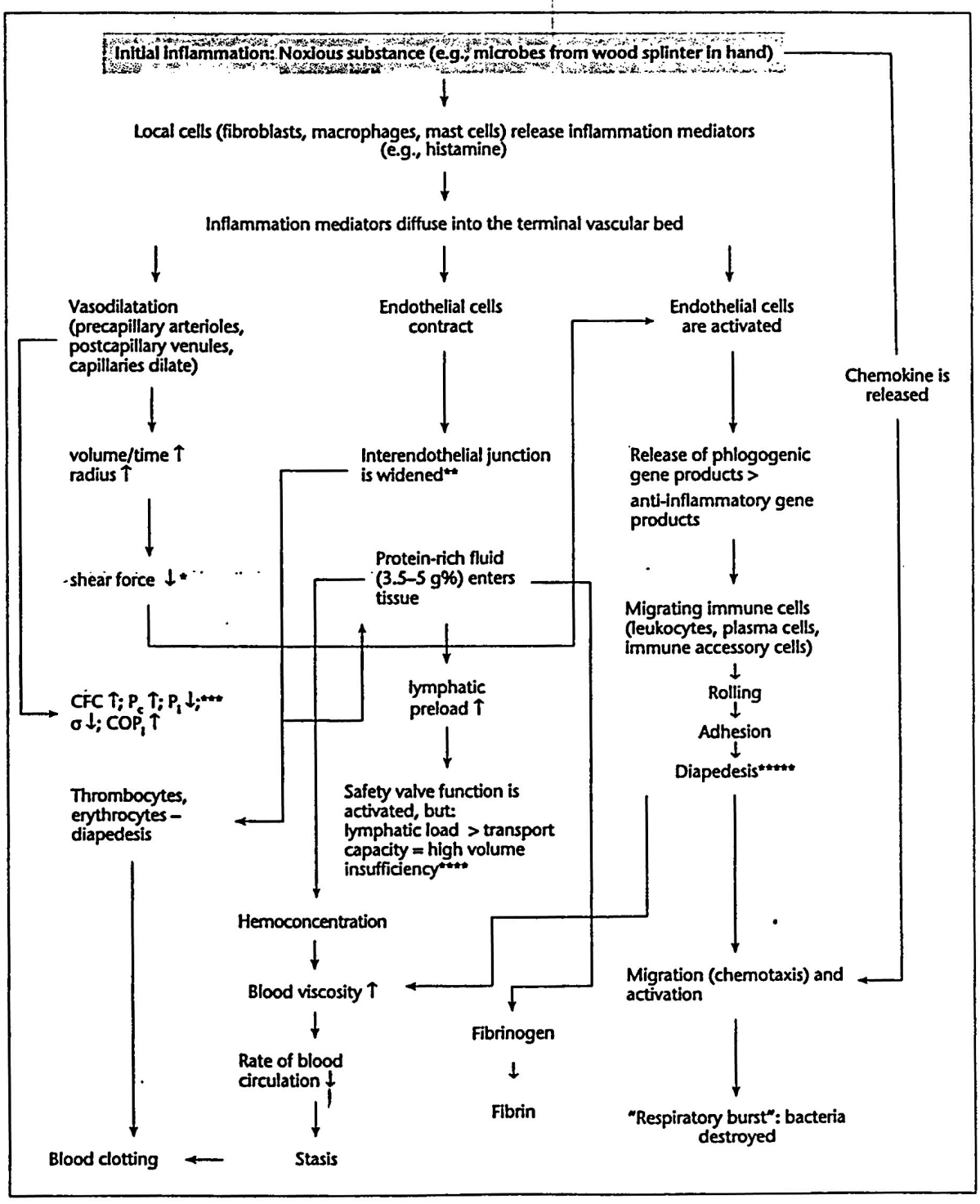

Fig. 8.2 The Cascade of Acute Inflammation

* Shear force is directly proportional to the volume per unit of time, and indirectly proportional to the cube of the diameter.

** Initially around the postcapillary venules; later also around the capillaries

*** "Starling's formula": see Chapter 4. Net ultrafiltration increases as a result of changes in the variables listed.

**** Lymph formation is impaired as a result of damage to the interstitium and lymph capillaries, and combination insufficiency develops as a result of lymphangitis/lymphonoditis. The consequence is a vicious cycle, since dead cells add to the severity of acute inflammation.

***** Diapedesis is an active process: After adhering to the endothelia, leukocytes form pseudopods. Metalloproteinases secreted by the endothelial cells make it easier to get through the basal membrane. [M 150]

ucts increases, while production of anti-inflammatory products declines.

High, stable shear force: anti-inflammatory genetic products of the endothelia > inflammatory genetic products. Low, irregular shear force (= shear stress): anti-inflammatory genetic products < inflammatory genetic products.

The result of this is "leukocyte trapping".

Neutrophil granulocytes possess granula[4], which are primarily useful in the battle against microbes. The granula contain various enzymes, such as myeloperoxydase, lysozyme, hydrolase, elastase, and collagenase. Besides the aforementioned enzymes, the granulocytes have additional lethal weapons: highly toxic free oxygen radicals (comparable to aggressive detergents) such as H_2O_2, hypochlorous acid, etc. These are released in the "respiratory burst" process.

As long as the lymph vessel failure is a dynamic insufficiency, the inflammatory exudate (the swelling) can be characterized as a "rapid turnover pool": the exudate discharged in the area of the noxious substance is continuously drained through the lymphatics. Phlogogenic[5] substances make their way into the blood in the lymph that flows into the blood stream at the venous angles. They then arrive at the site of the inflammation and intensify the inflammatory process. This process was demonstrated in 1972 by *E. Földi*[6] in laboratory animals. The severity of inflammatory edema is significantly reduced if the thoracic duct is cannulated and the lymph does not enter the blood circulation. New findings have confirmed this result: In an acute inflammation of the intestinal wall, toxic phlogogenic mediators reached organs such as the lungs, endothelium, bone marrow through chyle, and not through the portal veins.[7]

This self-limiting inflammatory reaction, in which the exudate flows through the inflammation lesion, is a useful response because:

- It dilutes destructive substances, which are then eliminated via the lymphatics
- It triggers immune responses in the lymph nodes
- The discharged fibrinogen results in a network of fibrin that retains bacteria
- It nourishes the numerous local and migrating cells and removes their waste products.

It should be noted that if everything is proceeding as it should, any bacteria that reach the regional lymph nodes are phagocytized and destroyed by the sinus histiocytes. However, the lymph node itself can become inflamed (lymphonoditis) and the inflammation can potentially spread to the perinodal tissue (perilymphonoditis). Under these circumstances the afterload will increase and thus lead to lymphatic insufficiency. Suppuration (ulceration) may also develop.

If the line of defense provided by the lymph nodes collapses completely, then bacteria enter the blood stream. This results in bacteremia. If the phagocytizing cells of the liver, spleen and bone marrow likewise fail, the consequences potentially include life-threatening illnesses such as meningitis, endocarditis, etc.

Reperfusion syndrome is a particular form of acute inflammation that plays an important role in the pathophysiology of post-ischemic, post-reconstructive lymphedema (see Chapter 5). If blood circulation is suddenly restored following ischemia, the shear force around the postcapillary venules rises briefly – but then declines again. After an hour, it is only half the normal value.[8] This process activates the endothelia of the tunica intima, and leads to margination, rolling, adhesion, and ultimately to diapedesis of leukocytes. Within the tissue, the activated leukocytes enter a "respiratory burst" condition. The result, as previously described, is acute inflammation. The fact that lymph vessels were damaged as a consequence of chronic insufficient blood circulation, and that lymph vessels were undoubtedly severed during surgery is an additional aggravating factor. In order to protect the vessels during the procedure, some vascular surgeons attempt to make the lymph vessels visible by injecting Patent Blue Violet into the exposed soft tissue. However, this does not succeed because the trauma from the operation causes the lymph vessels to contract. Hence, the lymph vessels do not absorb the dye, and remain undetected.

In a favorable outcome, the acute inflammation is resolved, i.e., it ends in complete recovery (*restitutio ad integrum*) from both a structural and functional perspective. This means that the alterations caused by the inflammation are reversed. The lion's share of waste disposal is provided by the lymph vessels: they remove the exudate with the accumulated protein molecules, although macrophages provide some assistance with this. The remains of dead bacteria, dead local cells, dead migratory cells, and necrotic interstitial substance also have to be removed. Fibrinolytic enzymes dismantle the fibrin precipitates into building blocks, and these are

[4] granula = little grains
[5] inflammation-producing
[6] E. Földi: Effect of external lymph drainage and of Coumarin treatment in thermal injury. Brit. J. Pharmacol. 46 (1972): 254–259.
[7] A. Mallick, A.R. Bodenham: Disorders of the lymph circulation. Br. J. Anaesth. 91 (2003): 265–272
[8] The radius increases as a result of active hyperemia. Although blood circulation does increase, shear force is directly proportional to the volume per unit of time – but indirectly proportional to the cube of the diameter. P. Kubes: The role of shear forces in ischemia/reperfusion – induced neutrophil rolling and adhesion. J. Leukocyt. Biol. 62 (1997): 458–464.

likewise removed through lymph vessels. If this removal process is not completed i. e., if there is residual fibrin, then fibrosis results and granulation tissue forms. This same process (organization) occurs with thromboses, as well as with hematomas, in wound healing, and in lymphedema (see Chapter 4). The end result is fibrosclerosis (scarring).

Sometimes, an acute inflammation become chronic (see Section 8.2), and fibrosis is one indication of this.

In an unfavorable outcome, ulceration occurs and an abscess forms.

It should be pointed out that in addition to the "physiological" (normal) acute inflammation discussed, there is also a pathological form of acute inflammation. This form develops if the leukocytes adhering to the endothelia are already activated in the lumen of the postcapillary venules and destroy the endothelial cells by their "respiratory burst" process. The consequence is fibrionoid necrosis, a type of vasculitis.

8.2 Chronic Inflammation

If an acute inflammation does not heal, after a few weeks or months it will turn into a chronic inflammation. In some cases an acute-inflammatory process will flare up on an occasional basis before ultimately turning into the chronic form. Inflammation that is chronic from its onset (***inflammatio chronica ad initio***) is the form of inflammation most relevant to the purposes of this textbook. In regard to this kind of inflammation, pathology textbooks typically mention only:

- Bacterial and viral diseases and certain mycoses associated with intracellular infection;
- Persistent trauma, e.g. the storing of substances in the tissue that cannot be broken down, such as asbestos or silicates;
- Autoimmune diseases like rheumatoid arthritis and inflammatory intestinal diseases.

However, there can be no doubt that lymphedema is also a kind of chronic inflammation.

Smoking represents one risk factor that can promote the transition from acute inflammation to chronic inflammation.

In chronic inflammatory processes, infiltration with mononuclear cells (see Chapter 6) goes hand in hand with bouts of inflammation – "transitory abacterial dermatitis" in lymphedema – tissue damage with angiogenesis, and regenerative manifestations associated with fibrosis.

As explained in Chapters 4 and 5, in lymphedema, the persistent phlogogenic noxa is the lymph congestion-related soaking of the tissue with structurally modified protein molecules, hyaluronan, free oxygen radicals and severe consecutive cellular damage.

8.3 Clinical Manifestations

- Stage I of Sudeck-Leriche syndrome (post-traumatic osteoporosis associated with vasospasm) corresponds to an acute inflammatory process. Blood capillary scintigraphy shows increased permeability of the capillaries to proteins; lymphscintigraphy shows accelerated transport of the tracer from the injection site to the regional lymph nodes. In stage II, there is a deceleration of the tracer transport.
- An acute episode of rheumatoid arthritis is an acute flare-up of an inflammation that is chronic from the beginning (***inflammation ab initio***). Activated arthrosis (osteoarthritis) is also an acute inflammation arising in a chronic degenerative disease.

  From animal models, it is known that blockage of the lymphatics in an extremity leads to lymphostatic arthropathy. High protein fluid accumulates within the joint cavity and the synovium shows histological features largely reminiscent of rheumatoid arthritis. In rheumatoid arthritis, lymphographic and lymphoscintigraphic investigations reveal obstruction of the lymphatics that drain the joints. In addition, it has been shown in rheumatoid arthritis that the prelymphatic channels of the affected tissue are blocked by fibrin precipitates.

  This means that not only lymph formation, but also lymph transport are impaired. Thus, it is not surprising that rheumatoid arthritis can be accompanied by a combination form of lymphedema (Fig. 8.3). This vicious circle plays a major role in all of the rheumatic inflammatory processes:

Pain → neurogenic inflammation → edema → pain

The typical morning stiffness of the joints in rheumatic arthritis is caused by the fact that various inflammation mediators, such as interleukins, prostaglandin, etc. increase the synthesis of hyaluronan (= hyaluronic acid). As discussed in Chapter 4, the large hyaluronan molecule is carried in the lymph. During nighttime immobility, lymph drainage from the joint is minimal. As a result, hyaluronan builds up in the joints; hyaluronan binds water.

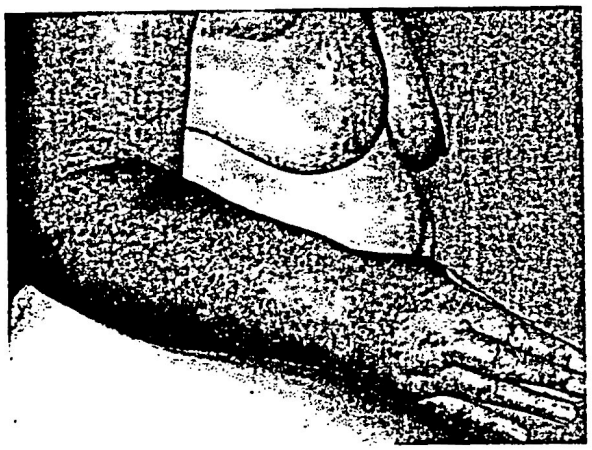

Fig. 8.3 Lymphedema in rheumatoid arthritis [M150]

- Lymphatic microangiopathy has been described in systemic sclerosis (sclerodermia) (Leu et al., 1998). Fluoresence microlymphangiography has shown abnormally extensive spreading of the fluorescence and dermal backflow. In some patients, no capillaries could be found.
- Atherosclerosis is a chronic inflammatory process.[9] As with other kinds of inflammation, it is accompanied by systemic responses (increased concentration of C-reactive protein in the blood). Chronic peridontitis causes damage to blood vessel endothelia throughout the body, and likewise results in an increased blood concentration of systemic inflammation markers. Smoking dramatically intensifies this effect. As a result of this systemic damage, atherosclerotic plaques become destabilized, rupture, and lead to apoplexia and coronary infarction.

8.4 Therapy

Although acute inflammation is a beneficial defense reaction against damaging agents, it often overshoots this goal and becomes noxious. This is the case in suppuration, for example, and thus the old medical maxim, *ubi pus, ibi evacua*[10] is as valid today as ever. The exudation, which is beneficial up to a point, is harmful if the edematous swelling becomes excessive. Therefore, there is good reason to ask whether MLD treatment is appropriate for these cases. One must answer this question in the affirmative, noting however that inflammatory processes that are caused by microbes are an absolute contraindication for MLD.[11]

The use of MLD would be contraindicated in treating, for example, the noxious agent described in Fig. 8.2 (a wood splinter with bacteria), and in treating acute inflammatory processes caused by chemical substances, radiation, heating/warmth, and shock. The chapters of this textbook that cover the practical application of MLD provide information about the use of MLD in the case of inflammatory edemas associated with injuries.[12]

Of course, MLD should not be considered the one and only treatment for scleroderma, Sudeck-Leriche syndrome, and rheumatic disease. In such cases, MLD should be part of a complex regimen consisting of drugs and other physiotherapy methods as well.

In connection with rheumatic disease, it should be remembered that a joint process accompanied by severe changes as shown on x-ray images might present with severe pain if the soft tissues are edematous and might be painless, if they are not. For this reason, acute episodes of rheumatoid arthritis and osteoarthritis are established indications for manual lymph drainage.

Drug treatment of acute inflammation is not within the scope of this textbook.

8.5 Further Reading

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Schmid-Schönbein, G.W., Kistler, E.B., Hugli, T.E.: Mechanisms for cell activation and its consequences for biorheology and microcirculation: Multi-organ failure in shock. Biorheology 38 (2001), 185–201.

[9] W. Koenig et al.: Atherosklerose als Inflammatorischer Prozess. Dtsch. Ärzteblatt 100 (2003): 108–115.

[10] "Where there is pus, drain it."

[11] There have been reports that MLD has been successfully administered in an inpatient hospital setting in cases of severe erysipelas that have not responded to antibiotics; in these cases, antibiotics continued to be administered, and MLD was cautiously used as a supplementary treatment.

[12] The favorable effect of MLD in posttraumatic inflammatory edema following wisdom tooth osteotomy was shown by Schultze et al. in a randomized study. The pain and severity of the edema were reduced, and wound healing was accelerated.