Pathogenesis of Fever

3

Core Messages

- Although infection is the most common cause of fever, fever is also a common finding in hypersensitivity reaction, autoimmune diseases, and malignancy.
- Febrile response is mediated by endogenous pyrogens (cytokines) in response to invading exogenous pyrogens, primarily microorganisms or their direct products (toxins).
- These endogenous pyrogens act on thermosensitive neurons in the hypothalamus, which ultimately upgrade the set point via prostaglandins.
- The body reacts by increasing the heat production and decreasing the heat loss until the body temperature reaches this elevated set point.
- Fever, in contrast to hyperthermia, will not climb up relentlessly because of an effective central control of the hypothalamic center.
- Cytokines play a pivotal role in the immune response by activation of the B cells and T lymphocytes. The production of fever simultaneously with lymphocyte activation constitutes the clearest and strongest evidence in favor of the protective role of fever.
- The protective processes of the immune response are optimal at high temperature (around 39.5°C).
- Not all effects resulting from fever generation benefit the host; some are harmful and even lethal. This occurs mainly by overproduction of the cytokines or imbalance between cytokines and their inhibitors, such as severe and fulminate infections and septic shock.

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3.1 History of Research

Research in fever has been centered on the hypothesis that fever results from physiological processes that are set in motion by an external stimulus. Egyptian scholars recognized that local inflammation was responsible for fever. In 1868, Billroth (1829–1894) attempted to confirm this ancient observation by injecting pus into animals, thereby producing a febrile response. In 1943, Menkin carried out similar experiments and isolated a product termed "pyrexin" [1]. Beeson in 1948 isolated a fever-inducing substance from a leukocyte, leukocyte pyrogens, which later became known as endogenous pyrogen (EP). Interleukin-1 (IL-1) was first identified as a cytokine by Gery and Waksman and proved to be identical with EP [2].

3.2 Definitions

- **Fever (pyrexia)** is a regulated body temperature above the normal range occurring as a result of IL-1-mediated elevation of the hypothalamic set point. Once fever is established, body temperature is regulated, as in health, by a net balance between heat production and loss.
- **Hyperthermia** is unregulated elevated body temperature above the normal range due to imbalance between heat production and loss. Interleukins are not involved and therefore the hypothalamic set point is normal.
- A **pyrogen** is a substance (infectious organisms or their product toxins, or cytokines) that provokes fever.
- **Exogenous pyrogens** are substances that originate outside the body and that are capable of inducing interleukins.
- **Endogenous pyrogens** are substances that originate inside the body and that are capable of inducing fever by acting on the hypothalamic thermoregulatory center. IL-1, tumour necrosis factor (TNF) and interferon (INF) are endogenous pyrogens.
- **Cytokines** are proteins produced throughout the body, mainly by monocytes, macrophages, and T cells to regulate the immune responses within the body and control inflammatory and haematopoietic processes and may induce fever. As they enter the circulation and act on distant organs, they are considered as hormones. Cytokines are pro-inflammatory cytokines, anti-inflammatory cytokines, interleukins, or lymphokines.
- **Pro-inflammatory cytokines** (IL-1, IL-6, TNF-α, INF-γ, granulocyte-macrophage colony-stimulating factor, GM-CSF) are responsible for initiating an effective defense against exogenous organisms. Their overproduction may be harmful by causing shock, multiple organ failure, and death.
- **Anti-inflammatory cytokines** (IL-1 receptor antagonist, IL-4, IL-10) antagonize pro-inflammatory cytokines. Their overproduction may also be harmful by suppressing the immune function.
- **Interleukins** are cytokines acting specifically as mediators between leukocytes, and hence their name. If their amino acid sequence is known, they are assigned an

interleukin number. If their sequence is not known, then they are named according to the biological property. IL-1 and IL-6 play a major part in the pathogenesis of fever.

- **Lymphokines** are cytokines that are secreted by lymphocytes (IL-2, IL-3, IL-4, IL-5, IL-6, IL-9, IL-10, IL-13, IL-14, TNF-β).
- **Acute-phase response** is the term used for haematological, endocrinological, and metabolic changes that follow (within hours or days) the onset of fever in response to local damage to a tissue. These changes are induced by several cytokines and are beneficial to the host. During the response, various acute-phase proteins, notably C-reactive protein (CRP) and serum amyloid A, are synthesized by liver and released into circulation in large amounts. CRP plays a role in complement activation, opsonization (engulfing and destroying microbes by phagocytes), and increasing platelet aggregation.

3.3 Exogenous Pyrogens (Fig. 3.1)

Exogenous Pyrogens (ExPs) initiate fever, usually within 2 h of exposure, by interacting with macrophages or monocytes, leading to IL-1 induction. Other mechanisms to initiate fever include the following:

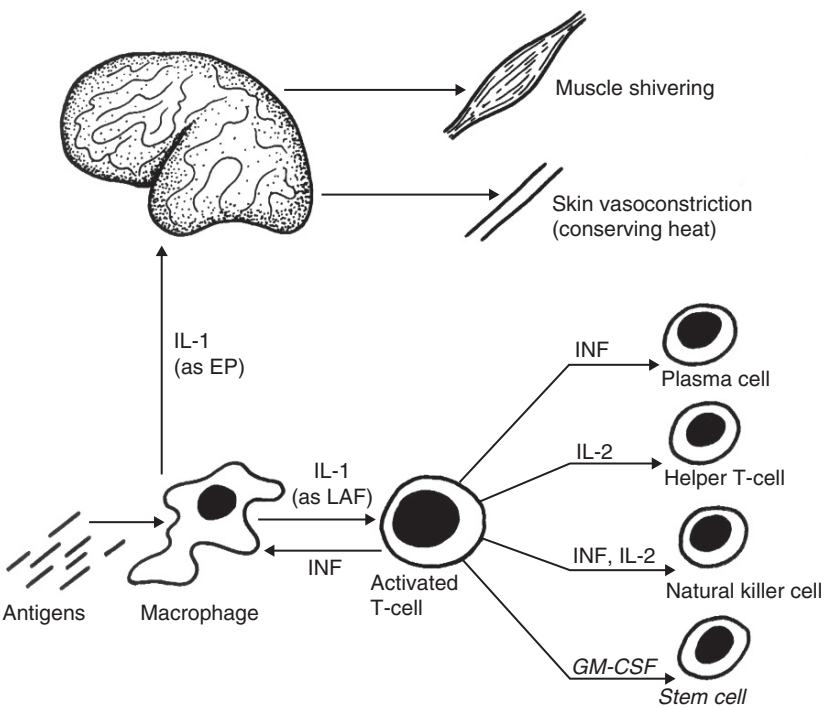

Fig. 3.1 The mechanisms of fever induction

- Some endotoxins, produced by bacteria, act directly on the hypothalamus to alter the set point. IL-1 is not involved. Radiation of the hypothalamus, DDT (dichloro-diphenyl trichloroethane) poisoning, and scorpion venom may also induce fever by a direct effect on hypothalamus.
- ExPs may activate lymphocytes to secrete lymphokines, particularly INF-y, which in turn stimulate macrophages and monocytes to produce IL-1.
- Some bacteria produce exotoxins that stimulate macrophages and monocytes to release IL-1. This mechanism operates in scarlet fever and toxic shock syndrome. In toxic shock syndrome, the shock is due to the toxin. Diseases involving exotoxins produced by Gram-positive bacilli are less fever inducing than those produced by pyrogenic Gram-positive cocci.
- *Borrelia spirochetes* (the cause of relapsing fever) do not contain endotoxin, and the attachment of these bacteria to the mononuclear cells induces the production of IL-1.
- Other bacteria, such as pneumococci, have no endotoxin or other pyrogens, and the mechanisms responsible for fever are presumably immunological.

3.3.1 Microbial Pyrogens

- **Gram-negative bacteria.** The pyrogenicity of Gram-negative bacteria (e.g., *Escherichia coli*, Salmonella) is due to a heat-stable factor, endotoxin. The active components are lipid and carbohydrate (lipopolysaccharide, LPS) elements of the outer membrane of these bacteria. Endotoxin causes a dose-related progressive increase in temperature. In severe cases, it causes vasodilatation, capillary leakage, and hypotension. Infection with Gram-negative endotoxin (e.g., septicemia) does not elicit fever in many situations:
  - **Neonates**, young infants, children with fulminating infection with septic shock (complicates septicemia in 20% of cases) and with malnutrition may present with normal temperature or hypothermia.
  - **Septicemia** presenting with hypothermia is a well-known clinical entity possibly due to inhibition of IL-6 and IL-1 by IL-10 [3].
- **Gram-positive bacteria.** The main pyrogen of staphylococci is peptidglycan of the cell wall. Endotoxin is more active per unit weight than peptidoglycan, which may explain the comparatively worse prognosis associated with Gram-negative infection.
- **Viruses.** It is well known in clinical practice that viruses cause fever. Mechanisms by which viruses may produce fever include direct invasion of macrophages, immunological reaction to viral components involving antibody formation, induction by INF, and necrosis of cells by viruses.
- **Fungi.** Live or killed fungal products are exogenous pyrogens that induce fever. The induction of fever mainly occurs when the fungi are in the bloodstream. Children with neoplastic diseases who develop fever associated with neutropenia are at high risk for developing invasive fungal infection.

3.3.2
Non-Microbial Pyrogens

- **Phagocytosis** is largely responsible for fever in blood transfusion reactions (once an infection is excluded) and immune hemolytic anaemia.
- **Antigen–antibody complexes.** An exogenous antigen may react with circulating, sensitized antibodies to form a complex that induces IL-1 production (immune fever). Examples of immunologically mediated fever include systemic lupus erythematosis and adverse drug reactions. Fever associated with penicillin hypersensitivity results from interaction of antigen–antibody complexes with leukocytes, which release IL-1.
- **Other non-microbial pyrogens** include some hormones, drugs, and intracranial lesions such as bleeding and thrombosis.
- **Steroids.** These are endogenous antipyretics, which suppress fever development through its inhibitory effects on IL-1 and TNF-α production. Certain steroids, however, are pyrogenic in humans. The most known steroid is etiocholanolone, an androgenic metabolite that may induce the release of IL-1. This steroid produces fever only when injected intramuscularly (not intravenously), hence fever may result from IL-1 released by subcutaneous tissue at the injection site. This steroid is thought to be responsible for fever in a few patients with adrenogenital syndrome and fevers of unknown origin.

3.4
Monocyte–Macrophage System (Fig. 3.2)

Mononuclear cells are leukocytes (3–8% of the leukocytes) and are largely responsible for the production of IL-1 and fever induction. Polymorphonuclear granulocytes are no longer thought to be responsible for IL-1 production because fever may occur in their absence, for example agranulocytosis. The mononuclear cells are either circulating monocytes in the peripheral blood or tissue macrophages (histocytes) scattered in organs such as lung (alveolar macrophages), lymphnodes, placenta, peritoneal cavity, and the subcutaneous tissue. The origin of both monocytes and macrophages is the granulocytes–monocyte colony-forming unit (GM–CFU) in the bone marrow. Monocytes enter the circulation either to remain there for a few days as circulating monocytes or to migrate to the tissue where they undergo functional and morphological transformation into macrophages, when their life span is several months. These cells play an important role in:

- Host defense, including engulfing and destroying the microbe (phagocytosis), recognition of antigen, and presenting it to attached lymphocytes and
- Activation of T lymphocytes and tumor cell destruction.

Situations associated with reduced function of the monocyte–macrophage system (MMS) include newborn infants, corticosteroid and other immunosuppressive therapy, systemic lupus erythematous, Wiskot–Aldrich syndrome (immune deficiency involving B and T cells, eczema, and thrombocytopenia), and chronic granulomatous disease. The two major monocyte–macrophage products (cytokines) are IL-1 and TNF.

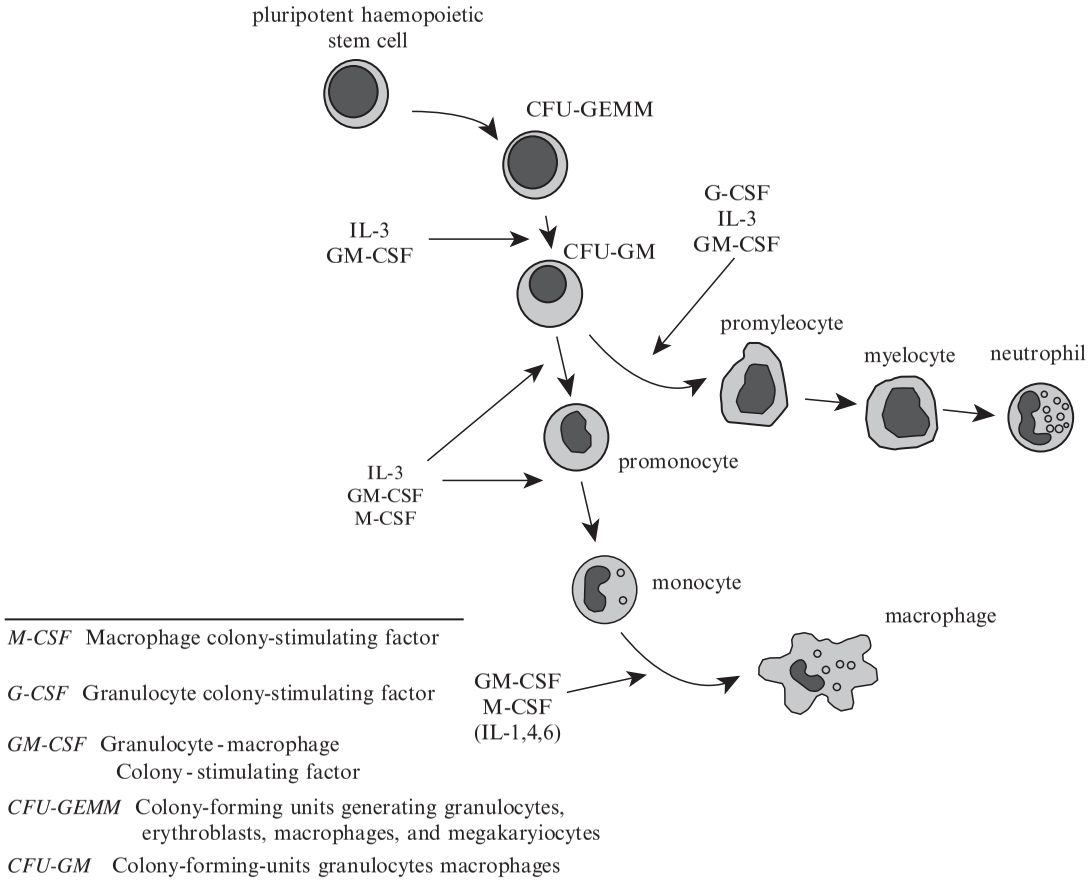

Fig. 3.2 Monocytes and Macrophages

3.5 Endogenous Pyrogens

3.5.1 Interleukin-1 (IL-1)

IL-1 is stored in an inactive form in the cytoplasm of secreting cells and is enzymatically converted to an active form before it is released across the cell membrane into the circulation. It affects distant organs and therefore acts as a hormone. The kidney is the principal site for its removal.

IL-1 consists of three structurally related polypeptides, two agonists (IL-1 α and IL-1β), and an antagonist (IL-1 receptor antagonist = IL-1ra) that inhibits the activities of the two agonists. The relative amount of IL-1 and IL-1ra in a disease influences whether the inflammation remains active or suppressed. IL-1 is produced by:

- Macrophages as the main source of IL-1 production.
- Hepatic Kupffer cells, keratinocytes, pancreatic Langerhans's cells.
- Astrocytes in the brain tissue, which may contribute to the immunological responses within the CNS and the fever secondary to CNS bleeding.
- Cells from certain malignant tumors (e.g., Hodgkin's disease, acute leukemia and renal carcinoma). This explains the frequent association of fever in these conditions in the absence of infection. and
- Monocytes in the circulation and reticuloendothelial system.

Interleukin-1 has multiple functions (Fig. 3.3):

- Induction of fever by acting on the hypothalamus to raise its set point.
- Playing a primary role in the induction of inflammatory responses, such as neutrophil accumulation and adherence, and vascular changes. IL-1 also mediates to neuro-inflammation and cell death in head injury.
- Playing an essential role in T-cell and B-cell proliferation and activation.

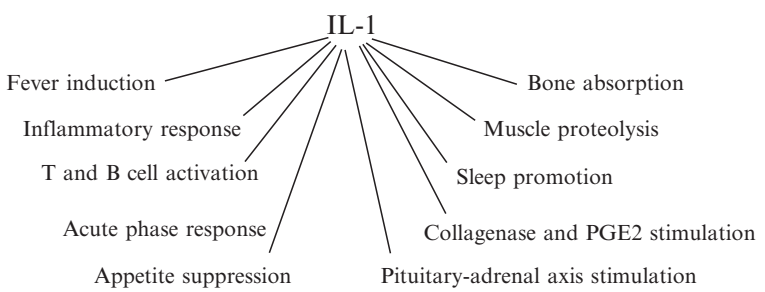

Fig. 3.3 Summary of the main functions of IL-1

- Stimulating the liver to synthesize certain acute-phase proteins, such as fibrinogen, haptoglobin, ceruloplasmin, and CRP. At the same time, the synthesis of albumin and transferrin decreases. Characteristically, there is a decreased concentration of iron and zinc and an increased concentration of copper. The low iron is the result of reduced intestinal assimilation of iron and increased liver storage of iron. These changes contribute to host defense by depriving invading microorganisms of essential nutrients, such as iron and zinc (The process is referred to as nutritional immunity).
- Appetite suppression, which results in a significant reduction of food intake, seen commonly in febrile illness [4]. This process occurs within the brain. IL-1 receptor antagonist attenuates the appetite-reducing effects by IL-1.
- Stimulating osteoclast differentiation and activation, resulting in bone loss.
- Production of Factor S, a peptide identical to IL-1 with sleep promotion effect leading to slow-wave sleep. It is produced in astrocytes of the brain. The factor may explain the observation of increased sleep in febrile illnesses.
- Stimulating the production of collagenase and prostaglandin E2 (PGE2), which play a major role in the pathogenic progression of various arthritides, particularly rheumatoid arthritis.
- Stimulating the pituitary–adrenal axis, causing increasing production of glucocorticoid hormones.
- Increasing protein breakdown, leading to myalgia, which commonly accompanies fever. This proteolysis, mediated by PGE2, is blocked by the PGE2 inhibitor indomethacin. Amino acids released during proteolysis can be metabolized within the muscle as a direct source of energy and are reused for the synthesis of new proteins. Other amino acids may become substrates for gluconeogensis.

In all these circumstances the activity of IL-1 is enhanced at elevated temperatures.
Antagonism of IL-1 (IL-1ra) has therapeutic effects in many diseases, including:

- Various forms of hereditary periodic syndromes and neonatal-onset multisystem inflammatory disease (Chap. 1).
- HIV replication. IL-1ra has suppressive effects on the virus.
- Bone erosions and loss, occurring, for example, in rheumatoid arthritis.

There is little or no IL-1 in healthy humans at rest. A long list of diseases, including meningitis, septicemia, Crohn's disease, rheumatoid arthritis, neonatal hypoxic–ischaemic encephalopathy, and acute organ rejection are associated with increased levels of IL-1 and poor outcome for the patients. Malnutrition (kwashiorkor and marasmus), on the other hand, is associated with a significant impairment of macrophage function and IL-1 production.

3.5.2 Tumour Necrosis Factor (TNF)

TNF, discovered in 1968, is a cytokine produced by monocytes and microphages (TNF-α), lymphocytes (TNF-β), natural killer cells, Kupffer cells, and astrocytes of the brain in

response to invasive or injurious stimuli. Like IL-1, TNF is regarded as an endogenous pyrogen because its acts on the hypothalamus to induce fever. Unlike IL-1, TNF has no direct effect on stem-cell and lymphocyte activation. TNF in small quantities has diverse beneficial biological effects, including:

- Sharing many biological properties with IL-1, for example, enhancing host defense against infection, promoting normal tissue remolding, including wound healing, and enhancing chemotaxis of macrophages and neutrophils as well as increasing their phagocytic and cytotoxic activity.
- Being the earliest and most important mediator of inflammation.
- Stimulating IL-1 production.
- Having a direct effect against certain tumor cells (e.g., by damaging the nuclear DNA and producing free radicals). Its use against human cancers, however, has been associated with poor outcome, mainly due to its systemic side effects.

When large amounts are released in tissue, however, TNF may lead to.

- Lethal tissue injury and shock (septic or toxic shock).
- Wasting (TNF is identical to cachectin), by inhibiting the activity of lipoprotein lipase, and producing negative nitrogen balance and glucose release, often associated with chronic infection and some tumors.

High serum levels of TNF correlate with the activity and prognosis of many infectious diseases, including bacterial meningitis, leishmaniasis, human immunodeficiency virus (HIV) infection, malaria, and intestinal inflammatory diseases. Increased TNF production in Kawasaki disease may play a role in the immune activation and damage to vascular endothelial cells occurring in the disease.

3.5.3 Interleukin-6

IL-6 is the third most studied cytokines. It is:

- A pro-inflammatory cytokine that is secreted by macrophages and T lymphocytes to stimulate immune response
- Synergistic with IL-1 and TNF-α, including induction of fever (Il-6 responds earlier than IL-1) and acute phase response. It parallels the duration of fever. Il-6 is an early marker (within 3–4 h of endotoxin stimulation)
- A stimulator on both B and T cell function
- Increased in many diseases, for example, sepsis, autoimmune diseases and juvenile idiopathic arthritis, Kawasaki disease, and epidural fever [5]

Anti-IL-6 receptor is available to treat IL-6-related immune-inflammatory diseases.
Other cytokines with their main effects are shown in Table 3.1.

Table 3.1 Common lymphokines produced by T cells and their main effect/use

Interleukin	Effects
IL-3	Stimulatory effect on haematopoietic cells (important after myelotoxic treatment with chemotherapy)
IL-4 (and IL-13, 14)	B-cell differentiation, induces IgE
IL-5	B-cell differentiation, eosinophil and IgA production
IL-7 (and IL-27)	Regulates B and T cells, natural killer (NK) cells
IL-8	Proinflammatory cytokine, potent neutrophil chemo-attractant and activator
IL-9	Stimulation the growth of mast cells and erythroid progenitor cells
IL-10 (& IL-20)	Inhibition of Th1 cell production, including Th1-dependent IL-2, and proinflammatory cytokines, implicated in inflammatory process of JIA and development of haematopoietic cells
Il-11 (and IL-22)	Production of acute phase proteins. IL-11 is effective for chemotherapy-induced thrombocytopenia
IL-12	Inhibition of IL-1 synthesis; plays a role in defence against mycobacteria and salmonella
IL-13 (and IL-14, 17)	Stimulating activated B cells to proliferate and produce IgM, IgG, and IgE
IL-16	Chemo-attracts immune cells
IL-17 (and IL-23)	Mediating the inflammatory differentiation of T cells
IL-18	Induces IFN-γ from T lymphocyte and natural killer cells but does not induce fever
Il-28 (and IL-29)	Playing a role in host defense against microorganisms
Il-31 (and IL-32, 33)	Induction of cytokines (TNF, Il-8) and helper T cells

3.6 Activated Lymphocytes

The antigen-specific cells of the immune system are lymphocytes, of which there are two main types:

- B cells are responsible for antibody production, whereas;
- T cells regulate antibody synthesis and mediate cytotoxic function as well as inflammatory response of delayed-type hypersensitivity. T-cells are either:
  - Th1 cells, which produce INF-γ, IL-2, and TNF-β and promote cell-mediated immunity and phagocytic activity, or
  - Th2 cells that produce Il-4, IL-5, IL-6, IL-9, and IL-10. These promote antibody production and play a crucial role in allergic responses (immediate-type hypersensitivity).

IL-1 has an essential role in the activation of lymphocytes. The T lymphocyte recognizes antigen only after the antigens are processed and presented to them by macrophages; only then do T lymphocytes become active.

3.6.1 Interferon (INF)

Interferon is known for its ability to 'interfere' (hence the name) with viral replication in infected cells. There are three molecules, TNF-α, β, and γ, differing in biological activity and amino-acid sequences. INF-α and INF-β are produced by a variety of cells (such as leukocytes, fibroblasts, and macrophages) in response to viral infection, whereas synthesis of INF-γ is restricted to T lymphocytes. Although the T cells from normal neonates function as effectively as those in adults, INF (particularly INF-γ) is considerably reduced, which may contribute to the increased severity of viral infections in newborn infants.
The functions of the INF-γ include:

- Macrophage and fever inducing, either by acting indirectly on macrophages to release IL-1 (a macrophage-activating factor) or directly on the hypothalamic thermoregulatory
- Stimulating B cells to increase antibody production
- Potentiating the antiviral and cytolytic activity of TNF
- Increasing the efficiency of natural killer cells
- Exhibiting antitumor activity either directly by inhibiting cell division through increasing the length of the cell multiplication cycle or indirectly by altering the immune response

The antiviral and antitumor activities of INF are enhanced at elevated temperatures. IL-4, which induces the synthesis of immunoglobulins IgE and IgG4, is blocked by INF-γ and α, indicating that these cytokines act as antagonists of IL-4.
INF is used as a treatment for a variety of illnesses, including

- Various viral infections, such as hepatitis B, C by INF-α
- Upper respiratory tract infection. INF-α in a nasal spray is capable of significantly reducing symptoms due to rhinoviruses, but not those due to influenza viruses, parainfluenza viruses, or coronaviruses
- Thrombocytosis associated with myeloproliferative disorders
- Hairy-cell leukaemia, which remains one of the most important indications for INF-α therapy, showing a response rate of more than 90%
- Childhood angiomatous disease results from INF-antiproliferative effect and
- Non-Hodgkin's lymphoma, malignant melanoma, basal cell carcinoma and chronic myelogenous leukaemia

Toxic effects of INF preparations are numerous, which include fever, chills, arthralgia, myalgia, severe headaches, somnolence, and vomiting. Fever may occur in over 50% of the patients who receive INF and may reach 40.0°C. These side effects are responsive to paracetamol and prednisolone. Severe side effects include hepatic and cardiac failure, neuropathy and pancytopenia. INF therapy is contraindicated in pregnancy owing to its antiproliferative effect.

3.6.2 Interleukin-2 (IL-2)

IL-2 is probably the second most important lymphokine (after INF) that is released by activated T lymphocytes in response to IL-1 stimulation. It has an essential effect on the growth and function of T cells, natural killer cells, and B cells. Cases of severe congenital combined immunodeficiency due to a specific defect in the production of IL-2 have been reported. Its effects are:

- Antitumor cytotoxicity (e.g., against neuroblastoma, melanoma) as a result of proliferation and activation of activated cytotoxic T lymphocytes and
- Stimulating the release of other cytokines, including IL-1, TNF, and INF-γ

IL-2 immunotherapy often causes side effects such as

- A reversible defect of neutrophils chemotaxis, leading to increased susceptibility to infection and
- Those that include malaise, fever, anorexia, and myalgia

3.6.3 Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF)

Of the four hematopoietic-colony stimulating factors (erythropoietin, granulocyte-colony stimulating factor (G-CSF), macrophage-colony stimulating factor (M-CSF), and granulocyte-macrophage-colony stimulating factor (GM-CSF)), the latter (GM-CSF) appears to have the most potential clinical benefits .[6] It is a proinflammatory cytokine, which is produced mainly by lymphocytes, although monocytes, macrophages, and mast cells are also capable of producing it. GM-CSF's principal function and potential therapeutic uses are the following:

- As a treatment and prophylaxis of neonatal sepsis, possibly due to improved INF-γ secretion. Neonatal neutrophils lack INF-γ
- To stimulate hematopoietic progenitor cells to proliferate and differentiate into granulocytes and macrophages and regulate some of their functions at maturity
- To treat chemotherapy-induced neutropenia, myelodysplasia, aplastic anemia, and bone marrow transplant regimens

The administration of GM-CSF may be associated with the development of fever, which is blocked by nonsteroidal anti-inflammatory drugs such as ibuprofen.

3.7 Thermoregulation

Thermoregulation requires intact peripheral mechanisms that balance heat production and loss, and a functioning hypothalamic thermoregulatory center regulating these mechanisms.

3.7.1 Heat Production

Heat production occurs by various mechanisms:

- At rest, as many organs such as brain, muscles, viscera, liver, heart, thyroid, pancreas, and adrenal glands contribute to heat production at the cellular level involving adenosine triphosphate (ATP).
- In the newborn infant, brown fat localized mainly in the neck and scapular area produces heat through nonshivering thermogenesis. This tissue is highly vascularized and contains a large quantity of mitochondria. Fatty acid oxidation in these mitochondria can increase heat production to twofold in response to cold.
- Older children and adults conserve heat by vasoconstriction and generate heat by shivering in response to cold. Blood flow, regulated by the CNS, plays a vital role in distributing heat throughout the body. In a warm environment or when core temperature is elevated, the hypothalamic thermoregulatory center activates efferent fibers of the automatic nervous system to produce vasodilatation. The increased blood flow to the skin causes heat loss from the core through the skin surface to the surroundings in the form of sweating. In colder environments or with decreased core temperature, reduced skin blood flow promotes retention of body heat.

Pathological uncontrollable increase of heat production occurs in malignant hyperthermia (Chap. 2)

3.7.2 Heat Loss

In response to a rise in body temperature, heat is lost from the body via the four physical modalities of radiation, evaporation, convection, and conduction. Failure of heat loss has been incriminated as the cause of infantile heat stroke, which carries a high mortality rate. Heat loss occurs through the following mechanisms:

- In general, 60% of the total heat is lost by radiation, which is the transfer of heat from the skin surface to the external surroundings by mean of electromagnetic waves.
- About one-quarter is lost by evaporation from the skin and lungs, which occurs as water is converted from liquid to gas: 243 kJ (58 kcal) is lost for every 100 ml of water.
- Convection (12% of the heat loss) is the transfer of heat through the movement of air or fluid surrounding the skin surface.
- Conduction (3% of the heat loss) is the heat transfer between two objects in direct contact and at different temperatures. This is the primary mode of heat loss from the core to the surface. A child in the lying position with a large contact surface has a higher heat loss through conduction than in the standing position.

Simultaneously, the hypothalamus stimulates vasodilatation to increase insensible loss (for every 1°C elevation of body temperature, there is a 10% insensible loss) and activates the sweat glands to increase perspiration production.

Physical factors obviously affect the ability to respond to temperature changes. The greater heat loss in the newborn infant is mainly due to a greater surface area compared to that of an older child. Failure of heat loss occurs in anhidrotic ectodermal dysplasia and during anticholinergic drug overdose.

3.7.3 Temperature Regulation at the CNS Level

Fever generation includes the following stages:

- The specific area of the IL-1 action is the pre-optic and anterior hypothalamus, which contains clusters of thermosensitive neurons localized within the rostral wall of the third ventricle. The site is called organum vasculosum laminae terminalis (OVLT), which has emerged as an interface between circulation and brain. The firing rate of these thermosensitive neurons changes according to the temperature of the area's blood supply and the input from the skin and muscular thermoreceptors. Warm-sensitive neurons have firing rates that increase with warming and decrease with cooling, whereas the firing rates of cold-sensitive neurons increase with cooling or decrease with warming.
- IL-1 enters the perivascular space of the OVLT through the fenestrated capillary wall to stimulate cells to produce PGE2, which diffuses into the adjacent pre-optic/hypothalamic region to cause fever.

  The view that the OVLT is the major port of entry for pyrogenic cytokines has recently been challenged [7]. In the endothelial and perivascular cells of the blood–brain barrier (BBB), pyrogenic cytokines are switched to PGE2. These cells probably represent a structure termed *circumventricular organ system* (CVOS), which consists of small clusters of neurons and is adjacent to the BBB. This structure serves as a communication channel between blood and neurons of the hypothalamus. When circulating pyrogenic cytokines are detected by the CVOS, PGE2 is induced [8].
- The ultimate result of these complex mechanisms is an upward shift of the thermostatic set point to a febrile level that signals efferent nerves, especially sympathetic fibers innervating peripheral blood vessels, to initiate heat conservation (vasoconstriction) and heat production (shivering). This is aided by behavioral means aimed also to increase body temperature, such as seeking a warmer environment or covering up with a blanket. The resulting temperature increase continues until body temperature approximates to the temperature of the elevated set point. The cations Na^+ and Ca^{2+} as well as cyclic adenosine monophosphate (camp) may also contribute to the alteration of body temperature, although their exact role is not yet clear. The raised set point is reset back to normal if the concentration of IL-1 falls or if antipyretics are administered, which blocks prostaglandin synthesis. Recently, the peptide angiotensin 11 has been shown to lower body temperature at the final step of fever [9].

Prostaglandin E2 has been found to exert a negative feedback on the release of IL-1, thereby tending to terminate the mechanisms that initially induced the fever. In addition, arginine vasopressin (AVP) acts within the CNS to reduce pyrogen-induced fevers. The normalization of temperature is initiated by vasodilatation and sweating through increased skin blood flow controlled by sympathetic fibers.

3.8 Summary of Fever Induction

The generation of fever involves the following steps:

- Numerous substances from outside the body, exogenous pyrogens, initiate the fever cycle. Endotoxin of Gram-negative bacteria, with their pyrogenic component lipopolysaccaride, is the most potent ExP. Fever is also a common finding in children without obvious evidence of infection, for example, hypersensitivity reaction, autoimmune diseases, and malignancy.
- The ExPs stimulate monocytes, fixed-tissue macrophages, and reticuloendothelial cells to produce and release identical substances, now collectively termed IL-1, which has multiple biological functions essential for the immune response.
- IL-1 acts on the hypothalamic thermoregulatory center through mediators, of which PGE2 is the most important, to raise the thermostatic set point. IL-1 thereby acts as an endogenous pyrogen. The hypothalamic thermoregulatory center accomplishes heat production by inducing shivering and heat conservation through vasoconstriction. At an established degree, fever is regulated (even at a temperature of over 41.0°C) and heat production approximates loss, as in health, though at a higher level of the set point. Therefore fever does not climb up relentlessly.
- In addition to the function as an endogenous pyrogen, IL-1 activates T lymphocytes to produce various factors, such as INF and IL-2, which are vital for immune response. The production of fever simultaneously with lymphocyte activation constitutes the clearest and strongest evidence in favor of the role of fever.

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