Chapter 20 | Fever

Part 2: Cardinal Manifestations and Presentation of Diseases | Part 2 – Cardinal Manifestations & Presentation | DETAILED EDITION

KEY CLINICAL POINTS

1. Fever is defined as a temperature >37.7°C (99th percentile for healthy individuals).
2. Hyperthermia is uncontrolled heat elevation exceeding the body's ability to lose heat; it does not respond to antipyretics.
3. Pyrogenic cytokines (IL-1, IL-6, TNF) induce fever by raising the hypothalamic set point via PGE2 synthesis.
4. Acetaminophen is the preferred antipyretic in children to avoid Reye syndrome risk associated with aspirin.
5. Temperature-pulse dissociation (relative bradycardia) is seen in typhoid fever, brucellosis, and leptospirosis.
6. Anticytokine therapy (anti-TNF, anti-IL-1) blunts the febrile response and increases risk of opportunistic infections.
7. Periodic fevers include malaria (every 3rd or 4th day), Hodgkin disease (Pel-Ebstein pattern), and cyclic neutropenia (every 21 days).
8. Fever increases oxygen consumption by 13% for every 1°C increase over 37°C.

FIGURES IN THIS CHAPTER

1. DEFINITION & OVERVIEW

Fever is a cardinal manifestation of disease. It is an elevation of body temperature that exceeds the normal daily variation and occurs in conjunction with an increase in the hypothalamic set point. Hyperthermia is a distinct condition characterized by an uncontrolled increase in body temperature that exceeds the body's ability to lose heat.

1.1 Normal Body Temperatures

Normal body temperature is maintained by the hypothalamic thermoregulatory center balancing heat production and dissipation.

Table 1 Normal Body Temperature Variations

Parameter	Value / Range
Mean Oral Temperature	36.6°C (95% CI 35.7–37.3°C)

Parameter	Value / Range
Fever Threshold (99th Percentile)	>37.7°C (>99.9°F)
Hyperpyrexia Threshold	>41.5°C (>106.7°F)
Rectal vs Oral Difference	Rectal is generally 0.4°C (0.7°F) higher
Age Effect	Lower by 0.02°C for every 10-year increase
Race Effect	African-American women have temperatures 0.052°C higher than white men
Comorbidity Effect	Cancer: +0.02°C; Hypothyroidism: -0.01°C

1.2 Fever vs. Hyperthermia

It is important to distinguish between fever and hyperthermia since hyperthermia can be rapidly fatal and characteristically does not respond to antipyretics.

1.3 Hyperpyrexia

A fever of >41.5°C (>106.7°F) is called hyperpyrexia. This extraordinarily high fever can develop in patients with severe infections but most commonly occurs in patients with central nervous system (CNS) hemorrhages. In the preantibiotic era, fever due to a variety of infectious diseases rarely exceeded 106°F.

2. EPIDEMIOLOGY

Body temperatures have diurnal and seasonal variation, with low levels at 8 a.m. and during summer and higher levels at 4 p.m. and during winter. After controlling for age, sex, race, vital signs, and comorbidities, an increase in baseline temperature of 0.15°C (or 1 standard deviation) translates into a 0.52% absolute increase in 1-year mortality.

2.1 Measurement Methods

Electronic devices for measuring oral, tympanic membrane, or rectal temperatures are reliable, but the same site should be used consistently to monitor a febrile disease.

2.2 Menstrual Cycle

In women who menstruate, the a.m. temperature is generally lower during the 2 weeks before ovulation; it then rises by ~0.6°C (1°F) with ovulation and stays at that level until menses occur. During the luteal phase, the amplitude of the circadian rhythm remains the same.

3. ETIOLOGY & PATHOPHYSIOLOGY

Fever is a prominent side effect of interferon α therapy. A wide spectrum of bacterial and fungal products induce the release of pyrogenic cytokines. However, fever can be a manifestation of disease in the absence of microbial infection. For example, inflammatory processes such as pericarditis, trauma, stroke, and routine immunizations induce the production of IL-1, TNF, and/or IL-6; individually or in combination, these cytokines trigger the hypothalamus to raise the set point to febrile levels.

3.1 Pyrogens

The term pyrogen (Greek pyro, 'fire') is used to describe any substance that causes fever. Exogenous pyrogens are derived from outside the patient; most are microbial products, microbial toxins, or whole microorganisms (including viruses).

3.2 Pyrogenic Cytokines

Cytokines are small proteins (molecular mass, 10,000–20,000 Da) that regulate immune, inflammatory, and hematopoietic processes. The pyrogenic cytokines include IL-1, IL-6, tumor necrosis factor (TNF), and ciliary neurotropic factor, a member of the IL-6 family. Each pyrogenic cytokine is encoded by a separate gene, and each has been shown to cause fever in laboratory animals and in humans. When injected into humans at low doses (10–100 ng/kg), IL-1 and TNF produce fever; in contrast, for IL-6, a dose of 1–10 μg/kg is required for fever production.

3.3 Elevation of the Hypothalamic Set Point

During fever, levels of prostaglandin E (PGE) are elevated in hypothalamic tissue and the third cerebral ventricle. The concentrations of PGE are highest near the circumventricular vascular organs (organum vasculosum of lamina terminalis)—networks of enlarged capillaries surrounding the hypothalamic regulatory centers. Destruction of these organs reduces the ability of pyrogens to produce fever. Most studies in animals have failed to show, however, that pyrogenic cytokines pass from the circulation into the brain itself. Thus, it appears that both exogenous pyrogens and pyrogenic cytokines interact with the endothelium of these capillaries and that this interaction is the first step in initiating fever—i.e., in raising the set point to febrile levels.

4. CLINICAL FEATURES

A thorough history can help distinguish between broad categories of disease processes that present with fever as a cardinal manifestation. The chronology of events preceding fever, including exposure to other symptomatic individuals or to vectors of disease, should be ascertained.

4.1 History and Physical Examination

Although these circulating cytokines lead to fever by inducing the synthesis of PGE, they also induce PGE in peripheral tissues. The increase in PGE in the periphery accounts for the nonspecific myalgias and arthralgias that often accompany fever. It is thought that some individuals systemic PGE escapes destruction by the lung and gains access to the hypothalamus via the internal carotid. However, it is the elevation of PGE in the brain that starts the process of raising the hypothalamic set point for core temperature.

4.2 Laboratory Tests

The workup should include a complete blood count; a differential count should be performed manually or with an instrument sensitive to the identification of neutrophil juvenile or band forms, toxic granulations, and Döhle bodies, which are suggestive of bacterial infection. Neutropenia may be present with some viral infections. Measurement of circulating cytokines in patients with fever is not helpful since levels of cytokines such as IL-1 and TNF in the circulation often are below the detection limit of the assay or do not coincide with fever. However, in patients with low-grade fevers or with suspected occult disease, the most valuable measurements are the C-reactive protein (CRP) level and the erythrocyte sedimentation rate. These markers of inflammatory processes are particularly helpful in detecting occult disease. Measurement of circulating IL-6, which induces CRP, can be useful. However, whereas IL-6 levels may vary during a febrile disease, CRP levels remain elevated.

4.3 Periodic Fevers

Some infections have characteristic patterns in which febrile episodes are separated by intervals of normal temperature. For example, Plasmodium vivax causes fever every third day, whereas fever occurs every fourth day with Plasmodium malariae. Another relapsing fever is related to Borrelia infection, with days of fever followed by a several-day afebrile period and then a relapse into additional days of fever. In the Pel-Ebstein pattern, fever lasting 3–10 days is followed by afebrile periods of 3–10 days; this pattern can be classic for Hodgkin disease and other lymphomas. In cyclic neutropenia, fevers occur every 21 days and accompany the neutropenia. There are also a number of periodic fever syndromes (e.g., familial Mediterranean fever, TNF receptor–associated periodic syndrome [TRAPS]) that differ in their periodicity, duration of attack, constellation of clinical features, genetic causes, and therapies.

5. DIFFERENTIAL DIAGNOSIS

Understanding these clinical differences can help tailor diagnostic testing to confirm the diagnosis and guide therapy. It is important to distinguish between fever and hyperthermia since hyperthermia can be rapidly fatal and characteristically does not respond to antipyretics.

5.1 Fever vs. Hyperthermia

In an emergency situation, however, making this distinction can be difficult. For example, in systemic sepsis, fever (hyperpyrexia) can be rapid in onset, and temperatures can exceed 40.5°C (104.9°F). Hyperthermia is often diagnosed on the basis of the events immediately preceding the elevation of core temperature—e.g., heat exposure or treatment with drugs that interfere with thermoregulation. In patients with heat stroke syndromes and in those taking drugs that block sweating, the skin is hot but dry, whereas in fever, the skin can be cold as a consequence of vasoconstriction. Antipyretics do not reduce the elevated temperature in hyperthermia, whereas in fever—and even in hyperpyrexia—adequate doses of either aspirin or acetaminophen usually result in some decrease in body temperature.

5.2 Anticytokine Therapy Risks

Patients receiving long-term treatment with anticytokine-based regimens are at increased risk of infection because of lowered host defenses. For example, latent Mycobacterium tuberculosis infection can disseminate in patients receiving anti-TNF therapy. With the increasing use of anticytokines to reduce the activity of IL-1, IL-6, IL-12/23, IL-17, or TNF in patients with Crohn disease, rheumatoid arthritis, or psoriasis, the possibility that these therapies blunt the febrile response should be kept in mind. The blocking of cytokine activity has the distinct clinical drawback of lowering the level of host defenses against both routine bacterial and opportunistic infections such as M. tuberculosis and fungal infections. The use of monoclonal antibodies to reduce IL-17 in psoriasis increases the risk of systemic candidiasis. In nearly all reported cases of infection associated with anticytokine therapy, fever is among the presenting signs. However, the extent to which the febrile response is blunted in these patients remains unknown. Therefore, low-grade fever in patients receiving anticytokine therapies is of considerable concern. The physician should conduct an early and rigorous diagnostic evaluation in these cases. The febrile response is also blunted in patients receiving chronic glucocorticoid therapy or anti-inflammatory agents such as nonsteroidal anti-inflammatory drugs (NSAIDs).

6. INVESTIGATIONS & DIAGNOSIS

The workup should include a complete blood count; a differential count should be performed manually or with an instrument sensitive to the identification of neutrophil juvenile or band forms, toxic granulations, and Döhle bodies, which are suggestive of bacterial infection. Neutropenia may be present with some viral infections. Measurement of circulating cytokines in patients with fever is not helpful since levels of cytokines such as IL-1 and TNF in the circulation often are below the detection limit of the assay or do not coincide with fever. However, in patients with low-grade fevers or with suspected occult disease, the most valuable measurements are the C-reactive protein (CRP) level and the erythrocyte sedimentation rate. These markers of inflammatory processes are particularly helpful in detecting occult disease. Measurement of circulating IL-6, which induces CRP, can be useful. However, whereas IL-6 levels may vary during a febrile disease, CRP levels remain elevated.

6.1 Diagnostic Algorithm

The key events in the production of fever are illustrated in Figure 20-1. The chronology of events preceding fever, including exposure to other symptomatic individuals or to vectors of disease, should be ascertained. Electronic devices for measuring oral, tympanic membrane, or rectal temperatures are reliable, but the same site should be used consistently to monitor a febrile disease.

Table 2 Diagnostic Approach to Fever

Step	Action	Considerations
1	Measure Temperature	Use consistent site (oral, rectal, tympanic). Rectal is 0.4°C higher than oral.
2	Assess Clinical Context	Distinguish fever (set point elevation) from hyperthermia (uncontrolled heat).
3	Laboratory Evaluation	CBC with differential (look for band forms, toxic granulations). CRP and ESR for occult disease.
4	Evaluate for Anticytokine Use	Blunted febrile response may mask infection in patients on anti-TNF, anti-IL-1, etc.
5	Identify Periodic Patterns	Malaria (3rd/4th day), Hodgkin (Pel-Ebstein), Cyclic Neutropenia (21 days).

7. MANAGEMENT & TREATMENT

In deciding whether to treat fever, it is important to remember that fever itself is not an illness: it is an ordinary response to a perturbation of normal host physiology. Most fevers are associated with self-limited infections, such as common viral diseases. The use of antipyretics is not contraindicated in these infections: no significant clinical evidence indicates either that antipyretics delay the resolution of viral or bacterial infections or that fever facilitates recovery from infection or acts as an adjuvant to the immune system. In short, treatment of fever and its symptoms with routine antipyretics does no harm and does not slow the resolution of common viral and bacterial infections. However, in bacterial infections, the withholding of antipyretic therapy can be helpful in evaluating the effectiveness of a particular antibiotic, especially in the absence of positive cultures of the infecting organism, and the routine use of antipyretics can mask an inadequately treated bacterial infection. Withholding antipyretics in some cases may facilitate the diagnosis of an unusual febrile disease.

7.1 Mechanisms of Antipyretic Agents

The reduction of fever by lowering of the elevated hypothalamic set point is a direct function of reduction of the PGE level in the thermoregulatory center. The synthesis of PGE depends on the constitutively expressed enzyme cyclooxygenase. The substrate for cyclooxygenase is arachidonic acid released from the cell membrane, and this release is the rate-limiting step in the synthesis of PGE. Therefore, inhibitors of cyclooxygenase are potent antipyretics. The antipyretic potency of various drugs is directly correlated with the inhibition of brain cyclooxygenase. Acetaminophen is a poor cyclooxygenase inhibitor in peripheral tissue and lacks noteworthy anti-inflammatory activity; in the brain, however, acetaminophen is oxidized by the P450 cytochrome system, and the oxidized form inhibits cyclooxygenase activity. Moreover, in the brain, the inhibition of another enzyme, COX-3, by acetaminophen may account for the antipyretic effect of this agent. However, COX-3 is not found outside the CNS. Oral aspirin and acetaminophen are equally effective in reducing fever in humans. NSAIDs such as ibuprofen and specific inhibitors of COX-2 also are excellent antipyretics. Chronic, high-dose therapy with antipyretics such as aspirin or any NSAID does not reduce normal core body temperature. Thus, PGE appears to play no role in normal thermoregulation.

7.2 Regimens for the Treatment of Fever

The objectives in treating fever are first to reduce the elevated hypothalamic set point and second to facilitate heat loss. Reducing fever with antipyretics also reduces systemic symptoms of headache, myalgias, and arthralgias. Oral aspirin and NSAIDs effectively reduce fever but can adversely affect platelets and the gastrointestinal tract. Therefore, acetaminophen is preferred as an antipyretic. In children, acetaminophen or oral ibuprofen must be used because aspirin increases the risk of Reye syndrome with certain viral infections. If the patient cannot take oral antipyretics, parenteral preparations of NSAIDs and rectal suppositories of various antipyretics can be used. Treatment of fever in some patients is highly recommended.

8. PROGNOSIS & COMPLICATIONS

After controlling for age, sex, race, vital signs, and comorbidities, an increase in baseline temperature of 0.15°C (or 1 standard deviation) translates into a 0.52% absolute increase in 1-year mortality. Fever increases the demand for oxygen (i.e., for every increase of 1°C over 37°C, there is a 13% increase in oxygen consumption) and can lead to hypothermia in patients with septic shock.

8.1 Mortality Risk

An increase in baseline temperature of 0.15°C (or 1 standard deviation) translates into a 0.52% absolute increase in 1-year mortality.

8.2 Anticytokine Therapy Complications

Patients receiving long-term treatment with anticytokine-based regimens are at increased risk of infection because of lowered host defenses. For example, latent Mycobacterium tuberculosis infection can disseminate in patients receiving anti-TNF therapy. With the increasing use of anticytokines to reduce the activity of IL-1, IL-6, IL-12/23, IL-17, or TNF in patients with Crohn disease, rheumatoid arthritis, or psoriasis, the possibility that these therapies blunt the febrile response should be kept in mind. The blocking of cytokine activity has the distinct clinical drawback of lowering the level of host defenses against both routine bacterial and opportunistic infections such as M. tuberculosis and fungal infections. The use of monoclonal antibodies to reduce IL-17 in psoriasis increases the risk of systemic candidiasis. In nearly all reported cases of infection associated with anticytokine therapy, fever is among the presenting signs. However, the extent to which the febrile response is blunted in these patients remains unknown. Therefore, low-grade fever in patients receiving anticytokine therapies is of considerable concern. The physician should conduct an early and rigorous diagnostic evaluation in these cases.

9. SPECIAL CONSIDERATIONS

In newborns, elderly patients, patients with chronic hepatic or renal failure, and patients taking glucocorticoids or being treated with an anticytokine may have active disease in the absence of fever because of a blunted febrile response. Temperature–pulse dissociation (relative bradycardia) occurs in typhoid fever, brucellosis, leptospirosis, some drug-induced fevers, and factitious fever.

9.1 Blunted Febrile Response

In newborns, elderly patients, patients with chronic hepatic or renal failure, and patients taking glucocorticoids or being treated with an anticytokine may have active disease in the absence of fever because of a blunted febrile response.

9.2 Pediatric Considerations

In children, acetaminophen or oral ibuprofen must be used because aspirin increases the risk of Reye syndrome with certain viral infections.

10. KEY PEARLS & CLINICAL TRAPS

Fever itself is not an illness: it is an ordinary response to a perturbation of normal host physiology. Most fevers are associated with self-limited infections, such as common viral diseases. The use of antipyretics is not contraindicated in these infections: no significant clinical evidence indicates either that antipyretics delay the resolution of viral or bacterial infections or that fever facilitates recovery from infection or acts as an adjuvant to the immune system. In short, treatment of fever and its symptoms with routine antipyretics does no harm and does not slow the resolution of common viral and bacterial infections. However, in bacterial infections, the withholding of antipyretic therapy can be helpful in evaluating the effectiveness of a particular antibiotic, especially in the absence of positive cultures of the infecting organism, and the routine use of antipyretics can mask an inadequately treated bacterial infection. Withholding antipyretics in some cases may facilitate the diagnosis of an unusual febrile disease.

10.1 Clinical Pearls

- Fever is an elevation of body temperature that exceeds the normal daily variation and occurs in conjunction with an increase in the hypothalamic set point.
- Hyperthermia is characterized by an uncontrolled increase in body temperature that exceeds the body's ability to lose heat.
- Antipyretics do not reduce the elevated temperature in hyperthermia, whereas in fever—and even in hyperpyrexia—adequate doses of either aspirin or acetaminophen usually result in some decrease in body temperature.
- In patients with heat stroke syndromes and in those taking drugs that block sweating, the skin is hot but dry, whereas in fever, the skin can be cold as a consequence of vasoconstriction.
- Temperature–pulse dissociation (relative bradycardia) occurs in typhoid fever, brucellosis, leptospirosis, some drug-induced fevers, and factitious fever.
- In newborns, elderly patients, patients with chronic hepatic or renal failure, and patients taking glucocorticoids or being treated with an anticytokine may have active disease in the absence of fever because of a blunted febrile response.
- An increase in baseline temperature of 0.15°C (or 1 standard deviation) translates into a 0.52% absolute increase in 1-year mortality.

and ciliary neurotropic factor, a member of the IL-6 family. Fever is a prominent side effect of interferon α therapy. Each pyrogenic cytokine is encoded by a separate gene, and each has been shown to cause fever in laboratory animals and in humans. When injected into humans at low doses (10–100 ng/kg), IL-1 and TNF produce fever; in contrast, for IL-6, a dose of 1–10 μg/kg is required for fever production.

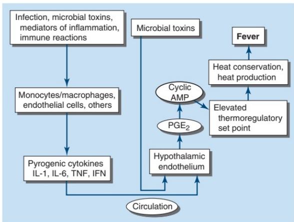
A wide spectrum of bacterial and fungal products induce the synthesis and release of pyrogenic cytokines. However, fever can be a manifestation of disease in the absence of microbial infection. For example, inflammatory processes such as pericarditis, trauma, stroke, and routine immunizations induce the production of IL-1, TNF, and/or IL-6; individually or in combination, these cytokines trigger the hypothalamus to raise the set point to febrile levels.

ELEVATION OF THE HYPOTHALAMIC SET POINT BY CYTOKINES

During fever, levels of prostaglandin E_2 (PGE_2) are elevated in hypothalamic tissue and the third cerebral ventricle. The concentrations of PGE_2 are highest near the circumventricular vascular organs (organum vasculosum of lamina terminalis)—networks of enlarged capillaries surrounding the hypothalamic regulatory centers. Destruction of these organs reduces the ability of pyrogens to produce fever. Most studies in animals have failed to show, however, that pyrogenic cytokines pass from the circulation into the brain itself. Thus, it appears that both exogenous pyrogens and pyrogenic cytokines interact with the endothelium of these capillaries and that this interaction is the first step in initiating fever—i.e., in raising the set point to febrile levels.

The key events in the production of fever are illustrated in Fig. 20-1. Myeloid and endothelial cells are the primary cell types that produce pyrogenic cytokines. Pyrogenic cytokines such as IL-1, IL-6, and TNF are released from these cells and enter the systemic circulation. Although these circulating cytokines lead to fever by inducing the synthesis of PGE_2, they also induce PGE_2 in peripheral tissues. The increase in PGE_2 in the periphery accounts for the nonspecific myalgias and arthralgias that often accompany fever. It is thought that some systemic PGE_2 escapes destruction by the lung and gains access to the hypothalamus via the internal carotid. However, it is the elevation of PGE_2 in the brain that starts the process of raising the hypothalamic set point for core temperature.

There are four receptors for PGE_2, and each signals the cell in different ways. Of the four receptors, the third (EP-3) is essential for fever: when the gene for this receptor is deleted in mice, no fever follows the injection of IL-1 or endotoxin. Deletion of the other PGE_2 receptor genes leaves the fever mechanism intact. Although PGE_2 is essential for fever, it is not a neurotransmitter. Rather, the release of PGE_2 from the brain side of the hypothalamic endothelium triggers the PGE_2 receptor on glial cells, and this stimulation results in the rapid release of cyclic adenosine 5′-monophosphate (cAMP), which is a neurotransmitter. As shown in Fig. 20-1, the release of cAMP from glial cells activates neuronal endings from the thermoregulatory center that extend into the area. The elevation of cAMP is thought to account for changes in the hypothalamic set point either directly or indirectly (by inducing the release of neurotransmitters). Distinct receptors for microbial products are located on the hypothalamic endothelium. These receptors are called *Toll-like receptors* and are similar in many ways to IL-1 receptors. IL-1 receptors and Toll-like receptors share the same signal-transducing mechanism. Thus, the direct activation of Toll-like receptors or IL-1 receptors results in PGE_2 production and fever.



PRODUCTION OF CYTOKINES IN THE CNS

Cytokines produced in the brain may account for the hyperpyrexia of CNS hemorrhage, trauma, or infection. Viral infections of the CNS induce microglial and possibly neuronal production of IL-1, TNF, and IL-6. In experimental animals, the concentration of a cytokine required to cause fever is several orders of magnitude lower with direct injection into the brain substance or brain ventricles than with systemic injection. Therefore, cytokines produced in the CNS can raise the hypothalamic set point, bypassing the circumventricular organs. CNS cytokines likely account for the hyperpyrexia of CNS hemorrhage, trauma, or infection.

APPROACH TO THE PATIENT

Fever

HISTORY AND PHYSICAL EXAMINATION

There are a range of disease processes that present with fever as a cardinal manifestation, and a thorough history can help distinguish between these broad categories (Table 20-1). The chronology of events preceding fever, including exposure to other symptomatic individuals or to vectors of disease, should be ascertained. Electronic devices for measuring oral, tympanic membrane, or rectal temperatures are reliable, but the same site should be used consistently to monitor a febrile disease. Moreover, physicians should be aware that newborns, elderly patients, patients with chronic hepatic or renal failure, and patients taking glucocorticoids or being treated with an anticytokine may have active disease in the absence of fever because of a blunted febrile response.

LABORATORY TESTS

The workup should include a complete blood count; a differential count should be performed manually or with an instrument sensitive to the identification of neutrophil juvenile or band forms, toxic granulations, and Döhle bodies, which are suggestive of bacterial infection. Neutropenia may be present with some viral infections.

Measurement of circulating cytokines in patients with fever is not helpful since levels of cytokines such as IL-1 and TNF in the circulation often are below the detection limit of the assay or do not coincide with fever. However, in patients with low-grade fevers or with suspected occult disease, the most valuable measurements are the C-reactive protein (CRP) level and the erythrocyte sedimentation rate. These markers of inflammatory processes are particularly helpful in detecting occult disease. Measurement of circulating IL-6, which induces CRP, can be useful. However, whereas IL-6

TABLE 20-1 Disease Categories That Present with Fever as a Cardinal Sign
Infectious diseases
Autoimmune and noninfectious inflammatory disorders
Cancer
Medication related (e.g., vaccines, drug fever)

Harrison's 22e · Figure 1

FIGURE 20-1 Chronology of events required for the induction of fever. AMP, adenosine 5′-monophosphate; IFN, interferon; IL, interleukin; PGE 2 , prostaglandin E; TNF, tumor necrosis factor. 2 — Figure 20-1: Chronology of events required for the induction of fever. The diagram illustrates the pathway from pyrogenic cytokines (IL-1, IL-6, TNF) binding to receptors on hypothalamic endothelium, leading to prostaglandin E2 (PGE2) synthesis, which elevates the hypothalamic set point via EP-3 receptors, resulting in vasoconstriction, shivering, and increased heat production.