

variation appears to be fixed in early childhood; in contrast, elderly individuals can exhibit a reduced ability to develop fever, with only a modest fever even in severe infections.

Rectal temperatures are generally 0.4°C (0.7°F) higher than oral readings. The lower oral readings are probably attributable to mouth breathing, which is a factor in patients with respiratory infections and rapid breathing. Lower-esophageal temperatures closely reflect core temperature. Tympanic membrane thermometers measure radiant heat from the tympanic membrane and nearby ear canal and display that absolute value (*unadjusted mode*) or a value automatically calculated from the absolute reading on the basis of nomograms relating the radiant temperature measured to actual core temperatures obtained in clinical studies (*adjusted mode*). These measurements, although convenient, may be more variable than directly determined oral or rectal values. Studies in adults show that readings are lower with unadjusted-mode than with adjusted-mode tympanic membrane thermometers and that unadjusted-mode tympanic membrane values are 0.8°C (1.6°F) lower than rectal temperatures.

In women who menstruate, the A.M. temperature is generally lower in the 2 weeks before ovulation; it then rises by ~0.6°C (1°F) with ovulation and remains at that level until menses occur. Body temperature can be elevated in the postprandial state. Pregnancy and endocrinologic dysfunction also affect body temperature.

FEVER VERSUS HYPERTHERMIA

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* (e.g., from 37°C to 39°C). This shift of the set point from “normothermic” to febrile levels very much resembles the resetting of the home thermostat to a higher level in order to raise the ambient temperature in a room. Once the hypothalamic set point is raised, neurons in the vasomotor center are activated and vasoconstriction commences. The individual first notices vasoconstriction in the hands and feet. Shunting of blood away from the periphery to the internal organs essentially decreases heat loss from the skin, and the person feels cold. For most fevers, body temperature increases by 1–2°C. Shivering, which increases heat production from the muscles, may begin at this time; however, shivering is not required if heat conservation mechanisms raise blood temperature sufficiently. Nonshivering heat production from the liver also contributes to increasing core temperature. Behavioral adjustments (e.g., putting on more clothing or bedding) help raise body temperature by decreasing heat loss.

The processes of heat conservation (vasoconstriction) and heat production (shivering and increased nonshivering thermogenesis) continue until the temperature of the blood bathing the hypothalamic neurons matches the new thermostat setting. Once that point is reached, the hypothalamus maintains the temperature at the febrile level by the same mechanisms of heat balance that function in the afebrile state. When the hypothalamic set point is again reset downward (in response to either a reduction in the concentration of pyrogens or the use of antipyretics), the processes of heat loss through vasodilation and sweating are initiated. Loss of heat by sweating and vasodilation continues until the blood temperature at the hypothalamic level matches the lower setting. Behavioral changes (e.g., removal of clothing) facilitate heat loss.

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, and there has been speculation that this natural “thermal ceiling” is mediated by neuropeptides functioning as central antipyretics.

In rare cases, the hypothalamic set point is elevated as a result of local trauma, hemorrhage, tumor, or intrinsic hypothalamic malfunction. The term *hypothalamic fever* is sometimes used to describe elevated temperature caused by abnormal hypothalamic function. However, most patients with hypothalamic damage have *subnormal*, not *supra-normal*, body temperatures.

Although most patients with elevated body temperature have fever, there are circumstances in which elevated temperature represents not fever but *hyperthermia* (*heat stroke*). Hyperthermia is characterized by an uncontrolled increase in body temperature that exceeds the body’s ability to lose heat. The setting of the hypothalamic thermoregulatory center is unchanged. In contrast to fever in infections, hyperthermia does not involve pyrogenic molecules. Exogenous heat exposure and endogenous heat production are two mechanisms by which hyperthermia can result in dangerously high internal temperatures. Excessive heat production can easily cause hyperthermia despite physiologic and behavioral control of body temperature. For example, work or exercise in hot environments can produce heat faster than peripheral mechanisms can lose it. [For a detailed discussion of hyperthermia, see Chap. 479e.](#)

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

PATHOGENESIS OF FEVER

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). The classic example of an exogenous pyrogen is the lipopolysaccharide (endotoxin) produced by all gram-negative bacteria. Pyrogenic products of gram-positive organisms include the enterotoxins of *Staphylococcus aureus* and the groups A and B streptococcal toxins, also called *superantigens*. One staphylococcal toxin of clinical importance is that associated with isolates of *S. aureus* from patients with toxic shock syndrome. These products of staphylococci and streptococci cause fever in experimental animals when injected intravenously at concentrations of 1–10 µg/kg. Endotoxin is a highly pyrogenic molecule in humans: when injected intravenously into volunteers, a dose of 2–3 ng/kg produces fever, leukocytosis, acute-phase proteins, and generalized symptoms of malaise.

PYROGENIC CYTOKINES

Cytokines are small proteins (molecular mass, 10,000–20,000 Da) that regulate immune, inflammatory, and hematopoietic processes. For example, the elevated leukocytosis seen in several infections with an absolute neutrophilia is attributable to the cytokines interleukin (IL) 1 and IL-6. Some cytokines also cause fever; formerly referred to as *endogenous pyrogens*, they are now called *pyrogenic cytokines*. The pyrogenic cytokines include IL-1, IL-6, tumor necrosis factor (TNF), and ciliary neurotropic factor, a member of the IL-6 family. Interferons (IFNs), particularly IFN-α, also are pyrogenic cytokines; fever is a prominent side effect of IFN-α used in the treatment of hepatitis. 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, trauma, tissue necrosis, and antigen-antibody complexes induce the production of IL-1, TNF,