

FIGURE 58-5. Thermoeffector responses. The hypothalamic drive on the x-axis is the output of the “controller” in Fig. 58-4.

Equation 58-8

$$\text{Thermoeffector Response} = 0.9 \alpha (T_{\text{core}} - 37.0^{\circ}\text{C}) + 0.1 \alpha (\bar{T}_{\text{skin}} - 34.0^{\circ}\text{C})$$

The proportional-control model is an oversimplification. As shown in Figure 58-5, skin temperature and other factors can modulate the effector response (i.e., sweating rate) to changes in core temperature (i.e., hypothalamic drive). Under normal conditions, the response increases linearly with an increase in hypothalamic drive. Increasing mean skin temperature has two effects: (1) shifting the threshold downward, and (2) increasing the sensitivity (i.e., slope) of the response. Training produces similar effects in an athlete—increasing heat loss for a given hypothalamic drive. On the other hand, lowering mean skin temperature shifts the threshold upward and decreases the sensitivity (i.e., slope). Dehydration, which limits the ability to sweat, has similar effects.

HYPERTHERMIA, HYPOTHERMIA, AND FEVER

Exercise Increases Temperature, Which Stimulates Sweating and Gradually Brings Heat Dissipation Into Balance With Heat Production—But at the Cost of a Persisting Hyperthermia of Exercise

At the onset of muscular exercise, the rate of heat production increases in proportion to the exercise intensity and exceeds the current rate of heat dissipation, causing heat storage and a rise in core temperature (Fig. 58-6). Hypothalamic thermoreceptors sense this increase in core temperature. The hypothalamic integrator compares this

temperature signal with a reference signal, detects an error between the two, and directs neural output that activates heat dissipation (see Fig. 58-4). As a result, skin blood flow and sweating increase as core temperature rises, promoting an increase in the rate of heat transfer from core to environment and slowing the rate of temperature rise. At some point, the rising rate of heat dissipation equals the rate of heat production and the rate of heat storage falls to zero. However, the now-elevated steady-state core temperature persists.

The steady-state core temperature during exercise is not “regulated” at the elevated level; rather, the hyperthermia of exercise is the consequence of the initial imbalance between rate of heat production and dissipation. This imbalance is unavoidable because temperature must increase to provide the error signal that culminates in increased heat dissipation and because the response is not instantaneous. In Figure 58-6, metabolic heat production rises rapidly to its maximal level. However, evaporative heat loss increases only after a delay and then rises slowly to its maximal level. Physical training (see Fig. 58-5) reduces the hyperthermia of exercise by reducing the threshold for sweating (so that sweating will begin earlier) and increasing sweating sensitivity (so that a given hypothalamic drive produces more sweating), thus providing a greater margin of safety between operating and limiting temperatures for exercise. To the extent that training enhances sweat-gland function (evaporative heat loss), one reduces reliance on cutaneous circulation (convective heat loss), thus preserving blood flow for perfusion of muscle.

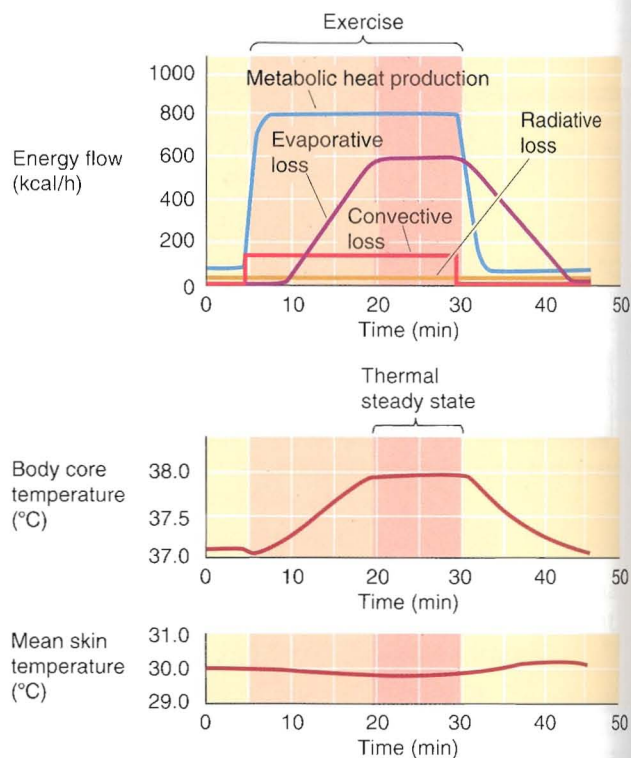


FIGURE 58-6. Whole-body heat balance during exercise.

The relative dehydration caused by continuous water losses during prolonged exercise elevates the temperature threshold for sweating and reduces the sensitivity (see Fig. 58–5). The result is a higher core temperature during exercise

Progressive Hyperthermia and Hypothermia Occur When the Heat-Transfer Potential of the Environment Overwhelms the Body's Regulatory Capacity

Although the body's temperature-regulating machinery is impressive, its capabilities are not limitless. Any factor that causes sufficiently large shifts—either positive or negative—in the rate of heat storage (Equation 58–6) could result in progressive hyper- or hypothermia (Equation 58–7). Because humans must operate within a fairly narrow core-temperature range, such temperature changes could become life-threatening.

The most common environmental condition that results in excessive **hyperthermia** is prolonged exposure to heat and high ambient humidity, particularly when accompanied by physical activity (i.e., elevated heat-production rate). The ability to dissipate heat by *radiation* falls as the radiant temperature of nearby objects increases (Equation 58–3), and the ability to dissipate heat by *convection* falls as ambient temperature increases (Equation 58–4). When ambient temperature reaches the mid-30s (°C), evaporation becomes the only effective avenue for heat dissipation. However, high ambient humidity reduces the skin-to-environment gradient for water vapor pressure, reducing *evaporation* (Equation 58–5). The combined reduction of heat loss by these three pathways can markedly increase the rate of heat storage (Equation 58–6), causing progressive hyperthermia.

It is uncommon for radiative or convective heat gain to cause hyperthermia under conditions of low ambient humidity, because the body has a high capacity for dissipating the absorbed heat by evaporation. Radiative heat gain can be excessively high during full exposure to the desert sun or during exposure to heat sources such as large furnaces. The most obvious protections against radiative hyperthermia are avoiding radiant sources (e.g., sitting in the shade) or covering the skin with loose clothing. The latter screens the radiation while allowing air movement underneath the clothing and maintaining evaporative and convective losses.

The most common environmental condition causing excessive **hypothermia** is prolonged immersion in cold water. Water has a specific heat per unit volume that is approximately 4000 times that of air and a thermal conductivity that is approximately 25 times that of air. Both contribute to a convective heat-transfer coefficient ($h_{\text{convective}}$ in Equation 58–4) that is approximately 100-fold greater in water than it is in air. The $h_{\text{convective}}$ is approximately 200 kcal/(m²h°C) at rest in still water but approximately 500 kcal/(m²h°C) while swimming. The body's physiological defenses against hypothermia include peripheral vasoconstriction (increasing insulation) and shivering (increasing heat production), but even these will

not prevent hypothermia during prolonged exposure because of water's high thermal conductivity. A thick layer of insulating fat retards heat loss to the water and postpones or even prevents hypothermia during prolonged exposures. Endurance swimmers use this knowledge to protect themselves, as they apply a thick layer of grease to the skin surface prior to an event. Herman Melville noted this principle nearly 150 years ago, when he referred to the low thermal conductivity of fat:

For the whale is indeed wrapt up in his blubber as in a real blanket. It is by reason of this cozy blanketing that the whale is enabled to keep himself comfortable in all seas. this great monster, to whom corporeal warmth is as indispensable as it is to man.

— Moby Dick

Like blubber, clothing adds insulation between skin and environment, thus reducing heat loss during exposure to the cold. The more skin one covers, the more one reduces the surface area for direct heat loss from skin to environment by convection and radiation. Adding layers of clothing increases the resistance of heat flow by trapping air, which is an excellent insulator. During heat exposure, the major avenue for heat loss is evaporation of sweat. Because evaporation also depends on the surface area available, the amount of clothing should be minimized. Wetting the clothing increases the rate of heat loss from the skin because water is a better conductor than air is. Water also can evaporate from the clothing surface, removing heat from the outer layers and increasing the temperature gradient (and rate of heat loss) from skin to clothing.

HEAT STROKE

As body core temperature rises, excessive cutaneous vasodilation can lead to a fall in arterial pressure (p. 579) and, therefore, to a decrease in brain perfusion. As core temperature approaches 41°C, confusion and, ultimately, loss of consciousness occur. Excessive hyperthermia (> 41°C) leads to the clinical condition known as **heat stroke**. High temperature can cause fibrinolysis and consumption of clotting factors and thus disseminated intravascular coagulation (DIC), which results in uncontrolled vascular thrombosis and hemorrhage. Heat-induced damage to the cell membranes of skeletal and myocardial muscle leads to rhabdomyolysis (in which disrupted muscle cells release their intracellular contents, including myoglobin, into the circulation) and myocardial necrosis. Cell damage may also cause acute hepatic insufficiency and pancreatitis. Renal function, already compromised by low renal blood flow, may be further disrupted by the high plasma levels of myoglobin. Ultimately, the central nervous system is affected by the combination of high brain temperature, DIC, and metabolic disturbances.

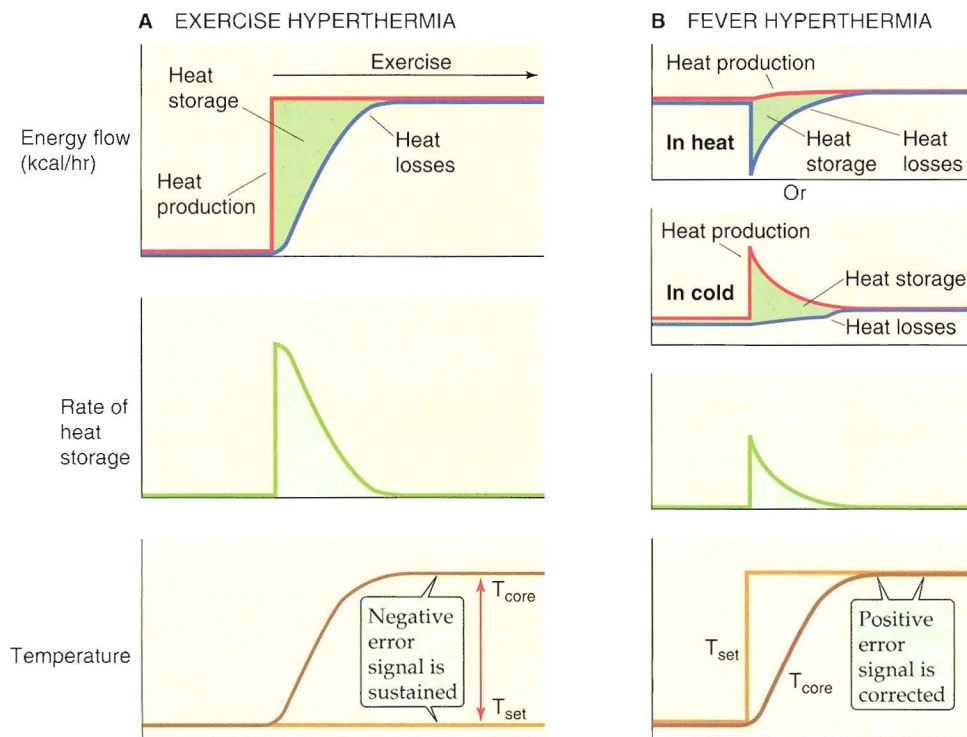


FIGURE 58-7. Exercise hyperthermia versus fever. A, The top panel shows how, during exercise, heat production temporarily exceeds heat loss, resulting in net heat storage. The middle panel shows that the rate of heat storage is highest initially and falls to zero in the new steady state. Finally, the bottom panel shows that as body core temperature rises away from the set point, the error signal gradually increases. In the new steady state, the error signal is maximal and sustained. B, The top pair of panels show how, during fever, net heat storage can occur because of either reduced heat loss or increased heat production. The third panel shows that, as in exercise, the rate of heat storage is highest initially. The bottom panel shows that as body-core temperature rises, it approaches the new elevated set point. Thus, the error signal is initially maximal and gradually decreases to zero in the new steady state.

Fever Differs From Other Types of Hyperthermia in that it Represents an Increase in the Set Point for Temperature Regulation

Fever is a *regulated* elevation of core temperature due to effects associated with infection or disease. Fever is caused by the action of circulating cytokines called **pyrogens**, which are low-molecular-weight polypeptides produced by cells of the immune system. As for the hyperthermia of exercise, fever begins when heat production temporarily exceeds heat dissipation. However, fever differs from other hyperthermias in that the hypothalamus actively regulates core temperature to an elevated set point.

Figure 58-7 illustrates the basic differences between the events leading to exercise hyperthermia and those leading to a fever. During the genesis of exercise hyperthermia (see Fig. 58-7A), the rate of heat production increases above the rate of heat dissipation for a period, causing net heat storage. Moreover, the temperature set point (T_{set}) is unchanged, and thus the error signal gradually increases to a new, sustained level. During the genesis of a fever (see Fig. 58-7B), T_{set} suddenly increases to a value that is above the normal temperature, so that the integrator “sees” the normal temperature as being below the new T_{set} . The fever is an appropriate response to this condition and develops as the heat-loss rate from the body falls or the heat-production rate rises until such time as core temperature increases to the new “regulated” level. Thus, the error signal is initially large but becomes smaller as the fever develops. In the new steady state, core temperature remains elevated until the signals responsible for the fever (i.e., pyrogens) subside and T_{set} returns to normal.

The subjective assessments of thermal comfort support this description. During exercise, one perceives the rise in core temperature as body heating and may choose to remove clothing to cool the body. During the onset of a fever, however, the individual feels cold and may choose to put on additional clothing and warm the body. If fever strikes when the patient is in a warm environment in which the cutaneous vessels are dilated (see Fig. 58-7B, top panel), the response to the T_{set} increase is to vasoconstrict, which decreases heat loss. On the other hand, if the patient is in a cold environment in which the cutaneous vessels are already constricted (see Fig. 58-7B, second panel), the response is to shiver.

Figure 58-8 summarizes the responses to fever-producing stimuli. Macrophages and, to a lesser extent, lymphocytes release cytokines into the circulation in response to a variety of infectious and inflammatory stimuli. Cytokines, the messenger molecules of the immune system, are a diverse group of proteins that are involved in numerous tasks in the host-defense response. The first is the *immune response* to foreign substances including stimulation of T-lymphocyte proliferation, natural killer cells, and antibody production. The second is the *acute-phase response* to foreign substances, a diffuse collection of non-specific host reactions to infection or trauma. Finally, cytokines may act as endogenous pyrogens (Table 58-2). However, no one cytokine, administered experimentally, can fully mimic the temperature increase that occurs during fever. Fever production may occur through a cascade that is initiated when interleukin ($IL-1\beta$), for example, interacts with the endothelial cells in a leaky portion of the blood-brain barrier (p. 409) located in the capillary bed of the *organum vasculosum laminae terminalis* (OVLT). The OVLT is highly vascular tissue that lies in the wall of the third ventricle (above the optic chiasm) in the brain.

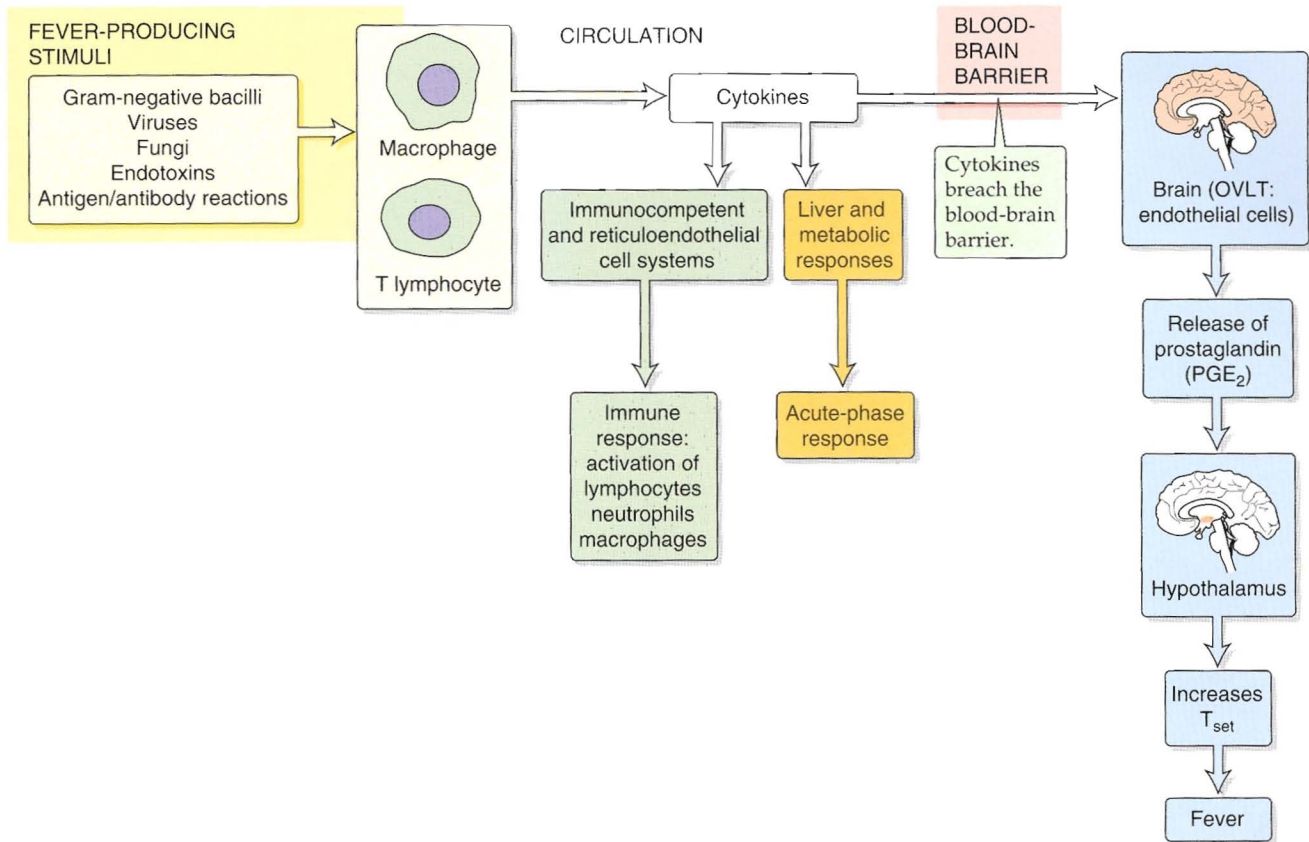


FIGURE 58-8. Host-defense response

TABLE 58-2

ENDOGENOUS PYROGENS	
PYROGEN	SYMBOL
Interleukin-1 α	IL-1 α
Interleukin-1 β	IL-1 β
Interleukin-6	IL-6
Interleukin-8	IL-8
Tumor necrosis factor α	TNF- α
Tumor necrosis factor β	TNF- β
Macrophage inflammatory protein 1 α	MIP-1 α
Macrophage inflammatory protein 1 β	MIP-1 β
Interferon- α	INF- α
Interferon- β	INF- β
Interferon- γ	INF- γ

IL-1 β triggers endothelial cells within the OVLT to release prostaglandin E₂ (p. 104), which then diffuses into the adjacent hypothalamus and—in a manner not yet understood—elevates T_{set} and initiates the febrile response.

The value of fever in fighting infection is still debated. A popular hypothesis is that the elevated temperature enhances the host's response to infection. This view is supported by the *in vitro* observation that the rate of T-lymphocyte proliferation in response to interleukins is many-fold higher at 39°C than it is at 37°C.

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