**Fever and Host Responses**

Steven P. Shelov

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# Fever and Host Responses

**Why Are Fever Temperatures Over 106°F Rare?** Dubois EF. *Am J Med Sci.* 1949;217:361
**Fever Revisited.** Kluger MJ. *Pediatrics.* 1992;90:846
**Impact of Temperature Elevation on Immunologic Defenses.** Roberts NJ, Jr. *Rev Infect Dis.* 1991;13:462
**Hyperthermia.** Simon HB. *N Engl J Med.* 1993;329:483

Even though fever, as part of the inflammatory response, is only a sign of an underlying pathologic stress, we seem to have the need to treat it with a drug or a sponge, as if it were the noxious culprit itself. In contrast to hyperthermia, fever rarely poses any threat to a child's well-being; in fact, it has been argued that as an energy-expensive process, it is not likely to have weathered evolution without conferring some survival benefit. Because fever is the most frequent signal of illness in children, serving as the chief complaint for as many as one third of all pediatric office visits, we do well to understand fever as a phenomenon distinct from the illnesses that cause it.

Not only is there confusion about what fever means physiologically, but it is not always clear whether a given temperature really represents a fever. As expected with any physiologic parameter, there is no single normal value to serve as the gold standard for body temperature. Rather, a range of normal values takes into account variations from person to person, fluctuations that reflect both a circadian pattern and age-related differences, and disparities that depend on the method and site of temperature measurement.

Young children tend to have higher normal body temperatures than do older children or adults, yet infants in their first month or two of life are less likely than older children to develop fever with an infectious illness. Normally, body temperature is higher in the late afternoon and early evening than it is late at night or early in the morning, with a swing of as much as 1.7°C (3°F). Probably the temperature cited most frequently as defining fever is 38°C (100.4°F) measured rectally. However, the variables that affect a particular person's body temperature make any specific number used to define fever arbitrary.

Physiologically, fever is a regulated elevation of body temperature, mediated by the anterior hypothalamus, in response to any insult that stimulates the body's inflammatory defenses. Like a thermostat, the hypothalamic set-point controls the temperature the body tries to maintain. Some provocation, most commonly in children a viral infection, induces macrophages to release low-molecular weight proteins called cytokines, such as interleukin-1 and -6 and probably tumor necrosis factor, that function as endogenous pyrogens. They circulate to the anterior hypothalamus, where they increase local levels of prostaglandin $E_2$ and produce a rise in the set-point. With the body's thermostat now "up-regulated," several mechanisms bring the core temperature, defined as the temperature of blood within the pulmonary artery, up to the new set-point. Because core temperature, even as it begins to elevate, is lower than the thermostat setting, a person developing fever feels chilled. The body's physiologic response is to generate more internal heat, setting skeletal muscles to shivering and stimulating cellular metabolism, while minimizing heat losses to the environment by vasoconstricting the skin and turning off sweat glands. The first strategy is analogous to heating up the furnace and the second to closing the windows.

Hyperthermia is an unregulated rise in core temperature to a level above the hypothalamic set-point, either from overproduction of heat (thyroid storm), a reduced ability to dissipate heat (a bundled-up baby), or a combination of the two, as with heat stroke from overexertion on a hot and humid day. The body's response to hyperthermia is the opposite of its response when a fever is induced. Instead of an initial chill, there is an intense flushing as blood vessels in the skin vasodilate and sweat glands activate in an attempt to lose as much heat as possible to the outside. The furnace is burning out of control; the only strategy is to try to open the windows wide.

Although hyperthermia may raise body temperature to dangerous, even deadly, heights, fever appears to be a homeostatic process, physiologically regulated within benign limits. Dubois first noted how unusual it was even for patients who had untreated serious infections to have fever exceeding 41.1°C (106°F). Reports based on large numbers of children presenting to emergency departments consistently have found that in only 0.05% of visits did the child have a temperature of 41.1°C or higher. Although data in the pediatric literature conflict about whether a temperature greater than 41.1°C, frequently termed hyperpyrexia, is a marker of particular risk for serious underlying infection, no study suggests that, except in the extraordinarily rare event of fever exceeding 41.7°C (107°F), the elevated temperature itself poses a threat to an otherwise healthy child. In fact, a child who has a temperature greater than 41.1°C is likely to have an element of hyperthermia, like dehydration, in addition to fever. Evidence is accumulating that as an intrinsic feature of the febrile response, the body releases endogenous cryogens, peptides that counterbalance pyrogens and modulate how high the hypothalamus sets its thermostat. Vasopressin and melanocyte-stimulating hormone as well as some of the cytokines that also may act as pyrogens appear to play a role in limiting how high a fever may climb.

As a centrally regulated response to an inflammatory insult, fever may serve as a helpful component of the body's acute phase reaction. A growing number of studies demonstrate that fever is an adaptive response widely present in the animal kingdom among both cold-blooded and warm-blooded species. When infected, at least some species of fish and lizards move to a warmer part of their environment, thus raising their body temperatures. This behaviorally induced fever has demonstrable survival benefit, which can be negated with antipyretic agents that lower temperature and increase mortality. Fever can retard the growth and reproduction of many pathogenic microorganisms, both bacterial and viral, and it appears to lower the amount of iron available to invading bacteria, for which many have an increased

requirement at higher temperatures. Among its other effects on human physiology, fever enhances neutrophil migration and production of superoxides; it promotes T-cell proliferation and increases the release and activity of interferon. Interestingly, some of fever's apparently beneficial stimulation of immunologic function may be reversed at very high temperatures, in the hyperpyretic range.

Unfortunately, no conclusive experimental information is available to prove that fever benefits humans clinically in the course of an infection, and some data suggest that at least within the context of endotoxemia, the metabolic cost of fever may contribute to mortality. As a stimulant of immunologic activity, fever may enhance protection against future illness following re-exposure to an infecting pathogen. Certainly in a teleologic sense, its metabolic cost argues for fever generally playing some protective role in the infected host. A process that results in a 7% to 10% increase in energy expenditure for every 1°C rise in temperature is not likely to have persisted so widely in nature among invertebrates, fish, amphibians, and reptiles, as well as birds and mammals, for so many millions of years without conferring some survival advantage.

*Henry M. Adam, MD*
*Editor, In Brief*

**Comment:** In this extremely content-rich Brief there are a number of different explanations for why some elevation in temperature may contribute to the body's improved immune response to an infectious agent. The pediatrician is in the best position to pass this information on to the parent, especially the anxious parent who worries about the effect of fever on his or her child. Perhaps we can make a real dent in the "fever phobia" that so often pervades those late night phone calls. Every little bit helps!

*Steven P. Shelov, MD*
*Professor of Pediatrics*
*Montefiore Medical Center*
*Bronx, NY*

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