

# Fever

## 10 Things to Know

By Karla Moeller

Fever, also known as pyrexia and febrile response, is defined as having a temperature above the normal range due to an increase in the body's temperature set-point. There is not a single agreed-upon upper limit for normal temperature with sources using values between 37.5 and 38.3 °C (99.5 and 100.9 °F). The increase in set-point triggers increased muscle contractions and causes a feeling of cold. This results in greater heat production

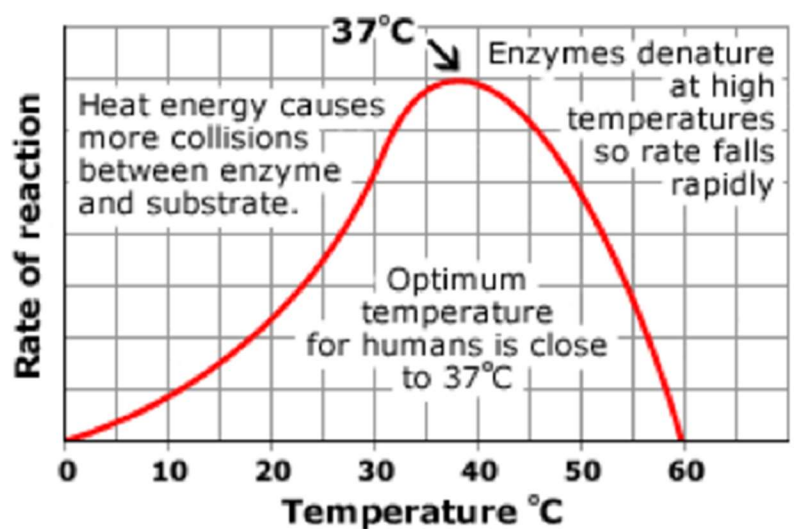


and efforts to conserve heat. When the set-point temperature returns to normal, a person feels hot, becomes flushed, and may begin to sweat. Rarely a fever may trigger a febrile seizure. This is more common in young children. Fevers do not typically go higher than 41 to 42 °C (105.8 to 107.6 °F).

## 1. Fever is a defensive response

Fever is a defensive response coordinated by several systems within our bodies.

Fever, an elevation in body temperature beyond an individual's normal levels, is also called pyrexia or controlled hyperthermia. Febrile is an adjective used to describe a state of fever. Most animals employ a fever response during infection; fever has also been found in certain plants. An individual's regular set body temperature and thermal tolerance may vary with many factors including age, time of day, status of digestion, or acclimation. Within a species, individuals may also vary in set body temperatures by a few degrees. In



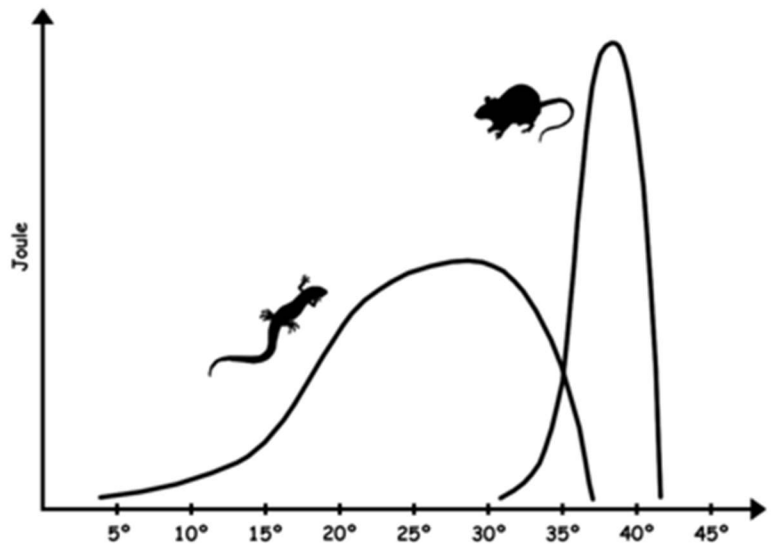
endotherms (animals that produce their own body heat) we call this set level normal body temperature; in ectotherms (animals that regulate heat using the environment) we call this preferred body temperature. The range considered normal in humans varies between 36.5 and 37.5°C. Human fever may cause increases in temperature of up to 1 to 4°C, but temperatures may be fatal over 40°C. Fever

can be helpful to reach optimal temperature of certain body processes, but there is a limit to how high we can increase temperature due to the instability of proteins at high temperatures. When the body encounters a pathogen infection, the pathogens release molecules that our physiology responds to; we call these molecules pyrogens because they are fever-causing chemicals. Our own immune cells, such as macrophages, also release pyrogens into the blood during infection. Pyrogens have many effects and are involved in process that affects the hypothalamus, which controls body temperature. When the hypothalamus senses chemicals produced in response to pathogen infections, it directs the body to raise its set temperature. Visit the [Merck Manual recommendations](#) for how to evaluate, interpret, and treat fever.

## 2. Increasing body temperature

Most animals have mechanisms that increase body temperature when they get infections, whether they do this physiologically or behaviorally. Some plants may also increase temperature during infection.

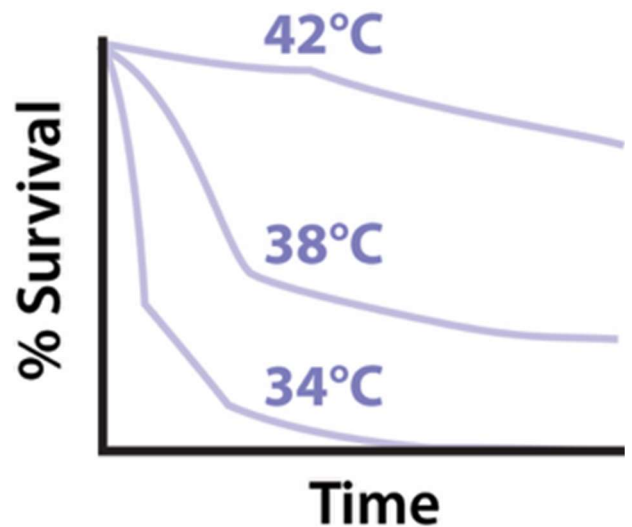
Endotherms (animals that produce their own body heat) can use several mechanisms that increase body temperature such as shivering, moving to warmer places, modifying blood flow, increasing metabolism, and adding to the external buffer layer (e.g., adding clothing or puffing fur or feathers). Many endotherms regulate temperature very tightly, so are called “homeotherms.” Ectotherms cannot produce their own body heat. Many ectotherms still regulate their body temperature, just over a larger range of temperatures, meaning they are “poikilotherms.” Ectotherms can move to warmer areas of their habitat, change body position, or modify blood flow to increase body temperature. For example, lizards will shuttle between sunlight and shade to maintain a temperature, or a butterfly will open or close its wings to control how much body surface area is exposed to sunlight. Both endotherms and ectotherms will often raise body temperature when fighting infection. Some animals are ectotherms in general, but can produce heat under specific circumstances. A few species of python can shiver to create heat when brooding eggs, and bumblebees can twitch flight muscles to warm up before flight. This ability is called facultative endothermy. Fever is signaled in part by the hormone prostaglandin E2 (PGE2); however, the initial process by which pyrogens trigger production of PGE2 is still unclear (though it’s thought that fever-induced PGE2 is produced in organs other than the brain). This [PLOS article](#) has more information on the interaction of hormones and fever production. Once fever has been triggered, endotherms raise body temperature by releasing noradrenaline, which constricts blood vessels and increases heat production in brown fat. Neurotransmitters are also involved in increasing body temperature by increasing metabolic rates. The shaking chill at the onset of some infections signals the arousal of mechanisms that increase body temperature. The sweat when a fever breaks signals the body’s cooling mechanisms turning on.



### 3. Fever can increase survival

Organisms experiencing immune challenges often show a higher chance of survival if they have increased body temperatures.

Similar experiments show positive effects of fever on survival in several vertebrates, including lizard, fish, mice, and rabbits, as well as in some species of plants. Many immune functions are temperature sensitive, including anti-bacterial and anti-tumor immune activity. The graph above shows percent survival during bacterial infection of desert iguanas held at differing temperatures. Lizards held at higher, "fever" level temperatures had much higher survival. Bacterial-induced fever has shown beneficial clinical effects in humans in fighting cancer as well as other bacteria, such as syphilis. Wagner Jauregg won a Nobel Prize in 1927 for giving people malaria on purpose to induce fever as a "fever therapy" to cure syphilis (at a time when no other treatments were available). Today, thermal treatments are being used in the fight against some cancers. [Local, regional, or whole-body hypothermia](#) (often in tandem with chemotherapy) may be used to treat cancer, according to the American Cancer Society.

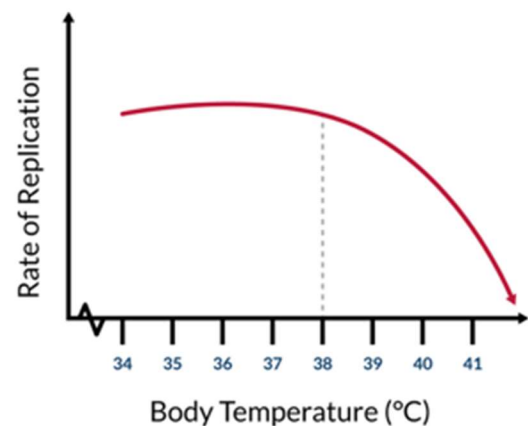


### 4. Fever is a defense signal

The increased temperature itself in some cases may make bacteria and viruses grow more slowly, but the higher temperature seems to be more useful as a signal to turn on other defensive systems.

Fever can have a direct effect on pathogens, reducing the ability of viruses to reproduce (replicate) or making bacteria more susceptible to the weapons of our immune system (like lysis). However, fever also seems to have an indirect effect on the pathogens, by stimulating the host's immune system to launch a stronger attack. Fever-range temperatures increase responsiveness of both the innate and adaptive immune systems. In the innate immune system, thermal stress increases the release of neutrophils from bone marrow, neutrophil recruitment to infection, elevated respiratory burst (increasing bacteriolytic activity), and natural killer cell cytotoxic activity, as well as improving the phagocytic

Effects of Body Temperature on Replication Rates of *Leprosy bacilli*



activity, as well as improving the phagocytic

potential of macrophages and dendritic cells. In the adaptive immune system, the abilities of antigen-presenting cells are increased under fever-level thermal stress. Fever temperatures also increase the production or release of cytokines, nitric oxide, and heat shock protein 70. Some of these effects may have negative outcomes, such as neutrophil accumulation (especially in the lungs) and impaired function of some white blood cells, but overall, fever temperatures seem to activate the body to improve the ability to fight pathogens. <https://www.scientificamerican.com/podcast/episode/fever-increases-numbers-of-immune-c-11-11-15/> See Evans, Repasky, and Fisher. 2015. **Fever and the thermal regulation of immunity: the immune system feels the heat.** *Immunology* 15: 335-349. <http://www.nature.com.ezproxy1.lib.asu.edu/nri/journal/v15/n6/full/nri3843.html>

## 5. The body defends fever temperatures

Fever is not just a result of faster metabolism, it is controlled by specialized brain centers that stabilize body temperature at a higher level. The higher body temperature during a fever is kept stable, and the body prevents it from moving either up or down.

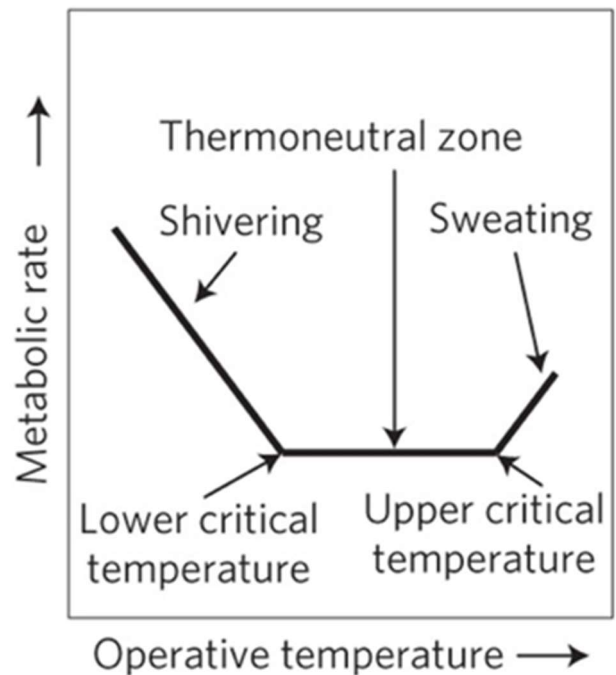
Infections trigger the production of cytokines by white blood cells. Interleukins 1 and 6 (produced by T cells and macrophages) rise in the peripheral (non-nervous) circulation during the early stages of response to infections. These interleukins are thought to accelerate the production of prostaglandin E<sub>2</sub>, which then acts on the hypothalamus, with resulting adjustment of the "set point" of body temperature regulation. This response is dependent on the location of infection; for an infection in the brain, a slower, slightly different response occurs. Cytokines don't easily cross the blood-brain barrier, so the trigger for increased prostaglandin in the brain may involve nitric oxide, the vagus nerve, or transduction involving some other peripheral organs. However the trigger for prostaglandin production occurs, the rate of production coincides with the magnitude of the fever. Once a fever is initiated and the "set point" for body temperature is increased (due to increased levels of prostaglandin E<sub>2</sub>), the body will work to maintain a higher temperature. Endothermic animals given cooling treatments still maintain fever-level body temperatures (NEED CITATION FOR THIS). Additional information: <https://www.scientificamerican.com/article/what-causes-a-fever/>

[http://mlearning.zju.edu.cn/G2S/eWebEditor/uploadfile/20111121083505\\_460699365083.pdf](http://mlearning.zju.edu.cn/G2S/eWebEditor/uploadfile/20111121083505_460699365083.pdf)

## 6. Fever is energetically costly

Higher body temperatures are energetically costly in terms of calories expended, about an extra 10 to 12.5% increase in metabolic rate per degree fever centigrade. Metabolic rate is highly temperature dependent, for both ectotherms and endotherms. The rates of cellular reactions depend on

temperature, so as the body heats up, ions and metabolites move around faster to keep cells functioning properly. The majority of calories that we spend per day are used to transport ions through ion channels, especially sodium-potassium channels. The faster we move chemicals around our bodies, the more energy we spend. Endotherms have a specific temperature range, called the thermoneutral zone, in which energy expenditure is at its lowest. Below the temperature range within that zone, our bodies will try to warm up by shivering, which expends a lot of energy. Above that zone, our bodies will try to cool down by sweating, which also expends a lot of energy.



**Figure from Kingma & van Marken Lichtenbelt. 2015. Energy consumption in buildings and female thermal demand.**

Fever causes an increase in set body temperature, which requires more energy to maintain. Thus, our bodies spend more calories when temperatures rise. This makes fever a costly defense, so fever is usually only a response used when it is needed to fight off infection.

## [7. Is reducing fever bad?](#)

Blocking fever sometimes makes it harder to fight infections, but the body has many other mechanisms to fight infection so sometimes blocking fever can be safe.

Antipyretics such as aspirin and ibuprofen are often used to reduce fever. This effect is achieved because most antipyretics inhibit cyclooxygenase, an enzyme responsible for part of the synthesis of prostaglandins (the hormones that trigger and regulate fever in the hypothalamus). These same pathways are triggers for heat-seeking behavior of some reptiles, fish, and invertebrates during infection. Antipyretics also inhibit this behavior in ectothermic animals. Though the fever response is well conserved across vertebrates and invertebrates, and has many benefits to fighting an infection, blocking fever may not always be detrimental. Our bodies still launch an immune response to invading pathogens without fever, though it may not be as substantial. This has made broad-sweeping recommendations about fever difficult for doctors to make.

## [8. What do doctors say about fever?](#)

Groups of scientists and doctors have steadily changed recommendations about fever in recent decades to reduce the use of drugs to reduce fever.

Historically, fever was thought to help fight illness, until analgesics were developed. At this point, pain and fever relief were linked, which led to the belief that fever was a negative influence during illness. In the last several decades, fever has been identified as having positive effects on the ability to fight

infection, so recommendations about the treatment of fever have changed. The American Academy of Pediatrics advises that treating fever in children should be more about making sure a child is comfortable rather than bringing body temperature back down to "normal." Increased temperature can be beneficial, but can sometimes be harmful, so each situation should be treated individually. Additional information: <https://www.aap.org/en-us/about-the-aap/aap-press-room/pages/AAP-Issues-Advice-on-Managing-Fevers-in-Children.aspx>

## **9. Fevers and seizures**

Epileptic seizures associated with fevers in children are usually not a direct result of the high temperature itself but of the infection.

Febrile seizures most often occur in children at temperatures above 39C, and occur in 1 out of every 20 to 50 children. Febrile seizures may be caused by mutations in ion channels. Ions within neurons are often dependent on temperature, though response threshold seems to depend on genetic variation. Febrile seizures have also been linked to bacterial or viral infections, especially herpesvirus 6. Short febrile seizures do not cause brain damage and does not indicate that a child has epilepsy; however, likely due to genetic factors, febrile seizures can be recurrent in an individual. Studies show that giving antipyretics (fever-reducing medications) does not seem to reduce risk of fever or of the recurrence of febrile seizures.

## **10. Reye's Syndrome**

Some children who take aspirin for fever can develop Reye syndrome.

Reye syndrome causes liver damage and swelling of the brain and can occur in children or adolescents following a viral infection. It affects less than one in a million children per year. The mechanisms causing Reye syndrome are still unclear, but it most often occurs in children who were treated with aspirin. For this reason, aspirin is not recommended for treatment of fever in children except under extenuating circumstances (e.g., Kawasaki disease).