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# The fever paradox

Fever can be deadly, but in moderation it could have some surprising upsides, as **Linda Geddes** discovers

**A**S NEWS about coronavirus spread around the world, paracetamol soon began to disappear from shop shelves as people stocked up at home. In some places, the price of the drug shot up. That probably comes as little surprise given that one of the key symptoms of the infection is a fever.

We tend to routinely use drugs such as paracetamol or ibuprofen to try to bring down a high temperature, believing fever to be, at best, a passive and unwelcome bystander to infection and, at worst, a direct contributor to our illness. Yet mounting evidence suggests that fever may, in fact, be a strategy the body uses to ramp up its defences. This new understanding of what is going on when we are burning up could help us come up with better approaches to fighting infection altogether.

Normal body temperature is generally thought of as 37°C, although anything between 36.5°C and 37.5°C is considered normal (see “Highs and lows”, overleaf). However, once your temperature hits 38°C, you have officially got a fever.

The most common cause of this is infection.

“When immune cells recognise the telltale signs of a germ in the body – and often this can be quite early on in an infection – they release secretions which act on a brain area called the hypothalamus,” says Daniel Davis, an immunologist at the University of Manchester, UK, and author of *The Beautiful*

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*Cure: Harnessing your body's natural defences.* The hypothalamus is responsible, among other things, for controlling body temperature, and it responds to these signals by releasing hormones that cause various heat-boosting responses. Blood vessels in our skin constrict so less heat is lost at the body's surface. Fat cells start burning energy and our muscles rapidly contract, causing shivering – both of which warm us up. As a result, the body's temperature starts to rise.

If it rises too far, that can be fatal. Our cells begin to die, releasing proteins into the blood that can damage the kidneys and other organs, resulting in their failure. The exact temperature this happens at probably depends on the source of a person's fever, as well as other factors such as how hydrated they are. “The number 40 [degrees] scares a lot of doctors,” says Mark Peters at the UCL Great Ormond Street Institute of Child Health in London.

Even so, many hospital doctors will routinely give fever-reducing drugs as soon as a patient's temperature hits 38°C. Even a mild fever comes at a great cost: raising your body temperature by just 1°C requires a 10 per cent increase in energy expenditure. Fever is associated with a higher pulse and breathing rate, placing additional strain on the heart and lungs that could be risky in seriously ill people.

So if fever can kill us, why does it happen? ▶

## HIGHS AND LOWS

Although 37°C is often cited as normal body temperature, it varies throughout the day, with thermometer readings some 0.8°C to 1°C lower first thing in the morning compared with the evening.

Body temperature also tends to be higher in women than in men – and even within women, it is approximately 0.4°C higher during the second half of the menstrual cycle compared with the first. Younger people also tend to have higher body temperatures than older people.

There is even evidence that our body temperatures may be falling over time – possibly because we are exposed to fewer pathogens in the modern world, meaning our immune systems are less active and our bodies less inflamed. One recent study found that, on average, body temperature in the US has fallen by around 0.03°C per decade since the early 19th century. Men born then were 0.59°C hotter than men today, while women's body temperature appears to have dropped about 0.32°C since the 1890s. The average body temperature for 21st-century humans is about 36.6°C – not 37°C as widely thought.

Fever-like responses are observed in many organisms, suggesting fever's evolutionary origins may stretch back hundreds of millions of years. Even some plants have been shown to increase their leaf temperature in response to fungal infections, while cold-blooded creatures will deliberately raise their body temperature if they have an infection, by sitting on a hot rock, for instance. In the case of the desert iguana, not being allowed to do so was seen to cause a 75 per cent reduction in survival rates.

That suggests fever might not be all bad. "Things that have a very high metabolic cost would not be preserved throughout evolutionary history unless they came with a clear survival advantage," says Peters.

The idea that fever might actually have medical benefits goes way back. The ancient Greek physician Hippocrates claimed that "those who cannot be cured by [medicine or] surgery can be cured by heat; and those who cannot be cured by heat are to be considered incurable". In 1927, the Nobel prize for medicine was awarded to the Austrian physician Julius Wagner-Jauregg for his discovery that triggering a high and persistent fever by inoculating people with malaria could treat their syphilis; the malaria was later treated with quinine.

### Fever reliever

Modern medicine has moved on considerably, and so has the way we think about fever. It is easy to see it as the thing that is making us ill, not a symptom along with other things like a runny nose or sore throat. "People often equate fever with the cause of the fever – even many doctors struggle to get their heads around that separation of fever being the response to a problem, and not necessarily the problem itself," says Peters.

Fever can also feel unpleasant, and many of us feel glad when our temperature drops after taking some medication. From all these perspectives, it makes sense to want to bring temperatures down as quickly as possible. That's certainly how the medical profession views things, says Peters. "Correcting fever has become a routine part of intensive-care practice, almost to the point where it's not discussed."

But there are hints we might be missing something. Take the common viral infection chickenpox. In a study of 72 children, those who weren't given drugs known to reduce fever recovered faster. Likewise, a study of

**Iguanas sit on hot rocks to raise body temperature when they have an infection**

## “By increasing your body temperature, you may be slowing the ability of a virus to multiply”

56 people infected with one of the viruses that causes the common cold found that those who took certain fever-reducing drugs remained infectious for longer.

Similarly, people who are admitted to intensive care units with infections and a slightly raised temperature tend to fare better than those who have a normal temperature, or one higher than 40°C. One reason for this may be that bacteria and viruses find it easier to replicate and infect cells at temperatures below 37°C. "By increasing your body temperature, you may be slowing down the ability of a virus to multiply," says Davis.

It also seems that the immune system works more efficiently when the body gets hotter. Immune cells that act as first responders to infection, such as dendritic cells, macrophages and neutrophils, have been shown to arrive at the scene faster, and have an improved capacity to engulf



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and destroy infectious agents at 38°C to 40°C. Fever also seems to make these cells better at recruiting and activating T-cells, which coordinate longer-term “adaptive” immune responses, such as antibody production. And T-cells and antibody-producing B-cells also better respond to instructions from the immune system at these temperatures.

Recent studies are providing new insights into how this happens. One published last year suggested that running a temperature of 40°C may help T-cells crawl out of the blood towards sites of infection, by producing proteins that allow them to anchor to the blood vessel wall.

Raising body temperature by just a few degrees also speeds up a cellular “clock” that controls the switching on of a set of inflammation-promoting genes, according to recent work by Mike White at the University of Manchester and his colleagues. “You see a dramatic change in the timing of this system, where pretty much every degree makes a difference,” he says.

This is unusual in biological systems: even the circadian clock, which generates roughly 24-hour rhythms in our physiology, is insensitive to temperature. That implies fever may be a deliberate strategy to bolster our immune defences in the face of infection. “It suggests that the immediate immune response is that bit faster at higher temperatures,” says White, which may explain the speedier resolution of some illnesses.

All of this raises the question of when – and how – fever should be treated. Peters recently



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### For a mild fever, rest and plenty of fluids can help

conducted a trial in 100 children who were critically ill with suspected infections. He wanted to explore whether it was feasible to let their temperatures rise as high as 39.5°C before administering fever-reducing drugs, instead of 38°C, which is the current practice in most UK hospitals. The children continued to receive other treatment. The trial showed that there were no adverse outcomes from treating at higher temperatures, but it wasn't designed to test if this resulted in faster recovery.

Meanwhile, a recent meta-analysis combined the results of various trials assessing the impact of treating mild fever in hospitalised adults. It concluded that there was no difference in survival between those who received more active management of their fever and those who received less. So far then, the results suggest there isn't a lot in it, although it is still early days.

It might be that we are focusing on the wrong problem, however. The question isn't whether we should treat fever, but in which patients we should do it, says Edward Walter, an intensive care doctor at Royal Surrey County Hospital in Guildford, UK, who recently reviewed the medical literature on fever. Rather than seeing it as a single thing, he says that running a high temperature can be a response to various problems. In addition to infection, these include brain injury, heatstroke and taking certain drugs such as ecstasy, so our response to it might need to be more nuanced, he says.

Another good question to ask is whether we have the means to treat the underlying cause of the fever. “If you're going to get an advantage from fever, it will probably be in populations where you cannot easily achieve control of the infection by existing means,” says Peters. With pneumonia triggered by a bacterial infection, for instance, antibiotics will often

treat the pneumonia, in which case there may be limited benefit to letting a fever run.

However, we currently have no effective drugs for pneumonia triggered by the new coronavirus, and so Peters speculates that mild fever could be helpful in such a situation.

Not everyone agrees. “You cannot really say fever is good, period, or fever is bad, period,” says Andrej Romanovsky at the University of Arizona, who edits the journal *Temperature*. “The only practical way to answer how we should treat fever is to run clinical trials in specific populations suffering from a specific disease and using specific [fever-reducing] drugs.”

In the case of covid-19, such trials may be years away. In the meantime, the UK's National Institute for Health and Care Excellence (NICE) is reviewing evidence on ibuprofen to try to clarify whether it is safe for treating the symptoms of covid-19 infections, after French health officials controversially urged people with symptoms to avoid the drug. The current advice from the World Health Organization is that either paracetamol or ibuprofen can be used to treat symptoms of the illness. In the UK, the advice from the National Health Service is to take paracetamol – although it doesn't say whether that is for fever or for other symptoms such as a sore throat.

“Fever is probably helpful in a very limited way, in those situations where we have light infections, but we should also consider how a person is sleeping and how they feel,” says Romanovsky. “For mild cases, it probably doesn't matter whether you take a drug to take the fever down.”

And most health services advise that a mild fever of up to 38.9°C, in the absence of more worrying symptoms, will probably get better with rest and fluids. So if your fever is mild, and you aren't in great discomfort, you might want to remember what is going on inside. “Permitting a fever in the viral condition is likely to allow your immune system to do its job – as it has been designed by millions of years of evolution – better,” says Peters. ■

This article is not medical advice. Very high temperatures can be dangerous. If you are feeling unwell, seek the advice of your doctor, especially if your fever is accompanied by other symptoms.



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