Some doctors say a fever isn't always bad news. Are they playing with fire, asks **Robert Matthews**

It is often the first sign that we're coming down with some bug: we feel groggy, tired – and hot. A thermometer or a hand to the forehead confirms that we have a fever, or as doctors call it, pyrexia.

One of the hallmarks of infectious illness, a fever is not just uncomfortable. In some cases it can trigger fits and perhaps even brain damage. The usual response is to bring down the temperature with antipyretic drugs, such as aspirin, paracetamol (aka acetaminophen) and ibuprofen.

It has long been acknowledged that such drugs could, in theory, be counterproductive – they do, after all, interfere with the body's natural response to infection. But these qualms have been set aside for a variety of reasons: the need to relieve discomfort; fears about brain damage; time-honoured practice; and, some would say, the urge to be doing something rather than nothing.

The upshot is that antipyretics are routinely used for any feverish illness, from the sickest of patients in intensive care to people using over-the-counter medicines at home. The standard advice for people with flu, for example, is to dose up with paracetamol. Parents of young children, who are especially prone to fevers, are well aware of the perils of inaction: febrile convulsions.

But now there's growing concern that these time-honoured approaches are at best misguided and at worst potentially life-threatening. New findings are starting to support a much older view of fever: that it is a key part of the body's disease-fighting strategy. The evidence is coming in from many sources, including insights into how the immune system battles infection, research into how bacteria respond to temperature and studies of critically ill patients. At the same time, the idea that antipyretics can prevent fits in children is looking increasingly shaky. It's not often that decades of clinical practice is overturned, but it looks like the game may be finally up for one of medicine's most basic precepts.

The idea that fever can be beneficial dates to the time of the Greek physician Hippocrates, 2400 years ago. Ironically, it was the emergence of modern medical science during the mid-19th century that led to fever being seen as harmful. The volte-face had its origins in a key concept of medicine: homeostasis. The idea was developed in the 1860s by the French physician Claude Bernard (pictured). It concerns the body's ability to maintain itself within the narrow range of conditions needed for health. Deviations from these ranges were deemed in need of correction. The most obvious deviation was fever – whose severity could be measured with impressive precision by a nifty new gadget: the small, mercury-filled clinical thermometer. Not surprisingly, doctors seized on new antipyretics like paracetamol and aspirin, which rapidly lowered soaring temperatures.

Notwithstanding a fashion in the early 20th century for "pyrotherapy" (see "Fever as cure", page 44), fever has come to be seen as something that should be fought at all costs. Could this be a mistake?

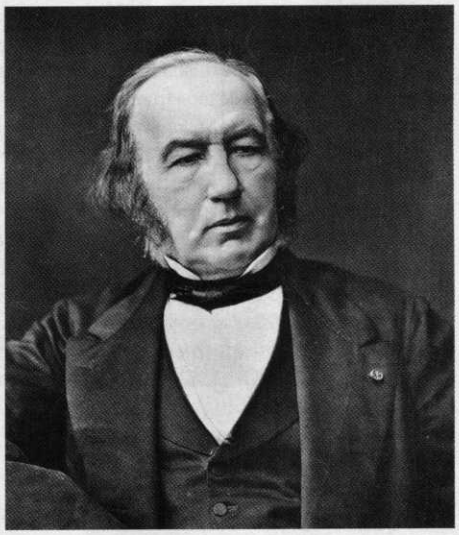
Physiologist Clark Blatteis at the University of Tennessee Health Science Center in Memphis has studied fever for over 30 years. He says it is clear that the process is an evolutionarily ancient disease-fighting system: "It's very old, existing not only in mammals and birds but also in fishes, amphibians and reptiles."

Fever arises when the immune system, sensing an infection, produces proteins known as pyrogens. These act on the hypothalamus, deep within the brain, to raise the body temperature's set-point. While our normal temperature is around 37 °C, with fever it typically rises to 39 °C or even 40 °C (see diagram, page 45).

Friendly fire

The first line of evidence for the benefits of fever comes from studies of the immune system. It now seems that many disease-fighting mechanisms work better in hotter conditions. For example, it enhances the ability of immune cells called T-lymphocytes to home in on the site of infection. Higher temperatures also appear to moderate the potentially dangerous effects of cytokines, proteins that orchestrate the immune response to infections.

It has also become clear that fevers are bad news for many microbes. A team led by microbiologist Garth Dixon at University College London investigated the effects of fever-level temperature on *Neisseria meningitidis B*, the cause of the much-feared bacterial form of meningitis. They compared the quantity of bacteria in blood samples at ›



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Claude Bernard developed the idea of homeostasis, or maintaining the body's internal conditions

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Pyrotherapy – fever as cure

The ancient idea that fevers can be beneficial enjoyed a renaissance around a century ago, following an observation by a physician in Vienna. Julius Wagner-Jauregg noticed that some of his psychiatric patients improved after fever attacks. After failed attempts at inducing fever in patients using microbes, Wagner-Jauregg injected blood from a person with malaria into a patient with syphilis, which is caused by the bacterium *Treponema pallidum*. The patient developed a fever – and then began to recover from the syphilis. Trials with more patients showed that the technique could cure people of this potentially fatal disease if used quickly. In 1927 Wagner-Jauregg was awarded the Nobel prize for medicine.

His success prompted further research into the benefits of artificially induced fevers. Hot baths, warm air, electric blankets and even high-frequency currents were used to raise the body temperatures to levels thought capable of killing pathogens – typically around 41 °C. By the mid 1930s, doctors in the US had treated hundred of patients in so-called Kettering Hypertherms – cabinets equipped with hot air blowers and temperature monitors. The results were impressive: just one 5-hour session in the devices seemed enough to bring syphilis under control, though permanent recovery typically required 50 hours or more.

Even then, however, the potential dangers were recognised. Patients deemed unable to cope with the metabolic stress – such as those over 60, or with heart or kidney problems – were excluded. Yet with cure rates of up to 80 per cent, it is easy to see why one leading proponent of pyrotherapy in the 1930s hailed it as a "new and powerful weapon".

Exactly how fevers helped remained a mystery. Yet by the late 1930s, the debate had been rendered academic by the emergence of wonder drugs that killed microbes directly. Those drugs were antibiotics. There was little mystery about either their action or effectiveness, and they rapidly became the treatment of choice for infections, leaving pyrotherapy to diminish into a historical footnote.

normal body temperature with those at 40 °C and found that levels plunged by almost 90 per cent after several hours' exposure to the higher temperature.

Reporting their findings in January in *BMJ*, the team argues that the results raise questions about routinely using antipyretics to quell fevers (DOI: 10.1136/bmj.c450). Allowing patients to stay hotter for longer may cut the levels of bacteria in the early stages of infection – a key determinant of recovery. "Fever may have an important role in this process," the team concluded.

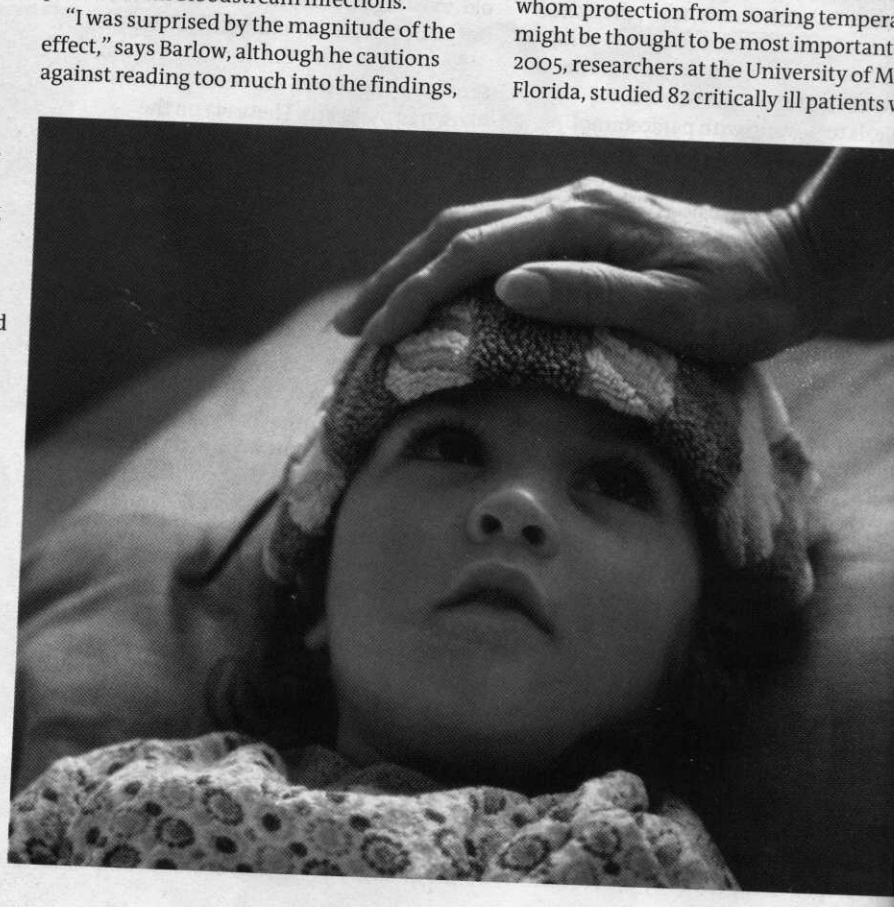
Experimenting on bacteria in the lab is one thing, but how does that extrapolate to real-life patients? Unfortunately there is a striking paucity of evidence in this area. The few existing studies are mainly "observational" ones, where researchers simply monitor people's treatment and outcomes – as opposed to the gold standard of medical research, the randomised controlled trial.

Still, observational studies done in the 1980s and 90s did suggest that antipyretics hinder, rather than help the body's response to the common cold, chicken pox and malaria. More recently, infectious disease consultant Gavin Barlow of the Hull and East Yorkshire Hospitals NHS Trust in the UK had a hunch about his patients with pneumonia. "I tended to be less concerned about the outcome of patients who had fever at admission compared with those who did not," he recalls.

Examining over 400 records, Barlow's team made a striking discovery: the more feverish the patient on admission, the better their chance of survival. Of those whose temperature was below 36 °C, one-third died within 30 days of admission. In contrast, just 8 per cent of patients with higher than normal temperature had died within the same period – and not one of those with fevers of 40 °C or more (*BMJ*, vol 340, p 382). The team found similar figures for patients with bloodstream infections.

"I was surprised by the magnitude of the effect," says Barlow, although he cautions against reading too much into the findings, as both studies were small and unable t out the possibility that some other fact at work. For example, older people tend to get as hot, and are also more likely to so this could be confusing the picture.

There has, however, been one randon trial. This was in patients in intensive ca whom protection from soaring tempera might be thought to be most important 2005, researchers at the University of M Florida, studied 82 critically ill patients



A cold compress won't reduce her core body temperature

"There were seven deaths in patients getting standard treatment and only one in those allowed to have fever"

did not have head injuries or other problems that make a high temperature risky. Patients were randomised to get either the standard treatment of antipyretics if their temperature went past 38.5 °C, or only receiving the drugs if their temperature reached 40 °C.

As the trial progressed, there were seven deaths in people getting standard treatment and only one in those allowed to have fever (*Surgical Infections*, vol 6, p 369). Although this difference was not quite large enough to be statistically significant, the team felt compelled to call a halt, feeling it would be unethical to allow any more patients to get standard treatment. "We struggled with whether to stop the trial or not, but our safety board all agreed it was the right thing," recalls critical care specialist Carl Schulman, who led the research.

This trial represents the best evidence yet to challenge the orthodoxy of treating fever aggressively. It has changed Schulman's practice – he uses antipyretics much less now. "I use them only when the patient appears uncomfortable or has adverse physiological changes due to the fever," he says.

Schulman is not the only intensive care doctor to have become more cautious about using antipyretics in recent years. "The pendulum is swinging that way," says David Menon, an intensive care doctor specialising in neurology at Addenbrooke's Hospital in Cambridge, UK.

Not so fast

Menon, however, believes there is not enough evidence yet to change practice. "It's one study. We have got to be careful that we don't get overtaken by the fad of saying let's not treat." He points out that there is plenty of evidence to show a raised temperature is harmful to the brain after a head injury or stroke, perhaps because it increases inflammation and levels of free radicals and excitatory amino acids. That may also apply to people whose fever is caused by an infection, he speculates.

What's more, many patients in intensive care due to an infection are so ill not because the microbe is overwhelming their body, but because of their body's excessive response to it – of which fever is a part. Long-term cognitive problems such as memory or concentration lapses are not uncommon after a stay in intensive care, even for those who had infections that were not neurological in origin, such as pneumonia. It is very likely that an excessive response to infection is a substantial contributor to such symptoms, says Menon. "If I were critically ill with an infectious illness I would worry if my temperature was allowed to rise significantly."

Another possible downside of fever is that it raises the metabolic rate, which very sick people may be unable to cope with. "Many intensive care patients are undergoing a severe stress test already, and if you add fever to that, it's more metabolic demand," says critical care specialist Kevin Laupland of the University of Calgary in Alberta, Canada.

Even doctors like Menon, however, acknowledge that antipyretics are probably overused for minor illnesses. In fact it is with minor illnesses in young children that the first official acknowledgement has come that fever may not always be a bad thing.

In the past, parents have resorted to sponging down feverish children, or even plunging them into cold baths, in a bid to prevent febrile convulsions. These days parents are usually advised to use ibuprofen or paracetamol, the only debate being whether it is safe to combine the drugs.

In 2007, however, guidelines from the UK's National Institute for Health and Clinical Excellence (NICE) noted the possibility that fever could be beneficial for a child fighting infection. The authors advised that antipyretics should be used only if the fever seemed to be causing a child distress.

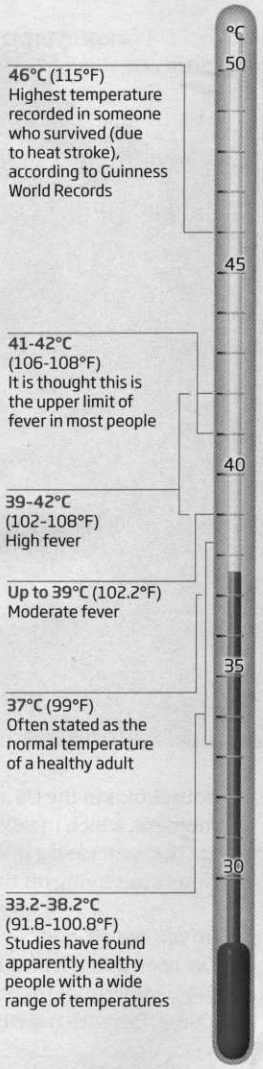
But what about febrile convulsions? While frightening for parents, these almost never cause any lasting harm, points out Edward Purssell, a lecturer in primary care at Kings College London, who co-authored the NICE guidelines. The main point, though, is that these fits cannot be prevented by antipyretics. They seem to be caused not by a high temperature per se, but by a rapid climb in temperature. So by the time you discover your child is hot, they are out of the risk period. "Quite often the first sign is the convulsion," says Purssell. "You can't really prevent them."

Purssell is not optimistic that his guidelines are having much influence. "Most people said they were a good idea. Not many people changed their practice." Perhaps that is inevitable until more trials investigate this long-standing question. "We are trying to overturn decades of practice," says Purssell. "It's like trying to turn around a supertanker."

Physicians such as Laupland believe the same is true for hospital medicine. "We need to do a large randomised trial – it is the only way we can find out for sure," he says. "The bottom line is that up to 50 per cent of my patients have fever during their stay. And that means 50 per cent are getting treatment which we don't know for sure actually works." ■

Mercury rising

When our bodies detect an infection, the hypothalamus in the brain raises our body temperature



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