# Fever—concepts old and new

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*J R Soc Med* 1997;**90**:391–394

The link between raised body temperature and disease has been known since time immemorial. The oldest extant medical text, the Edwin Smith Surgical Papyrus (circa 1700 BC) makes reference to fever being determined by touch. Long before the dawn of clinical thermometry the temperature course of malaria and enteric fever (typhoid and brucellosis) was well described in the Corpus Hippocraticum (circa 370–460 BC). In the *Bible*, fever is a punishment or a curse[2], and its later association with epidemics such as the Black Death caused it to be viewed as the sign of impending exodus from the world. Even in the early part of this century Sir William Osler declared that, of the three great scourges of man (fever, famine and war) fever was the worst[3]. Much of the fever 'phobia' of today is a legacy of the apprehension of past generations[4].

## THE DETECTION AND TREATMENT OF FEVER

One useful sign of fever was a fast pulse, and eighteenth century case records at Edinburgh Royal Infirmary show how the pulse was used to record responses to pharmacological concoctions and blood letting[5]. Some of the common remedies used at that time, such as brandy and Peruvian bark (which contains quinine), were evaluated in five dogs by the Reverend Stephen Hales in Cambridge in 1733. Despite his conclusion that there was no laboratory evidence of benefit from those substances they continued to be used[5]. Even after the invention of the thermometer, William Cullen and other Edinburgh physicians continued to use pulse as the primary method of diagnosing fever. Their rationale was the poor correlation between body temperature and symptoms; and they had some support from the work of James Currie in the 1790s and Alfred Donné in 1835, who both showed a good correlation between fever and pulse rate (except in typhoid fever)[5]. One sign of the low importance given to thermometry at that time is that the first edition of the *Encyclopaedia Britannica* (1771) discusses body temperature under pneumatics rather than medicine.[6]

## THE DAWN OF CLINICAL THERMOMETRY

In 1868 Carl Wunderlich, professor of medicine in Leipzig, published his magnum opus *Das Verhalten der Eigenwärme in Krankheiten*[7,8], indicating for the first time that fever is not a disease but rather a sign of disease. He drew attention to the variation of fever patterns with different diseases, thus explaining the Edinburgh physicians' inability to correlate symptoms with body temperature. To this day, Wunderlich's book remains the definitive work on clinical thermometry, and the inspiration for this work seems to have been Professor Ludwig Traube, who introduced the clinical thermometer onto his wards in Berlin in 1850. Starting in 1851 Wunderlich collected several million temperature readings on about 25 000 patients. His thermometers were 22.5 cm long and took 20 min to register. Measurements were made in the axilla as he considered the mouth and fist unreliable and the rectum indecent[7]. Wunderlich is often credited with having established normal body temperature as being 98.6°F (37°C), but Antoine Becquerel and Gilbert Brechset had long since made this observation (in 1835) with a thermocouple of iron and copper[10].

When Wunderlich's studies have been repeated with modern thermometers placed in the mouth, his observations have generally been confirmed—for example, the diurnal temperature variation, and the slightly higher temperature of women[11]. However, Wunderlich's axillary readings tended to exceed those obtained in the mouth with modern thermometers, even though mouth temperature is normally slightly higher. The likely reason for this discrepancy emerged when a Wunderlich thermometer in the Mütter Museum, Philadelphia, was tested against a National Bureau of Standards thermometer; it read 1.9°C (3.4°F) higher.

## THE SPREAD OF CLINICAL THERMOMETRY

A profound influence on the spread of clinical thermometry was exercised by Herman Boerhaave who introduced the Fahrenheit thermometer as a research instrument on his wards in Leiden. His many pupils, including van Swieten, de Haen and Martine, took thermometry to other centres in Europe. De Haen was one of the earliest physicians to use the thermometer regularly at the bedside in Vienna. Buried in his fifteen volume treatise on therapeutics *Ratio Medendi* (law of healing) there is some impressive information on clinical thermometry[12]. Because of the close association between Edinburgh and Leiden, thermometers came into Scottish hospitals and medical schools well before they were familiar in English hospitals[13]. Among the most prominent early fever researchers was the Scottish physician James

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Currie; moving to Liverpool he began a landmark series of thermometric investigations which he published in 1797[14].

Currie treated febrile patients with cold water baths and monitored their response by serial recordings of body temperature. Other Scottish graduates who made early use of thermometers were the army surgeon Archibald Arnott, who recorded Napoleon's temperature shortly before he died on St Helena (96°F), and David Livingstone who in 1853 measured body temperature while exploring in Africa[13].

In America the spread of clinical thermometry owed most to Edouard Seguin[15]. He promoted it not only to the medical profession but also to the public by writing articles in the lay press. He believed widespread use of thermometry by the public would eliminate quackery. His son Edward, writing in 1866 about three cases of pneumonia, coined the term 'vital signs' for temperature, pulse and respiration, which were illustrated in a chart designed by his colleague William Draper[16]. Within a decade such charts appeared at the bedside throughout America. Spread of thermometry was further facilitated by Austin Flint and Jacob Da Costa, who added sections on clinical thermometry to their medical textbooks in 1866–67[15].

## THERMOMETRY AFTER WUNDERLICH

Wunderlich's exposé of the 'myth' of fever altered perceptions and created a climate for scientific research. In the mid-eighteenth century the Edinburgh concept of the body maintaining its own temperature was not widely accepted. Body temperature was believed to be influenced by atmospheric temperature and some pundits recommended that atmospheric conditions should be monitored as a guide to health[15]. The work of John Davy and Blagden and Dobson helped dispel such notions. Davy showed that different races in varied climatic conditions around the world had a narrow normal range of temperature (97.5°–99.5°F)[17]. Experiments by Charles Blagden in 1775 and later by Dobson were to prove that body temperature remained constant in a heated environment[12,18].

In 1875 Von Liebermeister hypothesized that body temperature is regulated in the same way in both health and illness but that in illness fever arises because the 'thermostat' is set higher[19]. This notion was supported in 1892 by the work of Stern[20], who induced sweating after the same rise in temperature (0.1°–0.8°C) in normal and febrile subjects, whereas immersion in a cold bath induced shivering after the same fall in temperature in both groups. Von Liebermeister's hypothesis was finally proven to most people's satisfaction by Cranston and colleagues in elaborate experiments on febrile subjects, showing that the homoeostatic mechanisms were identical but functioned at a higher temperature[21].

Cranston and colleagues tried to identify the site of the thermostat (temperature control zone). Warm saline injected into the internal carotid artery caused body heat loss whereas injection of saline at body temperature elicited no response. They concluded that the thermostat was in that part of the brain supplied by the internal carotid artery[21]. On the basis of animal experiments we now know that it is situated in the anterior hypothalamus[22]. The work of Valy Menkin, Paul Beeson and others led to the discovery in rabbits then man of endogenous pyrogens which disturb the thermostat in fever. Pathogens cause a rise in temperature by stimulating the release of endogenous pyrogens from macrophages and other cells[22].

## CHANGING PERCEPTIONS OF FEVER

The negative perception of fever continued into the early part of this century. Despite the award in 1917 of the Nobel Prize to Wagner von Jauregg for his work on malarial induced fever as a treatment for neurosyphilis, fever was still generally regarded as of no benefit. This attitude persisted well into the middle of the century[23,24].

Why then, did opinions change? A key factor was Kluger's observation, in 1975, that warm body temperature confers immunological advantage in infected lizards[25]. A simple example of this phenomenon can be seen in the home by those who keep tropical fish. When the fish are sick they raise their temperature by congregating in the vicinity of the light—the heat source[26]. Kluger's work has been confirmed in all species including man[22]. Many micro-organisms grow best within a narrow range of temperature, and a rise in temperature inhibits their growth. Furthermore, antibody production increases when body temperature rises[27]. Studies in infected animals show a worse outcome in those treated with antipyretics[28,29]. In human beings the evidence is not so compelling, but it does suggest that antipyretics may be harmful in common third-world paediatric infections such as measles, chickenpox and pneumonia[30–32]. Now at last the benefits of fever are widely acknowledged—as indicated by the World Health Organization's 1993 recommendation against routine use of antipyretics for children in developing countries[33]. This perception of fever as a benign sign should not, however, detract from the fact that fever is a very important diagnostic sign of severe illness in young children, particularly in the first three months[34].

What, then, is the function of fever? We now know that, in Gram-negative and other serious infections, the clinical and humoral manifestations are mediated by endogenous pyrogens (cytokines). Survival in animals infected with Gram-negative bacteria is improved by administration of cytokine antagonists, and Mackowiak proposes a teleological explanation for this paradox—

namely, that in mild to moderate infections the febrile response accelerates recovery in the community, whereas demise is hastened in the sickest individuals who pose a risk of epidemics[35].

## TODAY—THE NEED FOR CHANGE

Despite the evidence that fever can serve a protective function, old habits die hard. The use of antipyretics is particularly worrying in children, whose body temperatures are higher than those of adults in both health and disease[26,36]. Currently, vast health service resources are squandered by unnecessary consultations and hospital admissions because parents harbour a misplaced fear of fever. Moreover, the unnecessary use of antipyretics is not without risk[37,38]. Paracetamol toxicity can occur at doses less than twice those usually recommended and only a little above the higher doses (20 mg/kg) often used for fever relief[38,39]. The total daily dose should not exceed 100 mg/kg.

The most frequent reason for the prescription of antipyretics by doctors is the comfort of the child[40]. In the benign condition of simple febrile convulsions paediatricians usually prescribe antipyretics despite evidence that antipyretics do not prevent further convulsions[41–43]. In a double-blind placebo-controlled trial paracetamol 10–15 mg/kg in children with fever, parents were unable to detect any advantage in comfort, mood, appetite or fluid intake from the antipyretics, though there was some improvement in alertness and activity[44]. In two of three studies in which paracetamol was given prophylactically for pain and fever after immunization, paracetamol reduced fretfulness[45–47], but this action can be ascribed to its potent analgesic properties. These studies have limited relevance to children with viral infections since pain is an uncommon accompaniment. The use of antipyretics to relieve discomfort which is not pain is clearly incongruous when large numbers of people derive pleasure from saunas and jogging in warm weather—activities causing a body temperature rise of 2°C or more[26]. When an infection does cause pain, such as the headache of influenza, then analgesia is clearly appropriate.

What about very high fever? It is true that cellular damage arises when temperature exceeds 41°C, but such a temperature in fever is very rare[48,49]. In children, fever seldom exceeds 40°C, a temperature commonly found in marathon runners after a race[50]. Furthermore, temperatures as high as 42°C are remarkably well tolerated by cancer patients undergoing therapeutic hyperthermia to slow tumour growth[50].

We know that the behaviour of parents can be effectively modified by education and reassurance about fever[51,52]. We must now see whether the prescribing habits of a generation of doctors can likewise be changed for the better.

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