

## THE ROLE OF FEVER IN THE PAST AND PRESENT

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#### INTRODUCTION

Fever is perhaps the most ancient hallmark of disease. It dates back as far as civilization itself. For most of the history, fever was feared by ordinary people as a manifestation of punishment, induced by evil spirits or a marker of death. For medical scholars, however the biological role of fever in disease was considered as beneficial, particularly so among Greek scholars (Ancient concepts). This concept underwent a radical transformation in the 19th century and scholars began to regard fever as harmful. The use of antipyretics was considered beneficial (Changing concepts). With the introduction of fever therapy in the 20th century, renewed interest in the role of fever began (Current concepts).

Various forms of antipyretic therapy have been used since ancient times to lower body temperature in febrile patients. Nowadays, antipyretics are among the most used drugs worldwide. Despite their widespread use and popularity, questions arise as how beneficial is the fever? Do antipyretics prevent fever from climbing unabated? What are the arguments in favour and against fever in the history, including religious doctrines? Is there any scientific evidence at present in support of the ancient belief about fever? The article summarizes the knowledge about fever and the changing concepts of its role in diseases from ancient cultures to our present time.

#### CONCEPTS OF FEVER IN THE HISTORY

The oldest civilizations (Egyptian, Mesopotamian, Chinese, Indian, and Greek) demonstrated extensive knowledge of fever, but tended to view it as being induced by evil spirits. Hence exorcism was used in many ancient cultures (to a lesser extent in Greek medicine) for the treatment of fever. Many ancient physicians, however, fostered mainly by the Greeks, believed in the beneficial effects of fever. Hippocratic writings, for example, contain evidence that fever was thought to be beneficial to the infected host (1). Rufus of Ephesus in the second century AD strongly advocated the beneficial role of fever. He recommended the use of "fever therapy" (such as by malaria) to treat various diseases, including epilepsy (2). Fever therapy was the principal form of treatment, not only for syphilis and gonorrhoea, but also for patients with rheumatoid arthritis and asthma. This belief, held for about 2000 years, should not be ignored. Virtually all cultures use some form of "fever therapy" in the form of "saunas," or "sweat lodges," or "steam baths," or other ways to raise body temperature artificially. This probably dates back to the Hippocratic era and is based on the "humoral" theory of disease, where one of the forms of therapy was to "cook" the bad "humour." Events in the history are known to repeat themselves, so are medical practice and concepts.

With the beginning of the Middle Ages (ca. 400-1400 AD), science and medicine became less important than theology and philosophy (3). Galen's writings remained a great influence on medicine during the Middle Ages. He

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had a philosophy embracing body, mind and soul, which was highly acceptable to the religion of the developing church (4). The central development of medicine was in anatomy learned mainly from animal dissections but a few were performed on humans. Anatomical studies began at Bologna (ca.1150 AD) and Padua University (ca.1222 AD). Physiology and pathology were still based upon the four humours (blood, phlegm, yellow and black bile). All diseases were characterized as hot, cold, moist or dry. 'Hot diseases' were treated by cooling, 'moist diseases' by drying. Bloodletting was widely used to treat febrile illnesses and practiced by Galen and some other ancient physicians. This was based on the notion of plethora, a theory that attributed disease to congestion of blood in part of the body. Apart from bloodletting, other methods attempted to cure acute fever included cooling, emollients and laxatives.

With the destructive epidemics of the Black Death (Bubonic Plague), which killed as much as one third (reportedly twenty-five million) of the European population in the 14th century (with the peak in 1348), fever became a marker of death. Medicine was not helpful in preventing or treating the illness. The wrath of fever was still attributed to demonic possession and therefore required exorcism to expel it in line with evolving theological doctrine. The belief that fever constituted divine punishment also prevailed, particularly among the devout.

#### CONCEPTS OF FEVER IN RELIGIONS

The roots of Hebrew medicine can be traced to the Torah or Old Testament (compiled between 1500 BC and 300 BC) and the Talmud (a book of rules and precepts completed between 70 BC and the second century AD) (5).

Magic, incantation, and mystics appear to be less significant than in other cultures. Certainly, the Biblical record contains no indication that fever was caused by demons or evil spirits. In the Old Testament, fever was part of God's punishment for sins. The Creator of heaven and earth, Yahweh, states "but break my covenant, then be sure that this is what I will do: I will bring upon you sudden terror, wasting disease and recurrent fever" (Leviticus 26: 16; Deuteronomy 28: 22).

In the New Testament fever is also mentioned on several occasions, always without comment on causation. The

first time, Jesus saw in Peter's house, "his wife's mother laid and sick of a fever and he touched her hand and the fever left her" (Matthew 8: 14-16, Mark 1: 29-34, Luke 4: 38-41). Elsewhere, Jesus healed the official's son with his words (John 4: 49- 52), and the apostle Paul prayed to God and placed his hands on Publius, who was then healed of fever and a bloody flux, meaning dysentery (Acts 28: 8).

Islamic Medicine originated from the time of the Prophet Mohamed (PUH). In Sahih Bukhari narrated by Fatima bint Al-Mundhir: Whenever a lady suffering from fever was brought to Asmaa' bint Abu Bakr, she used to invoke Allah for her and then sprinkle some water on her body, at the chest and say, "Allah's Apostle used to order us to abate fever with water." Prophet (PUH) recommended: barley for fever in a soup form.

Islamic teachings encouraged seeking medical knowledge as it is narrated in different narrations through Bukhari, Termithi, Ibn Majah and Muslim that the prophet (PUH) said: "Oh' people seek remedies as Allah has not created an illness except that He created its cure, however some people would know it while others won't. Unlike the 'dark period' in European medicine, Islamic medicine flourished to reach its golden age in the ninth and tenth centuries. The writings of both Hippocrates and Galen were carefully translated from Greek into Syriac and Arabic. Two scholars were outstanding in this period. Abu Ali Husayn ibn Abdulla ibn Sina (AD 980-1037), latinized as Avicenna<sup>7</sup> was, like Galen, a philosopher and physician. His best work, Qanun Fit-Tibb, or Canon of Medicine was a vast encyclopaedia.

The second great scholar was Abu Bakr Muhammad Zakariya Al-Razi (AD 864-923, latinized as Rhazes) was the first scholar to differentiate measles from smallpox with his original treatise on the two diseases (8). On smallpox he wrote: The eruption of the smallpox is preceded by a continued fever, pain in the back, itching in the nose and terror in sleep. There is redness in both cheeks, both eyes, heaviness of the whole body and distress and anxiety. Rhazes' best known medical work "Kitabul-Hawi Fit-Tibb" or Contents of Medicine" appeared in 25 volumes. He noted that for example "exercise excites heat and fuels it like blowing into fire", he also reported that fever in tuberculosis is mild and blun.

One of Rhazes' remarkable observations was his differentiation of fever (elevated central thermoregulatory set-point) from heat stroke (normal central thermoregulatory set-point): "there is another fever with a higher core temperature than the common fever, where patients are much thirstier and the body feels hot all over.<sup>9</sup> Rhazes was probably the first scholar to distinguish between the two terms fever and hyperthermia in the form of heat stroke. These two terms are often equated even nowadays.

### CHANGING CONCEPTS

In the 19th century, fever was still regarded as both: 1) Part of a symptom complex (as it is today) and 2) a disease in its own.<sup>10</sup> Examples of fever being regarded as a disease were 'autumnal fever, jail fever, and hospital fever'. Fever could also be described in terms of the severity of the disease, for example 'malignant fever' or 'pestilential fever', or even in terms of the supposed pathology of the fever, 'bilious fever' or 'nervous fever'. The multiplicity of names for fever reflects the lack of a breakthrough into an understanding of the causes of febrile illnesses. The breakthrough came with the science of bacteriology, which was able to reveal the etiology of many infectious diseases, such as the identification of the typhoid bacillus in 1880, and the discovery of the tubercle bacillus in 1882. These discoveries related fever to a sign of disease. Great scholars of this period include Claude Bernhard (1813-1878), the great French physiologist, recognised that body temperature was regulated in healthy organisms by the balancing of heat production and loss. He demonstrated that animals died quickly when the body temperature exceeded the normal level by 5-6°C, thus suggesting that fever may be harmful and that antipyretics, which were introduced later, may be beneficial (11). William Osler declared that 'the humanity has three enemies, fever, famine and war, but fever is by far the greatest'.

### CURRENT CONCEPTS

Fever is among the most common complaints and causes of seeking medical attention. The biological value of fever (i.e. whether it is beneficial or harmful) is a matter of dispute and fever is being treated with the

belief that this may prevent complications. Before reaching a conclusion as to whether fever is beneficial, neutral or harmful, there are arguments in favor and against fever being harmful which are discussed next.

#### A. Arguments for fever being harmful

1. *Prevailing concepts among physicians and Parents.* Fever is a frightening experience for parents who usually believe that fever is harmful and may bring about discomfort, dehydration, febrile convulsions, brain damage, and death. Antipyretics are parents' preferred method of managing fever and there has been an increase in this preference over the past two decades from 67% to more than 90% (13).

Most pediatricians agree that treatment of a febrile child with antipyretics is for the relief of the symptoms of fever. However, many tend to prescribe antipyretics for a child with any degree of fever. In a study<sup>12</sup> exploring the beliefs and practices of pediatricians in Massachusetts, USA, the majority (65%) of respondents believed that fever itself could be dangerous and can cause seizures, brain damage and death if the temperature is 40°C or greater.

2. *The risk of febrile seizures (FS).* Fever can cause a brief benign convulsion in 3% to 4% of all children. In a study<sup>14</sup> from the USA, 49% of pediatricians considered convulsions to be a principal danger of fever and 22% believed that brain damage could result from FS and that antipyretic measures should be administered to prevent FS and other complications of fever.

#### B. Arguments for fever being beneficial

1. *Fever is self-limiting and well-controlled.* With fever, unlike hyperthermia, body temperature is well regulated by a hypothalamic set-point that balances heat production and loss so effectively that the temperature will not climb up relentlessly and does not exceed an upper limit of 42°C. Within this upper range of 40 to 42°C, fever is not injurious to tissue. About 20% of children seen in the emergency room have temperatures over 40°C and they usually make a full recovery. If there is morbidity or mortality, it is due to the underlying disease. The associated fever may well be protective.

2. *Antipyretics do not prevent FS.* There is now abundant evidence against the previously assumed risks of FS. It is also known that antipyretics are ineffective in the prevention of FS. Two large population-based studies<sup>15-17</sup> found no deaths or persistent motor deficits directly attributed to FS. A temperature  $>40^{\circ}\text{C}$  with the first seizure was associated with a decreased incidence of recurrence of FS (18). An evidence-based research (19) concluded that antipyretic drugs are ineffective in preventing FS and should not be recommended for preventing further FS.

3. *The effects of fever on microorganisms.* Animal studies have demonstrated that Gram-negative bacteria, such as salmonella typhi, were shown to be increasingly susceptible to the antibacterial effects of serum when cultivated at a temperature  $>37^{\circ}\text{C}$  (20). Most viruses ceased to replicate at a temperature between  $40^{\circ}\text{C}$  and  $42^{\circ}\text{C}$ . The replication rate of poliovirus at  $37^{\circ}\text{C}$  was 250 times more than that at  $40^{\circ}\text{C}$  (21).

In human studies fever was the principal form of treatment for syphilis and gonorrhoea for centuries. Insufflation of humidified air at  $43^{\circ}\text{C}$  (three 30-minute sessions at 2-3 hourly intervals) into the nasal passages of patients suffering from coryza resulted in the suppression of symptoms in 78 per cent of patients (22). Fever may also be beneficial in patients with meningitis: the presence of fever greater than  $40^{\circ}\text{C}$  did not indicate a poor prognosis, but all children presenting with hypothermia died (23). A study from Japan (24) found that the frequent administration of antipyretics to children with bacterial diseases led to a worsening of their illness. In another study included 102 children with salmonella gastroenteritis from Finland (25) there was a significant negative correlation between the degree of fever and the duration of excretion of organisms. Subject with fever of greater than  $40^{\circ}\text{C}$  had the shortest duration of bacterial excretion whereas those without fever had the longest duration. Fever has therefore a favourable prognostic influence on the length of bacterial excretion.

4. *Effects of elevated temperature on defence mechanisms:* The mobility, phagocytosis and killing of bacteria by polymorphonuclear leukocytes are signifi-

cantly greater at temperatures above  $40^{\circ}\text{C}$  (26). Elevated temperatures of 38 and  $39^{\circ}\text{C}$  have a direct positive effect on lymphocyte transformation, the generation of cytolytic cells, B-cell activity, and immunoglobulin synthesis. Interleukin-1 is more active at febrile temperature (27, 28). Interferon (INF), a potent antiviral agent, has enhanced antiviral activity above  $40^{\circ}\text{C}$  (29,30). T-cell proliferative response to interleukin-2 and interleukin-1 was greatly increased at  $39^{\circ}\text{C}$  compared to  $37^{\circ}\text{C}$ .

Fever may act synergistically with antibiotics. Penicillin was found to have a progressive increase of its bactericidal activity as the temperature rose from  $35^{\circ}$  to  $41.5^{\circ}\text{C}$  (31).

There is evidence that elevated body temperatures in the range of  $41-42^{\circ}\text{C}$  can effect the growth of certain tumours. Occasional remissions of Hodgkin's disease occurred after an attack of measles. The metabolism of many types of cancer cell is selectively damaged at temperatures of  $42-43^{\circ}\text{C}$  (32). Lysosomal enzymes, IL-2 and INF have increased activity at such temperatures, and may contribute to tumour cell destruction.

5. *The Hygiene Theory:* The prevalence of asthma and allergic diseases as well as cancer has increased worldwide for many years and the hygiene theory has been offered to explain the rise (33,34). The theory proposes that early exposure to fevers caused by infections (in particular infection of the upper airways, hepatitis A and Helicobacter pylori) might protect children against allergic diseases and cancer later in life. It postulates that atopy, or allergy, is Th2-driven, which is primarily associated with IL-4, IL-5, IL-10 and IL-13 production, whereas infection is Th-1-driven, which is dominated by production of INF-gamma and IL-12. In association with reduced exposure to infections, Th-2 immunity dominates through critical childhood periods, resulting in higher incidence of atopy. In support of this theory are the following findings:

- The prevalence of atopy is lower among children of large families or those attending day-care nurseries than among children of small families or those not at nurseries.

- Children with older siblings are less likely to develop allergies than children with younger siblings or none at all.

- Children who experienced several febrile episodes during the first year of life have lower incidence of allergies than those with only one or no febrile illness.

- Children exposed to high levels of endotoxin (a major product from gram-negative bacteria) show reduced prevalence of atopy.

- The use of antibiotics during the first year of life is associated with increased incidence of asthma, hay fever and eczema later in life. Antibiotics could destroy the beneficial bacteria (probiotics) in the digestive tract.

- Atopic diseases are rare in countries with parasitic infestation.

- A study from Switzerland (35) demonstrated a significant association between febrile infections during childhood and the risk of developing cancer in adulthood.

Thus, we conclude from these intriguing data that exposure to infectious diseases in early childhood, particularly those that may be associated with modest fevers, may protect the child against a wide array of future diseases.

#### 6. Side-effects and fatalities from using antipyretics:

It is well-established that reducing the fever with antipyretics does not usually have a positive role on the underlying disease, nor does it reduce the time of infection.

Antipyretics are known to cause adverse reactions, such as gastrointestinal bleeding and renal failure, and some fatalities (37). In the UK, 10% of inquiries to the National Poisons Information Services and up to 43% of all hospital admissions for self-poisoning are due to paracetamol ingestion. In another study, paracetamol has been one of the most popular choices for suicide attempts in adolescents and adults, causing 100-150 deaths in the UK annually. In the USA, paracetamol-associated overdoses account for 56,000 emergency visits, 26,000 hospitalizations, with approximately 450 deaths each year. About 100 of these deaths are unintentional (36).

#### CONCLUSION

Over the past 40-50 years, intensive research has been carried out to investigate the role of fever. Although there is still debate whether fever is beneficial or harmful. There is evidence now indicates that the effects of fever are complex but overall beneficial. Accumulated data from extensive research suggest that fever has a protective role in promoting host defence against infection, rather than being a passive by-product. There is evidence that fever exerts an overall adverse effect on the growth of bacteria and some tumours, as well as on replication of viruses. It also enhances immunological processes.

Although scientific evidence does not support this practice, antipyretics are often prescribed automatically for children with fever whether the child is playful or appears toxic with significant discomfort due to fever. This current practice is widely accepted although gives the wrong impression to patients, parents and other health professionals that fever per-se is harmful and that antipyretics are needed. It is the underlying disease which we should be concerned about and not the fever per se. The presence of fever could be beneficial to the infected host.

As clinicians, we need to educate our patients and other health professionals about this fact and that antipyretics should be used sparingly in our clinical practice.

We should recognize that the issue as to whether fever is beneficial or not is still controversial and more efforts should be exerted to determine this function in every febrile disease. In particular, we need to know which diseases are likely to benefit from the presence of fever, so that minimal interference during their courses may be considered and in which diseases fever may be harmful and need to be treated. It is also important to determine what degree of fever is dangerous and measures must be taken to reduce it. Until these types of studies are conducted for a wide assortment of infections, the question of whether most fevers should be left alone or treated in the pediatric or adult patient will remain unanswered.

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