Role of Fever in Disease

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ABSTRACT: Infection, trauma, and injury result in a stereotypical response that includes loss of food appetite, increased sleepiness, muscle aches, and fever. For thousands of years fever was considered a protective response, and fevers were induced by physicians to combat certain infections. But with the advent of antipyretic drugs, physicians started to reduce fevers, and fever therapy was virtually abandoned. As a result of (1) studies on the evolution of fever, (2) further understanding of just how tightly the process of fever is regulated, and (3) detailed studies on how fever affects host morbidity and mortality, the view of fever as a host defense response has reemerged. However, data indicate that not all fevers are protective and that high fevers are maladaptive. These issues are discussed in the context of the evolution of host defense responses versus modern medical technology. In short, we speculate that patients who would not have survived severe sepsis in the past are now being kept alive and that the occasionally high fevers seen in these patients may be maladaptive.

Considerable evidence exists that fever is generally a host defense response, which decreases morbidity and mortality. In a recent review, Hasday1 summarized the effects of febrile temperatures on specific and nonspecific immunity. However, the results were not convincing either for or against fever being protective, because many studies reviewed had used “hyperthermia” rather than febrile temperatures. Clearly the data obtained at excessively high temperatures may have no physiologic relevance. In general, temperatures that simulate naturally occurring fever (e.g., 38° to 39°C) enhance host defenses.

Examination of the effects of temperature on individual host defense responses provides only a small picture of the potential adaptive value of fever. Several aspects of fever that support the hypothesis that it is an adaptive response are discussed.

FEVER, A HIGHLY REGULATED RESPONSE

As discussed throughout this symposium, fevers are triggered by the release of “endogenous pyrogens” from different types of macrophage-like cells. These pyrogens include the cytokines interleukin (IL)-1, IL-6, and others. They act at the level of the anterior hypothalamus to raise the thermoregulatory set point, and various physiologic and behavioral responses are initiated that result in the elevation of body temperature (e.g., see ref. 2). In addition to the release of endogenous pyrogens, endogenous antipyretics or cryogens are also released. They act to modulate the febrile rise in body temperature, thus generally preventing it from rising to dangerous levels. Over the last

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10 years, investigators have shown that arginine vasopressin, α-melanocyte stimulating hormone, glucocorticoids, and, in some cases, tumor necrosis factor (TNF)-α may act as endogenous antipyretics. This highly regulated nature of fever serves to support the argument that fever has evolved as a host defense response.

EVOLUTIONARY HISTORY OF FEVER

With few exceptions, both endothermic and ectothermic vertebrates (as well as invertebrates) develop fevers in response to injections of endotoxin or other substances pyrogenic to mammals. The body temperatures of these animals rise as a result of their “feeling” cold and therefore selecting a warmer microclimate. Although studying present-day organisms does not directly relate to the question of the evolution of fever (or any other variable), it is probable, based on its widespread occurrence, that the febrile response evolved hundreds of millions of years ago. Fever even appears to exist in the single-celled paramecium.

There have been a few reports of ectothermic vertebrates that have failed to develop fever. Negative results should always be viewed with caution, particularly in the area of the biology of fever. A fever might not develop in an animal for several reasons. First, the pyrogen used may not be the appropriate stimulus for that species. For example, a dose of lipopolysaccharide (LPS) that might cause a high fever in the rabbit (e.g., 5 ng/kg) may not cause any detectable fever in the rat. A bacterium that might cause sickness and perhaps even death in one species might be “seen” as an innocuous stimulus in another and, therefore, not trigger an elevation in the thermoregulatory set point. Second, the dose of pyrogen might be too high; for example, in the rabbit a dose-dependent fever will develop in response to ng/kg doses of LPS, but at a high dose (e.g., 50 μg/kg) endotoxic shock will occur, and body temperature will fall. Doses of LPS within the μg/kg range produce a high fever in the rat, whereas 2.5 mg/kg is required to produce high fevers in the mouse.

Another reason to be particularly cautious when interpreting negative results is that fever is a complex response that presumably requires the release of endogenous mediators, an elevation in the thermoregulatory set point, and ultimately behavioral and physiologic responses that raise body temperature. A “stressed” animal might not develop a fever for several reasons. One reason could be related to the suppressive effects of glucocorticoids, which are elevated during stress, on the release of endogenous pyrogens or on the production of prostaglandins. The phenomenon of “stress-induced hyperthermia” may also be involved. In rats, for example, exposure to novel environments or handling produces rises in body temperature of as much as 2°C (reviewed in ref. 2). Rises in body temperature of humans in response to psychologic stress have also been reported. If body temperature is already elevated as a result of some aspect of the experimental design, then it might be impossible to demonstrate a fever in response to an injection of some exogenous pyrogen.

A key element is usually missing in negative studies pertaining to fever—the lack of a positive control. It is essential that investigators demonstrate that their animals are thermoregulating and that injection of some substance known to elevate body temperature (e.g., catecholamines, biogenic amines, and opioids) actually raises the body temperature of the species being studied. If a drug elevates body temperature, but a series of doses of putative pyrogens does not affect body temperature, then this would provide critical evidence that the species does not respond to that pyrogen by developing a fever.

How might the seemingly long evolutionary history of fever relate to the role of fever in disease? One clue may be the severe cost to the organism of developing a fever.
In endotherms such as birds and mammals, maintenance of body temperature of 2°C or 3°C above afebrile levels often results in an increase in their energy consumption by 20% or more. This is the result of the Q_{10} effect of increased temperature on various biochemical reactions. In ectothermic vertebrates, the amount of excess energy expended during fever is unknown, although a recent study by Sherman and Stephens^{12} showed that febrile temperatures increase metabolic rate of toads with a Q_{10} of 1.8 for control animals and a Q_{10} of 4.1 for LPS-injected animals. If fever did not have an adaptive function, then it is unlikely that this energetically expensive phenomenon would have persisted for millions of years in so many groups of organisms.

**EFFECTS OF FEVER ON MORBIDITY AND MORTALITY**

Perhaps the most convincing way to determine if fever is protective is to study its effects on morbidity and mortality. We believe that the evidence overwhelmingly points towards the role of fever in enhancing specific and nonspecific immunity. These studies can be divided into (a) correlational, (b) antipyretic, and (c) hyperthermic and hypothermic studies.

**Correlational Studies**

Clinical studies in humans generally have shown that the magnitude of a fever is associated with the severity of the infection.^{13} As a result, patients with the highest fevers tend to have the highest mortality rate. Unfortunately, studies involving humans are completely uncontrolled. Often, results are confounded because some patients receive certain drugs that others do not. Furthermore, the patients clearly have not been infected with identical doses of pathogens. In addition, patients seek medical attention at different stages of infection. Nevertheless, impressions can be formed from the clinical literature, some of which will be discussed below.

In studies that have correlated body temperature with survival rate, several investigators have found that fever is associated with better prognoses during bacterial infections.^{14-17} In one study, no correlation was found between fever and survival rate, but hypothermia in adults or newborns was associated with a higher mortality rate.^{18}

Assimondi et al.^{19} showed that fever during the first 7 days after the onset of cerebral ischemia is a predictor of poor outcome. These data support findings in animal studies that show that higher temperatures are maladaptive during stroke.

New Zealand white rabbits respond to infection with Pasteurella multocida by developing large fevers. Most rabbits developed a fever of less than 2.25°C, and within this temperature range, survival rate is increased as body temperature is elevated.^{20} A small number of animals developed fevers above 2.25°C and showed a decrease in survival rate.

Another correlational study was reported by Toms et al.^{21} In this study, ferrets (Mustela sp.) were infected with different strains of influenza virus, and the resultant fever was correlated with the presence of live viruses in their nasal passages. Groups of three to six ferrets were inoculated intranasally with a constant dose of virus. At 4-hour intervals, the nasal passages were washed, and the fluid was collected and assayed for the presence of live virus. Statistically significant (p <0.01) negative correlations were found between the ferrets' rectal temperatures and the presence of live viruses in the nasal washes, suggesting that fever might lead to inactivation of viruses. In vitro observations from this same laboratory, in which organ cultures of ferret nasal turbinates were grown in the presence of influenza virus, are consistent with the in vivo data just
described. That is, elevation in temperature of the cultures decreases the replication of the viruses. Interestingly, the more virulent strain of virus is less sensitive to the effects of temperature.

In summary, the results of correlational studies with human and animal subjects are consistent with the theory that under most conditions moderate fevers are beneficial in fighting infection, whereas high fevers are indicators of overwhelming insult and may be maladaptive.

*Antipyretic Studies*

In several studies a population of mammals were infected with identical amounts of pathogens and the effects of antipyresis on mortality or morbidity quantified. Some of these studies combined antipyretic drug therapy with the use of other drugs (e.g., glucocorticoids or antibiotics), and thus the results are difficult to interpret (e.g., ref. 23). Others used “antipyretic” drugs such as aspirin, acetaminophen, or ibuprofen, but no temperature measurements were noted, and thus it is impossible to relate morbidity to temperature.

Van Miert et al. studied the effects of flurbiprofen, a nonsteroidal anti-inflammatory and antipyretic drug, on *Trypanosoma vivax* infection in goats. They found that this drug blocks febrile responses during the acute phase of the infection, with the antipyretic drug alone not affecting afebrile body temperature. Sixteen of 17 goats given *T. vivax* without flurbiprofen had a mild infection. All five infected goats treated with an antipyretic dose of flurbiprofen died. Vaughn et al. studied the effect of administering an antipyretic drug directly into an area of the brain of rabbits implicated in the control of fever, the preoptic-anterior hypothalamus, on their mortality rate during infection with *Pasteurella multocida*. Fevers in the rabbits infused with the antipyretic drug were reduced about 50%. This group of infected rabbits demonstrates a significant increase in mortality compared to the group of infected rabbits infused with control solution. Husseini et al. studied the effects of suppression of fever to influenza in ferrets using sodium salicylate and found that treatment with the antipyretic drug results in attenuation of fever and an increased concentration of virus in washes, as well as an increase in the duration of illness.

Small et al. investigated the effects of body temperature on bacterial growth rates in experimental pneumococcal infection in rabbits. Rabbits were injected with *Streptococcus pneumoniae* intracranially and developed fevers averaging 1.5°C. To lower body temperature, rabbits were anesthetized with pentobarbital or urethane and the ambient temperature was maintained at febrile or afebrile temperatures. The growth rate of bacteria was significantly higher in anesthetized rabbits maintained at afebrile body temperatures. The correlation between changes in bacterial titer in the cerebrospinal fluid and body temperatures (from 38.5°C to 41°C) was −0.70 (p < 0.001) suggests that elevated temperatures suppress the growth rate of the bacteria. Kurosawa et al. studied the effects of antipyretics in rinderpest infection in rabbits. Rabbits were infected with the lapinized Nakamura III strain of RPV (L strain) and then treated with mefanamic or acetylsalicylic acid or not treated. Administration of antipyretic drugs led to varying amounts of reduction in body temperature. Treatment with either drug resulted in increased mortality and slower recovery among the survivors.

Ectothermic vertebrates have also been used to study the role of fever in disease. Bernheim and Kluger studied the effects of sodium salicylate-induced antipyresis on survival of the lizard *Dipsosaurus dorsalis*. Lizards were injected with live bacteria (*Aeromonas hydrophila*) along with a dose of sodium salicylate. Seven of the 12 animals treated with the antipyretic drug failed to select a febrile temperature in a thermal
gradient. All febrile lizards survived, whereas the afebrile lizards died. To determine whether the dose of sodium salicylate used in these experiments was toxic, eight lizards were injected with live bacteria and sodium salicylate and placed inside a constant temperature chamber. Their body temperatures were maintained at the febrile level by adjusting the chamber temperature to 41°C during the day (about the average temperature selected by febrile lizards in the simulated natural environment) and at low temperatures at night (again, as in the simulated natural environment). Only one of these eight lizards died, indicating that the dose of sodium salicylate used in the experiments was not toxic. These data indicate that the administration of sodium salicylate to the infected lizards is harmful only when it results in a reduction in body temperature to the afebrile level. When sodium salicylate fails to produce antipyresis, the survival rate of infected lizards is not adversely affected by the drug.

Thus, the increase in morbidity and mortality in studies using antipyretic drugs to attenuate fever also supports the hypothesis that fever is a host defense response.

**Hyperthermic and Hypothermic Studies**

Although it is difficult to draw definitive conclusions concerning the role of fever in disease based on studies of hyperthermia or hypothermia, the weight of evidence supports an adaptive function for fever during infections with certain bacterial or viral pathogens.

Strouse\(^{30}\) showed that the natural resistance of pigeons to pneumococci is related to their normal body temperature of about 41.5°C. When their body temperatures were reduced by peripheral cooling or the administration of drugs, they became susceptible to the infection and died. Similar findings were reported by Muschenheim et al.\(^{31}\) for pneumococcal infections in rabbits. The experimental group was infected with pneumococci, and hypothermia was induced by one of several methods so that the rectal temperatures of these rabbits were maintained between 30°C and 34°C. The control group was infected, and their body temperature was maintained at normal to low febrile levels, between 39°C and 41°C. All of the hypothermic rabbits died, whereas only 5 of the 31 control rabbits died. These investigators concluded that hypothermia is clearly harmful to the infected host and that the development of fever enhances the host defense mechanism.

Vaughn et al.\(^{32}\) found that even though treatment of rabbits with antipyretic drugs increases the mortality rate to *P. multocida*, physical cooling of rabbits decreases mortality rate. In this study, rabbits were cooled for 48 hours after injection with bacteria by passing cold fluid through a small cuff surgically placed around the abdominal vena cava. The cooled rabbit maintained average body temperature at about the normal afebrile temperature for rabbits (38.98°C), and the non-cooled rabbits had body temperatures averaging 40.92°C. The cooled rabbits would presumably have a body temperature below their thermoregulatory set point and as a result would be activating a variety of heat conservation and production effector responses. The investigators of this study suggested that thermoregulatory effector mechanisms involved in cold defense may enhance survival. These data are similar to those of Banet\(^{33}\) for rats infected with *Salmonella enteritidis*. In this study, the spinal cords of rats were cooled, resulting in an increased metabolic rate (oxygen uptake) and a survival rate that was borderline significantly higher than that in infected animals whose spinal cords were not cooled (*p* = 0.06). Interestingly, no differences were noted in core temperatures between control and experimental rats. Banet\(^{34}\) then showed a correlation between survival rate and the increase in metabolic rate during the rising phase of fever in rats infected with *S. enteritidis*. In rats infected with an LD\(_{50}\) of bacteria, there was a negative correlation between
the highest fever obtained and survival rate at fevers above 38.7°C. What this might mean, however, is that the sickest animals mounted the greatest febrile responses, but despite any beneficial effect of fever, they had a higher mortality rate. Banet argued that some of the effects of endogenous pyrogens on the altering metabolism, presumably the neuroendocrine changes, are beneficial and that the elevation in temperature itself may often be harmful.

The febrile response of the newborn is an area that has received considerable attention. It has long been known that many newborn mammals have a labile body temperature during their first few days of life. Furthermore, in response to infection, newborn human infants or other infant mammals, such as rabbits, tend to have a limited febrile response. Haahr and Mogensen suggested that hyperthermia (or more precisely a rise in body temperature) during certain viral infections is beneficial to newborns. To support their claim, they cited several studies that demonstrated that elevations in body temperature during various viral infections have reduced the mortality rate in newborn mice, dogs, and human beings. For example, Teisner and Haahr found that when 2-3-day-old mice were infected with Coxsackie virus and held at an environmental temperature of 34°C, they had a mean body temperature of 35.8°C, some 2°–3°C higher than that of control mice held at room temperature of 22°–24°C. Those mice held at 34°C had a considerably lower mortality rate than did the control mice. Carmichael et al. reported similar findings for 2-5-day-old dog pups that were inoculated with canine herpesvirus. When the pups were held at an environmental temperature of 28°–30°C, they had a rectal temperature of about 35°–37°C; those held at an environmental temperature of 36.7°–37.7°C had a rectal temperature of 38.3°–39.4°C, approximately normal rectal temperatures for adult dogs. Following inoculation with herpesvirus, dogs with lower rectal temperatures died within 8 days, whereas those with higher rectal temperatures survived 9 days or longer. The investigators concluded that the elevation of body temperature to the adult level is beneficial to the infected pups. Based on these data, Haahr and Mogensen suggested that one reason generalized herpes-simplex infections are greatly overrepresented in premature babies may be attributable to their restricted temperature regulation and poor febrile response. Thus, although newborns might not develop fevers due to inadequate metabolic machinery or the ability to behaviorally thermoregulate, allowing them to have an elevated body temperature during infections appears to be protective.

Bell and Moore found that housing mice inoculated with rabies virus in a warm ambient temperature (35°C) leads to decreased mortality. The average body temperatures of mice in the warm environmental temperature were 2°C higher than those of mice in the control environment (20°C). Yerushalmi and Lwoff found that treatment of human subjects with local hyperthermia (i.e., inhalation of warm humidified air) decreases the magnitude of acute rhinitis (“infective Coryza”). However, in a follow-up study, Macknin et al. found a slight improvement in patients with rhinitis who were provided with cool vapor compared to the warmed air.

Mice infected with influenza develop a regulated hypothermia (anaplexa) rather than a fever. This regulated reduction in body temperature appears to be protective. A large body of literature shows that hypoxia induces a reduction in body temperature that enhances host survival, and preliminary data of Kozak and Malvin support the hypothesis that the reduction in body temperature in influenza-infected mice is, at least in part, attributable to hypoxia.

Many hypothermia/hyperthermia studies have also been designed to investigate the role of fever using ectothermic species. For example, to investigate whether the rise in body temperature in the bacterially infected desert iguana (Dipsosaurus dorsalis) had survival value, lizards were injected with live A. hydrophila and placed in incubators at 34°, 36°, 38°, 40°, and 42°C. Control lizards were inoculated with saline solution and
then placed into the incubators. The relation between the lizards' temperatures and percentage survival following bacterial infection was highly significant ($p < 0.005$). Within 24 hours, approximately 50% of the infected lizards maintained at the afebrile temperature of 38° were dead. However, lizards maintained at the febrile temperatures of 40°C and 42°C had only 14% and 0% mortality, respectively. Conversely, infected lizards maintained at 36°C and 34°C, temperatures that are hypothermic for this species of lizard, experienced mortalities of 66% and 75%, respectively. After 3 1/2 days, all the lizards at 34°C were dead. After 7 days the percentages of mortalities were as follows: 34°C, 100%; 38°C and 36°C, 75%; 40°C, 33%; and 42°C, 25%. By contrast, lizards injected with saline and maintained at 34°C, 38°C, and 42°C for 7 days experienced 0%, 0%, and 34% mortality, respectively. At the highest temperature tested, the pattern of deaths was similar for the controls and the infected lizards. Whereas most lizards died within 3 1/2 days when maintained at 34°–40°C, virtually all deaths at 42°C occurred after 3 1/2 days. Apparently, maintenance at 42°C for a period exceeding 3 1/2 days is harmful in itself. This suggests that the deaths at 42°C were not due to the bacterial infection, but to some undetermined adverse effect of long-term elevation in body temperature in lizards.

Several studies have examined the effects of temperature on the mortality rate of fish. One study, by Covert and Reynolds,46 entailed infecting goldfish with live A. hydrophila and monitoring their survival rate over 3 days. These investigators reported that several species of freshwater fish developed fevers in response to infections with these bacteria.46,47 In their survival study, they held the infected goldfish at temperatures of 25.5°C, 28.0°C, or 30.5°C, which represented, respectively, hypothermic, normothermic, and febrile temperatures. Goldfish maintained at a febrile temperature of 30.5°C had a survival rate of 84%; those maintained at 28.0°C had a survival rate of 64%; those at 25.5°C had a survival rate of 24%. Another 10 fish injected with the same dose of live A. hydrophila were allowed to thermoregulate in a shuttlebox. These fish selected an ambient temperature that allowed them to develop a fever averaging almost 5°C and had a mean body temperature of 32.7°C. None of these fish died. Covert and Reynolds concluded that a fever in response to infection with A. hydrophila increases the survival rate of goldfish.

Louis et al.48 infected crickets (Gryllus bimaculatus) with the intracellular parasite Rickettsiella grylli. When infected and allowed to select a body temperature in a temperature gradient, the crickets selected a temperature averaging 33.0°C; when not infected, they selected an average body temperature of 26.6°C. When infected crickets were reared at different ambient temperatures, those maintained at temperatures > 29°C survived this infection.

Boorsttein and Ewald49 inoculated grasshoppers (Melanoplus sanguinipes) with the protozoan Nosema acridophagus and found that this resulted in an increase in preferred body temperature of about 6°C (to about 40°C). Maintenance of grasshoppers at febrile and afebrile temperatures demonstrated that fever enhances both survival rate and growth. Infected grasshoppers maintained at febrile temperatures demonstrated increased fecundity, as quantified by numbers of eggs laid, compared to those maintained at afebrile temperatures.

More recently, Kurz et al.50 studied the effect of perioperative normothermia on the incidence of surgical wound infection in humans. They found that the group allowed to become hypothermic during and after colorectal surgery (final intraoperative temperature = 34.7°C) had significantly more infections and longer hospital stays than did those patients who were maintained at normothermic temperatures (36.6°C). They concluded that maintenance of normal body temperature decreased the incidence of infectious complications in patients undergoing colorectal resection and shortened their hospitalizations.
SUMMARY

Based on the results just described, we conclude that fever is an adaptive response. Fever has a long evolutionary history and is a highly regulated response that involves numerous cytokines, hormones, effector responses, and feedback loops. Many studies of the effects of core temperature on morbidity and mortality show that fever is beneficial. Furthermore, many host defense responses are enhanced by small elevations in body temperature.

However, under some conditions fever is maladaptive. Why should this be the case? We speculate that fever tends to be maladaptive under circumstances in which cytokines and other inflammatory mediators are overproduced. This leads to exaggerated inflammatory responses, including very high fevers and other potentially harmful effects such as vascular leakage. Fever, by enhancing inflammation, probably results in exacerbation of vascular leakage. This may partially explain the damaging effect of fever in stroke patients.19

Why should severe illness occasionally result in a breakdown of host defenses? One possible explanation is that, unlike specific immune responses, nonspecific host defense responses are highly stereotypical. Infection with any number of different organisms will produce similar acute phase responses characterized by loss of food appetite, lethargy, increased sleep, fever, hypoferremia, hypozincemia, synthesis of a wide array of acute phase proteins, etc. If we assume that some large percentage of the time (e.g., >95%) the acute phase responses induced by infection, injury, or trauma are beneficial, we can readily see why the stereotyped acute phase responses have evolved and been retained. So long as the cost-benefit ratio is weighted towards the benefit side, fever (and other host defense responses) would be selected for, even if this leads to increased morbidity and mortality on rare occasions.

But why would cytokines be overexpressed even in a small number of cases, resulting in massive inflammation, fever, and ultimately death. As we evolved, it is probable that the overexpression of cytokines, which clearly results in increased morbidity and mortality, would have led to death in virtually all individuals. Although fever during massive inflammation is probably maladaptive, in some respects this fever can be considered an artifact of modern medicine, which can now keep moribund patients alive (e.g., use of antibiotics, oxygenation, and diuretics). The damaging effects of fever in this population of patients probably have little significance in terms of understanding of the role of fever in the vast majority of infections.

REFERENCES

8. Hong, S. C. L. & L. Levine. 1976. Inhibition of arachidonic acid release from cells as the


