

Fever: Is It Beneficial?

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Data obtained in lizards infected with live bacteria suggest that fever may be beneficial to their survival. An adaptive value of fever has also been inferred in mammals, but the results are equivocal. Findings that certain leukocyte functions are enhanced *in vitro* at high temperatures have provided a possible explanation for the alleged benefits of fever. However, serious questions exist as to whether results from experiments in ectotherms¹ and *in vitro* can properly be extrapolated to *in vivo* endothermic conditions. Indeed, various studies have yielded results inconsistent with the survival benefits attributed to fever, and fever is not an obligatory feature of all infections under all conditions. Certainly, the widespread use of antipyretics, without apparent adverse effects on the course of disease, argues against fever having great benefit to the host. In sum, although fever is a cardinal manifestation of infection, conclusive evidence that it has survival value in mammals is still lacking.

Fever is probably the oldest and best known manifestation of infectious disease [1,2]. It has been the subject of study and comment for well over 2,000 years, yet it is still a matter of controversy whether it has important adaptive value or whether it is a harmful or trivial side effect in the host's response to infection. Although febrile illness was alternately praised and feared during early times [2], a rise in temperature gradually came to be viewed as an attempt of Nature to heal itself and, therefore, to be beneficial [3]. Indeed, fever was often induced as a therapeutic measure, until the widespread and apparently harmless use of antipyretics seemed to refute its beneficial effects. But recently interest in the potential benefits of fever has been revived by findings that fever may have survival value in some infected ectotherms, and that certain host defense responses are enhanced *in vitro* by high temperature. There is as yet no direct evidence that these results apply equally to endotherms *in vivo*. The purpose of this paper is to review the available evidence and to speculate on the possible significance of the febrile reaction in the outcome of infection.

FEVER AND SURVIVAL IN ECTOTHERMS

The strongest experimental evidence in favor of the adaptive value of fever probably comes from the elegant studies of Kluger and his associates in ectotherms. They demonstrated that the desert iguana, *Dipsosaurus dorsalis*, which thermoregulates fairly precisely and develops a behavioral fever following injection of various reptilian

¹Ectothermy defines a pattern of thermoregulation in which body temperature is actively maintained within a fairly narrow range, largely by behaviorally regulated heat uptake from or loss to the environment. Reptiles, fishes, and amphibians are ectotherms. Mammals and birds are endotherms, i.e., their body temperature depends on a high and controlled rate of heat production and autonomically regulated heat exchange with the environment.

pathogens [4], survives infection with live *A. hydrophila* when either placed in [5] or given the opportunity to select [6] a warm environment in a thermal gradient, i.e., when enabled to raise its body temperature. Animals maintained in a cool environment that prevented them from raising their body temperature promptly died. The administration of antipyretics prevented the behavioral fever and also led to death [6]. Subsequently, Covert and Reynolds [7] found that the survival of goldfish infected with live *A. hydrophila* was similarly enhanced when they were allowed to choose a warm environment. Kluger et al. undertook their original experiments in ectotherms because the febrile rise of these animals, lacking or possessing only minimal autonomic means of control, can be obviated simply by preventing the animals from selecting a warmer microclimate, thereby permitting the effect of temperature on survival to be more readily isolated. Since infectious fevers can also be induced in certain amphibians (reviewed by [8,9]) and even in invertebrates (reviewed by [10])—albeit their effects on survival have not yet been studied—it is often stated that any phenomenon that has withstood evolutionary pressures for so long must be good! Unfortunately, Kluger's findings in iguanid lizards could not be replicated in several families of cordylid lizards by Laburn et al. [11], who were unable to evoke a febrile response in these more primitive animals when they were injected with killed *A. hydrophila*, whether they placed the animals in a warm environment or allowed them to choose a thermopreferendum in a gradient. Indeed, their animals, injected or not, all selected identical temperatures rather lower than those chosen by Kluger's animals. It would seem, therefore, that the available data do not permit generalization about the ubiquity of fever in ectotherms, let alone its benefits. More studies are needed using a greater variety of pathogenic and host species to elucidate these conflicting results.

It is uncertain, in any event, whether results in reptiles can readily be transferred to mammals, since among other reasons host responses to pathogens are vastly more complex in the latter. Indeed, Bernheim et al. [12] could find no difference between infected and noninfected iguanid lizards in a variety of leukocyte functions that are characteristic of mammalian host defense responses; they also could not demonstrate any effect of temperature on these mechanisms. The only difference that emerged was that the bacterial count at the site of inoculation was reduced in the animals that had developed a fever. They concluded, therefore, that fever, i.e., heat, may enhance the local inflammatory response, perhaps by facilitating leukocyte migration to the infected site. It should be noted, however, that the measurement of these nonfebrile reactions was performed 12 hours after bacterial challenge, i.e., before they are usually evident in endothermic systems. Grieger and Kluger [13] subsequently reported that the plasma iron levels of infected lizards are reduced as compared to noninfected controls. Iron is an essential co-factor for the growth of many bacteria [14], so that its reduction inhibits growth, an effect which is enhanced by high temperature [15]. In some lizards, therefore, it may be that fever, in synergism with low iron, reduces the bacterial count and thereby enhances survival. If so, fever may indeed represent a vital host defense response in iguanid lizards, which apparently lack at this phylogenetic time-point other, more complex, host defense mechanisms.

FEVER AND SURVIVAL IN ENDOTHERMS

Only a few studies have specifically investigated whether the absence of a febrile rise also may correlate with low survival rates in endotherms. The results have been ambiguous. Kluger and Vaughn [16] found that the rise in body temperature of rabbits

infected with live *P. multocida* correlated with survival, with the greatest benefit occurring when the rise was on the order of 1.50–2.25° C. Fevers above or below this level were detrimental to survival; most deaths occurred within 30 hours after challenge. Unfortunately, absolute temperatures were not reported in this study so that these results cannot be related to actual febrile heights; febrile rises per se are subject to many variables and bear no consistent relation to febrile heights [17]. Paradoxically, the systemic administration of antipyretics (sodium salicylate and acetaminophen co-infused continuously) increased the survival rates of the infected rabbits, albeit their body temperatures were reduced by this treatment [18]. To exclude non-antipyretic effects of the drugs on survival, Vaughn et al. [19] then continuously infused sodium salicylate directly into the pre-optic area of rabbits, beginning one hour before injection of live *P. multocida*. Under these conditions, the animals' temperatures rose approximately 0.7°C, to 40.2°C, as compared with 1.5°C (41°C) in the control animals. The former stabilized at this level at circa 17 hours, when suddenly their temperatures increased rapidly to hyperpyrexia levels. All the animals receiving the antipyretic died during this phase, while the controls survived. Subsequently, these authors [20] reported greater bacterial numbers in liver, lung, and spleen, but not blood, of the salicylate-treated rabbits and suggested that the initially lower fever may have caused the rapid multiplication of bacteria, which then overwhelmed the animals. However, the body temperatures of these animals were high enough that, in synergism with the low plasma iron levels that should have prevailed throughout the study period [15], bacterial reproduction would have been impaired. There is a further apparent incongruity. In most cases, when the infectious burden becomes too great, the affected animals develop septic shock, become moribund, and die in hypothermia. Indeed, in this regard, febrile heights are not simply determined by the severity of infection since lethal and sublethal infections induce the same average febrile temperatures [21]. Hence, the hyperpyrexia of Vaughn's rabbits could have been due to other factors. The pattern of its development suggests that a disorganization of the thermoregulatory system may have occurred, resulting in a fulminating hyperpyrexia, as though the usual "hyperthermic ceiling" had been broken. A similar "escape" phenomenon has been observed in rats infected with live *S. enteritidis* whose fevers were being depressed by pre-optic heating; it did not, however, result in increased deaths [Banet M: personal communication]. It should also be noted that, in these studies, the animals were challenged by the intravenous administration of a rather large dose of bacteria. Although evidently tolerable, since the controls survived, these conditions do not adequately mimic those of real life where microorganisms typically enter the body through the skin, or the respiratory, gastrointestinal, or urogenital tracts, and variable periods pass during which an array of host defense mechanisms are marshalled that do not always include fever [22]. Hence, these results in rabbits are insufficient to permit general conclusions about the benefits of fever.

Indeed, contrary evidence was adduced by Banet [23,24]. He enhanced the febrile response of rats to live *S. enteritidis* by cooling their pre-optic anterior hypothalamus, a procedure which stimulates the animals to maintain higher body temperatures, and found that this treatment decreased survival. Fever in these animals peaked at circa 41°C, a temperature which normally is not harmful to rats and which significantly inhibits the growth of *S. enteritidis*. Under these conditions, the metabolic rate during the rising phase of fever was not increased significantly above the level of the infected controls. On the other hand, when the rats' spinal cords were cooled, their metabolic

rate increased by 40 percent, but the normal febrile rise was not affected because the extra heat thus produced was taken up by the cool thermodes. Yet survival increased. Banet concluded, therefore, that some response associated with the production of fever enhances the defenses of the infected host, while the resulting rise in temperature per se may depress them. His hypothesis is further discussed in another paper in this symposium.

Data regarding the effect of fever on the outcome of infections in humans are also few and ambiguous. For instance, in one study [25] no correlation between fever and survival was found, while in others [26–29] a correlation was observed. However, in these surveys, the patients all were treated, which would affect prognosis. Since the available diagnostic and therapeutic procedures have become more effective in recent years, thereby presumably enhancing survival, these could have biased the latter results (since 1978) as compared with the earlier ones (through 1966).

Other studies often cited supporting or refuting a beneficial role for fever in infected mammals (reviewed by [8,30,31]) are not directly relevant to the issue because, in most instances, body temperatures were altered by the induction of hypo- or hyperthermia, a procedure which does not result in a shift of the set-point temperature but rather elicits thermoregulatory mechanisms different from those evoked during fever production. It also involves additional stress to the hosts. Moreover, in many cases the animals were challenged with endotoxins rather than with live organisms; some also received various drugs. Indeed, a number of species do not ordinarily develop a fever but rather become hypothermic in response to endotoxic injections—e.g., rats, mice, hamsters—without apparent untoward consequences. Yet these species do mount fevers against live bacterial challenges. Since repeated exposure to endotoxins causes the development of tolerance to their febrile effects and, indeed, enhances survival, either fever per se is not necessary for survival or the responses to systemically injected endotoxins are not relevant to the question of the benefits of fever. Therefore, those studies will not be considered here.

ANTIPYRESIS AND SURVIVAL

Since the use of antipyretics is a prototypical part of the home or medically prescribed treatment of most infectious diseases with, in general, no untoward effect on the course of the disease, it may be contended that the correlation between fever height and survival revealed by the studies of Kluger and Vaughn [16,18] in rabbits is not supported by common experience. For if the use of antipyretics led to morbidity and mortality, this fact would presumably have been noted clinically and confirmed experimentally long ago. In fact, the administration of large doses of prostaglandin synthetase inhibitors to mice, rats, and rabbits suffering either chronic or acute infections does not adversely affect survival or resistance to infection [32]. Furthermore, several recent studies [33–35] have demonstrated that the concatenation of adaptive metabolic changes termed the acute-phase reaction which accompanies fever and is induced by its endogenous mediator, interleukin-1, is not affected by cyclooxygenase inhibitors, albeit fever is depressed by these agents. Hence, in mammals, host defense mechanisms would appear to exist which can contribute to recovery and survival independently of fever. Indeed, fever is not an invariable occurrence in every infection [22,36]. Moreover, individual variations in the febrile response are very large

and generally unpredictable. Some susceptible subjects appear to develop high fevers at the slightest provocation, while others may not become febrile at all; within an individual, this responsiveness may be characteristic [37]. It is true, however, that these variations are more frequently seen in connection with so-called "trivial" infections rather than with more widespread, systemic infections [36]. Nevertheless, the variability in the occurrence of fever argues that it is not a vital requirement for survival in all cases. Indeed, aged rats [38] exhibit reduced febrile responses while neonates of most species do not generally develop fever in the first few days of life [39], yet they produce acute-phase reactants [38,40,41] and survive infection [38], suggesting again that other factors in the more complex host defense responses of mammals may have supplanted the apparent dependence of ectotherms on fever for survival.

TEMPERATURE AND MICROORGANISMS

It seems clear that exposure to hyperthermia *in vitro* generally reduces the growth of many microorganisms [42,43]. The thermal susceptibility of spirochetes and treponemes is particularly well known. Indeed, fever therapy was a principal form of treatment before the antibiotic era for syphilis, gonococcal infections, and chancroid. However, the depressing effect of hyperthermia on microbial growth is most prominent at temperatures not usually observed during most infectious fevers, i.e., at temperatures greater than 41°C. Moreover, since most organisms possess a thermal range for optimal growth, it might be expected that those with lower optimal temperatures would be more easily affected by febrile temperatures, and that consequently fever might be a crucial defense mechanism in infections caused by them. But, in fact, thermolabile microbes such as *T. pallidum* and *N. gonorrhoea* rarely induce temperatures that would cause them to be destroyed, while microbes that evoke high temperatures, like the malaria parasite, are unaffected by these temperatures [42]. It would seem, therefore, that fever as an antimicrobial mechanism may be of less importance to the infected mammalian host than has been thought.

On the other hand, the interaction of high temperature with a low availability of iron [15] could be potentially beneficial. Nevertheless, these data have to be interpreted with caution because *in vitro* experiments involve important variables other than temperature that may affect the results [44]. For example, differences in the chemical composition of the growth medium, its pH and O₂ content all affect the thermal susceptibility of the organisms. The phase of growth of the organisms also is important, since bacteria that are dividing rapidly are less resistant to increases in temperature than bacteria in the stationary phase. These variables have not been controlled consistently. Moreover, most studies have been conducted under conditions in which the high temperature was sustained for prolonged hours, which is not the usual occurrence in infections. Natural fever is characterized by variations in temperature of ≈2°C over a few hours, which could allow microorganisms to adapt to degrees of hyperthermia that otherwise would be inhibitory. Also, while there is an implicit assumption that lower bacterial counts signify less severe infection, as already mentioned this does not necessarily correlate with fever height [21] or bear any direct relation to the organisms' virulence and infectivity [45]. Moreover, organisms often develop resistance to the host's defenses [46]. Finally, it should be noted that many of the metabolic changes accompanying infection themselves contribute to increased host resistance against the pathogens [47].

TABLE 1
Effects of Temperature Variations on Some Leukocyte Functions *in Vitro*
Effective Temperatures (°C)

Host Defense Function	Enhanced	Unchanged or Depressed	Reference
PMN ^a Motility	40–42		[48–50]
Phagocytosis (<i>S. aureus</i>)	41–43	40	[51]
	38–40		[52]
(Opsonization)		41	[53]
Bactericidal activity			[54]
<i>E. coli</i> , <i>S. typhimurium</i> , <i>L. monocytogenes</i>	(PMN) 39–40	(MN) 39–40	[55]
<i>S. aureus</i>		(PMN) 39–40	[55]
<i>E. coli</i>		39–41	[56]
<i>Pneumococci</i>	39–41		[56]
NK activity		40	[51]
		39–40	[57]
		40–42	[58]
Lymphocyte proliferation and activation (to diverse mitogens and *IL-1)	36–38		*[59]
	39		[60]
			[55]
		(LPS) 39	*[61]
	(T _H) 39.5	(B, T _S) 39.5	[61]
	40		*[62]
Antibody synthesis	40		[63]
Interferon production	30–34		[64]
			[65]

^aAbbreviations: PMN = polymorphonuclear cells; MN = monocytes; IL-1 = interleukin-1; NK = natural killer cells; LPS = lipopolysaccharide (endotoxin); T_H = helper T cells; B = B lymphocytes; T_S = suppressor T cells.

FEVER AND IMMUNE REACTIONS

Recently, data have been provided indicating that fever may potentiate certain immunoregulatory responses. These findings have been taken to support the view that fever represents a basic, beneficial host defense mechanism. Thus, it has been proposed that the role of fever in endotherms may be to enhance the nonfebrile reactions to infection, i.e., to function as an “immunological amplifier.” However, the evidence for this proposition all comes from *in vitro* data. Although *in vitro* studies eliminate many of the complicating factors inherent in *in vivo* studies, can the results be safely extrapolated to *in vivo* conditions? Indeed, many studies have been reported on the temperature sensitivity of various leukocyte functions (reviewed by [22]), but the results are equivocal (Table 1). Enhancement, when it occurs, does so at temperatures that, again, generally are at levels not usually attained during most infectious diseases. However, significantly, those responses which are induced specifically by interleukin-1 (*IL-1, Table 1), the endogenous mediator which activates the concatenation of host defense responses [22,66], appear to be consistently enhanced at febrile temperatures. It is possible, therefore, that IL-1-driven febrile and nonfebrile responses have adaptive value when occurring in concert. But it should be reiterated that generalizations from these *in vitro* conditions must be made with care, since, in order to demonstrate the effect of heat on these reactions, all other factors were controlled. *In vivo*, of course,

these other factors do co-exist and probably influence the results, thereby perhaps minimizing the importance of heat alone. For example, Brandt and Banet [67] have suggested that the immunostimulation associated with fever may be due to factors other than the rise in temperature per se and have implicated the neuroendocrine system in this effect. It may be supposed, therefore, that if all the actions of IL-1 are present together, the defenses of the host are at their optimal levels; but if one, such as fever, is absent, no great consequence would ensue because of the redundancy of the system.

CONCLUSIONS

The importance of fever as a clinical diagnostic and prognostic sign of disease—particularly infectious disease—cannot be minimized. But it is amusing to note that for most people, and parents especially, fever is a bad sign that should be prevented. Schmitt [68] coined the phrase “fever phobia” to describe this concern. Yet it is generally accepted that high fevers (greater than 40.5° C) can have detrimental effects on the host, including dehydration, delirium, focal lesions of certain organs, cardiopulmonary strain, and negative nutrient balance. Even moderate fevers, if prolonged, can be detrimental. It follows that fevers of any degree may be a risk to certain patient categories and therefore should be abated [39]. But it is not yet resolved whether a moderate febrile rise, although tolerable, is in fact *beneficial* to endothermic hosts, even though it may convey some benefits to certain ectotherms. The available data indicate that fever almost certainly is not *essential* to the host defense of endotherms. But it may have an enhancing role in connection with the manifold interleukin-1-induced nonfebrile reactions that usually occur following an infectious challenge. Clearly, many more studies are needed to clarify whether the development of fever in response to infection is adaptive, maladaptive, or irrelevant in mammalian, and especially human, hosts. A most difficult task will be to separate fever from all the other coincident events influencing recovery and survival.

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