

Fever in Mammals: Is It Beneficial?

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Fever appears to protect ectotherms against infectious disease perhaps because it increases their aerobic metabolic capacity, which is temperature-dependent. Mammals, however, have a high aerobic capacity and normally regulate a high body temperature. Thus, the further increase in temperature induced by interleukin-1 may be dangerous, and the resulting increase in aerobic capacity may not be necessary for an effective defense. In fact, recent evidence suggests that although the neuroendocrine cold defense responses that are stimulated in fever enhance the defenses of the host, the increase in temperature harms these defenses. Data, however, are scarce and equivocal, and the function of fever in mammals is still uncertain.

The improvement in tertiary syphilis following infection with malaria [1], and the discovery that the behavioral fever of ectotherms improves survival from infectious disease [2,3] are perhaps the most important single events influencing our present belief that fever evolved as a host defense against microorganisms. However, there were always doubts that the predominant action of malaria was due to the resulting increase in body temperature [1], and some ectotherms appear to lack the ability to develop fever [4,5], suggesting that this response may not have been that important in evolution. Nevertheless, the febrile increase in temperature is still widely believed to be the most important, if not the only factor contributing to the assumed survival value of fever in mammals [6,7,8]. This contention is supported by experiments *in vitro* which suggest that febrile temperatures inhibit the rate of growth of some microorganisms and stimulate some host defenses [9]. Since the central nervous system modulates or mediates most of the host defenses [10,11,12,13], however, it is unwarranted to extrapolate *in vitro* data to the real *in vivo* situation.

The singular importance of the modulating host factors can be illustrated by a single experiment. In rats, an increase in body temperature induced by cooling the pre-optic area elicits immunostimulation, but the same increase in body temperature elicits immunodepression if it is induced by heat exposure [14]. In view of these results, the effect of an increase in body temperature can only contribute to our understanding of the function of fever if it elicits the same non-thermal responses induced by fever.

Fever is a thermoregulatory disturbance elicited by endogenous pyrogen (interleukin-1), a protein, or family of closely related proteins, produced primarily by mononuclear phagocytes but also by other cells [15]. The mechanism of the pyretic action of endogenous pyrogen is not yet completely understood. This protein, however, increases the firing rate of hypothalamic cold sensors and decreases that of the warm sensors [16], and thus it causes a negative load error. This load error stimulates the cold defense responses, and body temperature then rises until the signals from both types of sensors are again of equal intensity. If the load error is small, the behavioral

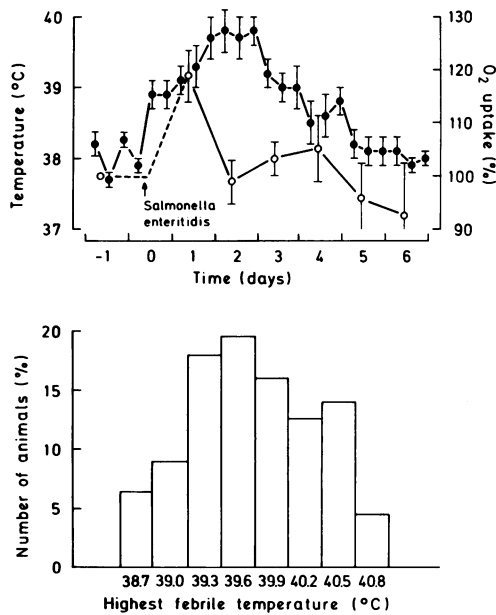


FIG. 1. The febrile response of the rat to infection with *S. enteritidis*. The upper panel shows the changes in oxygen consumption (O) and body temperature (●) in 16 animals, while the lower panel shows the frequency distribution of the highest fever in 112 animals. Drawn from data of Banet [23].

and autonomic responses that reduce heat loss predominate, whereas a larger load error will not only stimulate heat production but will also enhance various endocrine responses that support the increased metabolic effort. Thus, the cold defense responses are an integral part of the febrile response, but the febrile response, as we shall see, is not stereotyped.

From the above considerations, it follows that hyperthermia does not simulate a febrile response because it inhibits the cold defense responses. Pyrogens do, of course, induce fever and antipyretics inhibit it, but these substances also have multiple other effects that may per se influence the course of infectious disease [15,17,18,19]. Local cooling of the pre-optic area, on the other hand, stimulates the cold defense responses and thus it increases body temperature in a manner analogous to fever. Furthermore, because it does not increase the level of prostaglandin E in cerebrospinal fluid [20], it can be assumed that pre-optic cooling does not release interleukin-1. Therefore, this method can be expected to evoke or enhance a febrile response [21,22] without influencing the release of interleukin-1 elicited by an ongoing infectious disease or immune response. Thus, the effect of cooling the pre-optic area can be attributed to the manipulation of the febrile response rather than to the enhancement of the immune and non-thermal acute-phase actions of interleukin-1 [15], as would be the case if its release were increased.

Because fever may affect the various host defenses differently, its biological value can only be determined by studying its effect on the course or outcome of infectious disease. In my experiments on the effect of fever on survival in the rat, the animals were infected with *Salmonella enteritidis*, a common pathogen of this species. This pathogen induces a slowly rising fever which peaks on the second day of infection at any level between 38.6 and 41°C (Fig. 1). This variation in fever height cannot, however, be attributed to the severity of infection because sublethal and lethal doses of

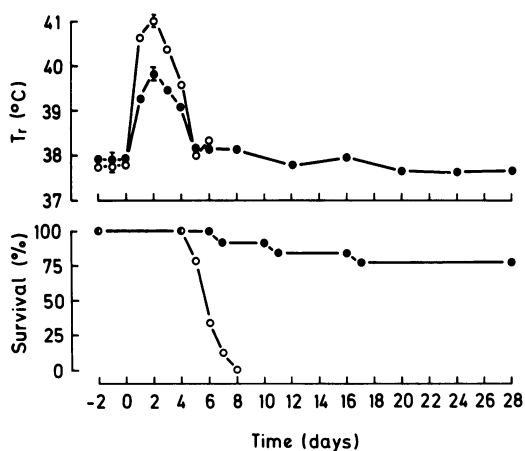


FIG. 2. Body temperature and survival rate in rats infected with *S. enteritidis*. In some animals the course of disease was not interfered with (●), while in the others the pre-optic area was continuously cooled for the duration of the natural fever or until death (○). From Banet [21], courtesy of Springer Verlag.

S. enteritidis induce the same febrile increase in temperature [23]. Metabolic rate generally increases only during the rising phase of fever (Fig. 1), but there is again a large individual variation. Some animals increase their temperature by raising heat production, whereas others decrease only heat loss. After the fever has been established, however, metabolic rate generally returns to the resting level.

If the normal febrile response to *S. enteritidis* is increased by about 1°C by cooling the pre-optic area, survival decreases from 77 percent in the control animals to zero in those animals in which the pre-optic area was cooled (Fig. 2). Because the *in vitro* rate of growth of the bacteria is retarded at 40–41°C [21], this drastic drop in survival can be attributed to a harmful effect of cooling the pre-optic area on the host. This effect could be due to the increased body temperature or to the stimulation of the cold defense responses elicited by cooling the pre-optic area. However, if the cold defense responses are stimulated by another means, such as by cooling the spinal cord [24], survival from infection increases slightly from 37 percent in the control animals to 57 percent in those

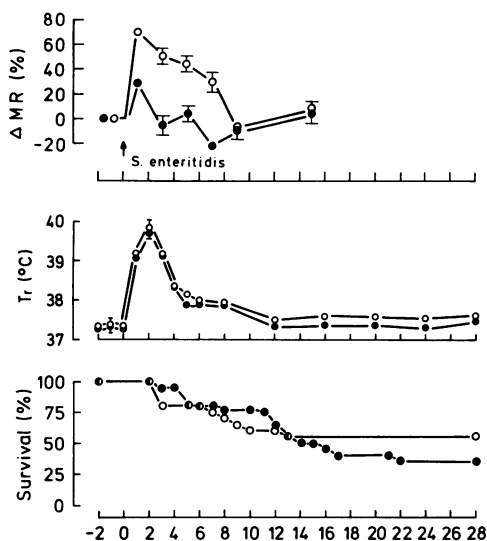


FIG. 3. Oxygen consumption, body temperature, and survival in rats infected with *S. enteritidis*. In some animals the course of disease was not manipulated (●), while in the others the spinal cord was continuously cooled for the duration of the natural febrile response (○). Note that cooling the spinal cord did not affect body temperature because the amount of heat taken up by the heat exchanger was equal to the increase in heat production induced by cooling the thermosensors in this region. Redrawn from data of Banet [24].

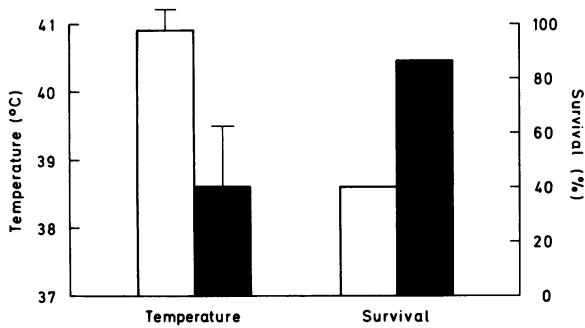


FIG. 4. Body temperature and survival in rabbits infected with *Pasteurella multocida*. In some animals the course of fever was not manipulated (open bars), while in the others febrile temperature was decreased by cooling a heat exchanger placed around the abdominal vena cava. Drawn from data of Vaughn, Veale, and Cooper [26].

animals in which the spinal cord was cooled (Fig. 3). Since cooling of the spinal cord did not influence the febrile temperature, this increase in survival can be attributed to a beneficial effect of the cold defense responses. Consequently, the harmful effect of cooling the pre-optic area can reasonably be attributed to the high body temperature.

In rabbits infected with *Pasteurella multocida*, intrapre-optic injection of sodium salicylate decreases survival from 70 percent in the control animals to zero in those treated with the antipyretic [25]. The antipyretic treatment, however, was effective only for a few hours, and then body temperature increased to a level above that of the control animals. Since most of the treated animals died during this period of hyperpyrexia, it also seems likely that the elevated temperatures harmed the hosts. On the other hand, physical antipyresis, induced by cooling a heat exchanger applied around the abdominal vena cava, increases survival from 40 percent in the control animals to 88 percent in those physically cooled (Fig. 4). This increase in survival rate is higher than that elicited by cooling the spinal cord in rats. The reason for this higher effect may be twofold: first, because physical antipyresis reduces the febrile body

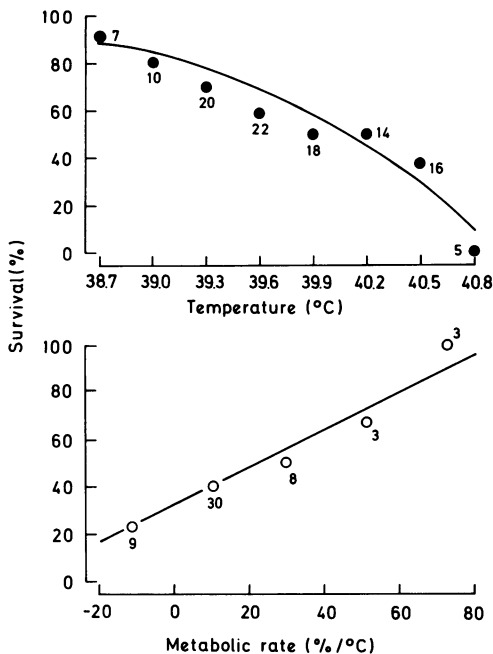


FIG. 5. Correlation between survival and highest febrile temperature (upper panel), and between survival and the standardized metabolic cost of fever during its rising phase (lower panel) in rats that were infected with *S. enteritidis*. The digits show the number of animals in each subgroup. From Banet [22], courtesy of Verlag Chemie.

temperature, and, second, because it also enhances the cold defense responses, as the animals attempt to regulate their temperature at the febrile level.

If febrile temperatures were harmful for the host, as the above experiments suggest, the rate of survival from infection could be expected to decrease with the height of fever. A positive correlation between fever height and survival has, however, been reported in humans with gram-negative bacteremia [27], but these patients were undergoing treatment. In untreated patients with pneumococcal pneumonia, on the other hand, survival was reported to decrease paralleling the height of fever [28]. Furthermore, survival in the rat also decreases inversely to the febrile temperature (Fig. 5). Since the severity of salmonellosis does not affect the height of fever, this inverse correlation between temperature and survival suggests that the animals with poor defenses develop high fevers or, alternatively, that high fevers are harmful for the host. The latter interpretation is supported by the experiments in which the pre-optic area was cooled. Furthermore, temperatures of 40°C may disrupt cellular metabolism [29] and inhibit an immune response [30]. On the other hand, healthy rats can sustain a body temperature of 40°C for at least five days with no overt signs of untoward effects [30], and humans can be maintained at 42°C for up to eight hours without persistent side effects [31]. In view of these data, it seems unlikely that febrile temperatures cause lethal heat damage. Therefore, the decreased survival associated with the height of fever can be attributed to a harmful effect of febrile temperatures on the defenses of the host.

As might be expected in view of the above results and the wide range of febrile temperatures, the increase in metabolic rate during the rising phase of fever correlates poorly with survival. However, if the metabolic cost of fever is standardized as the percentage change in metabolic rate per degree Celsius of increase in body temperature, then there is a positive correlation between the metabolic cost of fever during its rising phase and survival (Fig. 5). This correlation suggests that the animals that increase body temperature by decreasing heat loss have a lower probability of survival than those in which heat production increases. The cause of this correlation is not clear. However, it might be that the high load error necessary to raise heat production also enhances the neuroendocrine cold defense responses. Several of these hormones stimulate the defenses of the host [22], and this beneficial effect could override the harmful effect of the increased body temperature.

It has long been thought that fever might stimulate the production of antibodies. In fact, a fever-like response elicited by cooling the pre-optic area induces an increase in antibody titer which is nearly as large as that induced by a sublethal infection with *S. enteritidis* [32]. These experiments suggest that the immunostimulation induced by infection can to a large extent be attributed to the febrile response. To my knowledge, this enhancement of the humoral immune response is the only host defense that has been shown to be stimulated by a fever-like response.

But the question that interests us here is whether this immune effect is due to the increase in temperature or to the stimulation of some cold defense responses. Cold exposure has been shown to increase antibody titer in rabbits [33]. Furthermore, not only cooling but also heating the pre-optic area increase antibody titer, provided that body temperature does not rise or fall, respectively, more than about 2°C [30]. All together, these experiments suggest that the immune effect of the thermoregulatory system is mediated by some unspecific response to thermal stress. The best known unspecific response to thermal stress, in fact to any stress, is an increase in adrenocorti-

cal activity. Corticosteroids have traditionally been thought to inhibit the immune system. More recent evidence suggests, however, that at physiological levels they may stimulate the differentiation of immunocompetent cells [34].

To test the hypothesis that the increased adrenocortical activity induced by cooling the pre-optic area stimulates the immune system, we injected diazepam in some animals. Diazepam inhibits the release of corticosteroids induced by stress but does not affect their normal plasma level [35]. In our experiments, diazepam did not affect the immune response of the control animals, but it drastically inhibited the increase in antibody titer induced by cooling the pre-optic area (Fig. 6). These experiments appear to confirm the hypothesis but, of course, the effect of diazepam could be unrelated to its inhibition of the stress-induced release of corticosteroids.

The results discussed here cannot be explained if one assumes that the febrile increase in temperature is beneficial for endotherms and the only relevant febrile factor. In fact, they suggest that some febrile cold defense responses have a beneficial effect on the host defenses, while the increase in temperature harms these defenses [22,23]. This does not, however, mean that every host defense is inhibited at elevated temperatures, nor does it mean that every increase in temperature harms the defenses of the host. Because the effect of temperature increases exponentially, moderately increased temperatures are likely to induce little or no thermal damage to the host's defenses. But if these moderately increased temperatures do stimulate the defenses of the host, then I suggest that this effect is small and probably irrelevant.

Although the capacity to develop fever may not be as general among ectotherms as was once thought to be the case, the long and apparently common phylogenetic history of this response suggests that it has survival value not only in ectotherms but also in mammals [36]. However, it could be argued that the evolutionary forces leading to the development of endothermy have cancelled the advantages of a temperature higher than normal.

The evolution of many host defenses and of temperature regulation began in ectothermic vertebrates. Interleukin-1 (endogenous pyrogen) appears to be an essential mediator of nearly all host responses: it elicits several aspects of the acute-phase reaction, and it also seems to provide essential signals for humoral as well as cell-mediated immune responses [15].

A common denominator of all host defenses is a need for energy for the reproduction of cells and synthesis of cell products. Ectotherms, however, have a low capacity for aerobic metabolism, and their ability to sustain an elevated metabolic rate is therefore very limited [37]. Since the aerobic capacity increases with temperature, one could presume that at some time in the course of evolution, interleukin-1 gained control of the thermoregulatory system, inducing it to regulate a higher temperature. The resulting increase in aerobic capacity and metabolic rate—in ectothermic vertebrates, metabolic rate increases by up to 70 percent at febrile temperatures [38]—could then allow the host defenses to proceed at a higher rate. On the other hand, the elevated temperature would probably cause little thermal damage—first because ectotherms have a relatively high resistance to heat, and second because climatic conditions and the night-day changes in temperature may prevent them from maintaining high temperatures for too long.

The selective advantage behind the evolution of endothermy appears to have been the increase in aerobic capacity. Since this capacity increases with temperature, this type of selection would have favored a high body temperature [37], a temperature that

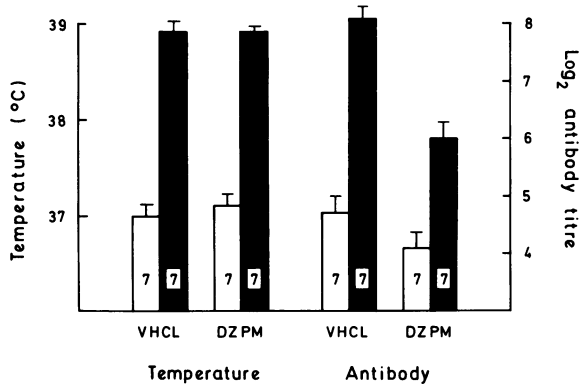


FIG. 6. Body temperature and high-titer antibody response in rats in which either diazepam (DZPM) or its vehicle (VHCL) were injected in the first five days after immunization with sheep erythrocytes. The open bars represent the response of the control animals, while the solid bars represent that of the animals in which the pre-optic area was additionally cooled. The digits indicate the number of animals in each group. From M. Banet and S. Brandt [unpublished].

perhaps approaches the limits of tolerability. That this may well be so is suggested by the highly developed mechanisms against overheating that developed with endothermy. Because of the high aerobic capacity of mammals at their normal body temperature, the further increase in aerobic capacity elicited by interleukin-1 may not be all that useful, while the increase in temperature might even be dangerous. This does not, however, mean that the febrile response is necessarily harmful in mammals. The evidence already discussed suggests that some endocrine cold defense responses stimulate the defenses of the host against infection, and this effect, particularly in moderate fevers, could not only oppose but perhaps even prevail over the harmful effect of elevated temperature. At the present time, however, there is not sufficient evidence to allow clear-cut conclusions about the function of fever in mammals.

Obviously, more studies in a variety of host and pathogen species are needed, but a clear understanding of the role of the febrile response in infectious disease may have to await a better understanding of the mechanisms controlling fever. Recent evidence, for example, suggests that α -melanotropin [39] and vasopressin [40] have antipyretic effect. Melanotropin appears to reduce the febrile rise in set-temperature [39] and thus it may attenuate the whole febrile response; that is, the harmful, thermal, as well as the beneficial, non-thermal responses. Vasopressin, on the other hand, appears to inhibit thermoregulatory heat production [41], and it could thus prevent body temperature from reaching the febrile set level. If this were the mechanism of the antipyretic action of vasopressin, this neuropeptide would also attenuate the harmful rise in temperature. On the other hand, because it would increase the load error, it might enhance the beneficial neuroendocrine responses to cold.

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