THE ADAPTIVE VALUE OF FEVER

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Fever

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HISTORICAL BACKGROUND

The ancient Greeks, including Hippocrates, believed that fever was a beneficial sign during infection. [22] [94] Because of the strong beliefs in the wisdom of the ancients, the concept of fever being beneficial did not change for almost two millennia. For example, the noted English physician Thomas Sydenham (1624-1689), apparently influenced by the writing of Hippocrates, wrote that "Fever is Nature's engine which she brings into the field to remove her enemy." [66] Fever therapy was used in different societies world-wide. For example, the American Indians of the Northwest (the "Flathead" tribe) used fever therapy to treat disease: "The red men had killed a horse, slit open its belly, thrust the naked white man 'into the foaming mass of entrails' and kept him there until the carcass cooled. Putting him to bed, they repeated the process a few days later, apparently willing to keep it up as long as their horses held out. The second treatment, however, restored the patient to health..." [50]

By the late 1800s, the view that fever was protective had begun to change. For example, Liebermeister, a German physician who extensively studied the biology of fever and was the first to accurately define "fever" as the regulation of body temperature at a higher level, believed that fevers were dangerous if they were too high or persisted for too long. [51] Liebermeister, however, believed that moderate fevers or those of high magnitude (if they occurred for a short period) were beneficial. He hypothesized that the positive aspects of fever were related to the effects of high temperatures on the growth of microorganisms. The dangers of fever were thought to be related to a general body wasting

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leading to a reduction in body weight, appetite, and a degeneration of organs. Liebermeister urged that antipyretic drug therapy be used only for high fevers of long duration ("cutting off the peaks").

Shortly after the widespread availability of antipyretic drugs in the late 1800s, many physicians began to advocate that fevers be reduced. (Fever had been "transformed" to a harmful by-product of infection rather than a host-defense

response.) Because there had been no experimental data supporting either concept of fever and its role in disease, why had antipyretic drug therapy become so popular? It is probable that the answer to this is simply that most of these drugs, such as the salicylates, are not only antipyretics but also analgesics. It is possible that a drug that is purely antipyretic would have no effect on the pain that accompanies most infections, but a drug such as aspirin, by having a dual function, may lead the individual to believe that his or her feeling better is the direct result of the lowering of the fever.

What about experimental data on the question of the function of fever? In 1960, Bennett and Nicastri [7] reviewed the literature relating to this question and, based on the data available to them when they wrote their review, could not determine whether fever was adaptive to the infected host. Since the publication of Bennett and Nicastri's excellent review, considerable data have appeared, most of which support the hypothesis that fever is a host defense response. Some of these data are discussed below.

ADAPTIVE VALUE OF FEVER

Experiments that relate to investigations of the function of fever can be divided into four general categories: evolutionary, correlational, antipyretic, and hyperthermia and hypothermia studies. A fifth type of evidence can be used to support an adaptive role for fever--its highly regulated nature. In evolutionary studies, the phylogeny of fever is investigated. The argument is made that it is unlikely that the energetically expensive increase in body temperature associated with most infections would have evolved and been retained without this rise in temperature having some net benefit to the host. In correlational studies, the magnitude of the febrile response of some organism to an infectious agent is compared with some aspect of the host's immunologic defense mechanisms. The simplest comparison is between fever and mortality rate. As in all correlative studies, it is impossible to determine whether the correlated variables have a causal relationship (for example, persons with the likelihood of developing lung cancer also have a tendency to smoke). The third type of study involves the use of antipyretic agents to reduce the fever of an organism (lower its thermoregulatory "setpoint") and then, as in the correlational studies, the magnitude of the fever is compared with some aspect of the host's physiologic state such as mortality or morbidity rate. The problem with these studies is that in the process of producing antipyresis, drugs are used that produce many

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side-effects, some undoubtedly helpful and others harmful. As such, the results of these studies are difficult to interpret. The fourth type of study involves altering the body temperature of infected organisms by physical means (for example, using high or low environmental temperatures). These infected organisms will be either "hypothermic" (body temperature below the thermoregulatory set-point) or "hyperthermic" (body temperature above the thermoregulatory set-point) and will attempt to raise or lower their body temperatures to achieve an equilibrium between their core temperature and their set-point temperature. Because hypothermia and hyperthermia lead to an increase in various autonomic reflexes (for example, peripheral vasoconstriction or vasodilation) that are not found in animals that are normothermic (body temperature equivalent to the thermoregulatory set-point), the results of these investigations are also difficult to interpret. With this brief introduction into the hazards of interpreting data obtained from investigations into the role of fever in disease, the results of these four types of experiments are described subsequently.

Evolutionary Studies

The use of the comparative method has been a potent tool in the hands of experimental biologists and has allowed them to select the most appropriate animal model to answer their specific questions. AV Hill summarized the elegance of this approach as follows: "By the methods of comparative physiology or of experimental biology, by the choice of a suitable organ, tissue or process, in some animal far removed in evolution we may often throw light upon some function or process in the higher animals or man." [68]

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 (Table 1) . The body temperature of these animals rises as a result of their "feeling" cold and therefore selecting a warmer microclimate.

There have been a few reports of ectothermic vertebrates that have failed to develop fever. The lizard *Cordylus cataphractus* did not respond with fever to rabbit endogenous pyrogen or to heat-killed bacteria, [46] the leopard tortoise *Geochelone pardalis* to lipopolysaccharide (LPS), [96] the snakes *Psammophis phillipsii* and *Lamprophis*

fuliginsus to LPS or killed bacteria, [95] the teleost fish *Lepomis gibbosus* to endotoxin or to prostaglandin E_1 , [58] and the snail *Limnaea auricularia* to a variety of pyrogens. [14] 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. One is that the pyrogen used may not be the appropriate stimulus for that species. For example, a dose of LPS that might cause a large fever in the rabbit (for example, 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

TABLE 1 -- FEBRILE RESPONSES OF ECTOTHERMIC VERTEBRATES AND INVERTEBRATES

	Activator of Fever	Ref. No.
Reptiles		
Dipsosaurus dorsalis	bacteria, endogenous pyrogen	86
Iguana iguana	bacteria	39
Crotaphytus collaris	bacteria	27
Terrepene carolina	bacteria	60
Chrysemys picta	bacteria	60
Sauromalus obesus	bacteria	62
Alligator mississippiensis	bacteria	47
Callopistes maculatus	bacteria	31
Amphibians		
Hyla cinerea	bacteria	38
Rana pipiens	bacteria	19
Rana catesbeiana	bacteria	19
Rana esculenta	bacteria, PGE_1 ,endogenous pyrogen	65
Necturus maculosus	PGE_1	35
Bufo marinus	Lipopolysaccharide	76
Fishes		
Micropterus salmoides	bacteria	71
Lepomis macrochirus	endotoxin, bacteria	72
Carassius auratus	endotoxin, bacteria	71
Invertebrates		
Cambarus bartoni(crayfish)	bacteria	17
Gromphadorhina portentosa (cockroach)	endotoxin, bacteria	11
Gryllus bimaculatus(cricket)	*Rickettesiella grylii*	52
Melanoplus sanguinipes(grasshoppers)	*Nosema acridophagus*	10
Homarus americanus(lobster)	PGE_1	18
Penaeus duorarum(shrimp)	PGE_1	18
Limulus polyphemus(horseshoe crab)	PGE_1	18
Buthus occitanus(scorpion)	PGE_1	13
Androctonus australis(scorption)	PGE_1	13
Onymacris plana(tenebrionid beetle)	endotoxin	59

innocuous stimulus in another and, therefore, not trigger an elevation in the thermoregulatory set-point. The dose of pyrogen might be too high; for example, in the rabbit, a dose-dependent fever develops in response to LPS, but at a high dose (such as 50 µg/kg) endotoxic shock occurs and body temperature falls. This same dose of LPS (50 µg/kg) produces a large fever in the rat, [83] whereas 2.5 mg/kg is required to produce a large fever in the mouse. [44]

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, the elevation in the thermoregulatory set-point, and ultimately behavioral and physiologic responses that raise body temperature. A "stressed" animal, for several reasons, might not be able to develop a fever. One possible reason for this could be

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related to the suppressive effects of glucocorticoids, which are elevated during stress, on the release of endogenous pyrogens [28] [78] or on the production of prostaglandins. [33] [49] Another reason might be related to the phenomenon of "stress-induced hyperthermia." Exposure to novel environments or handling produces rises in body temperature of as much as 2°C in rats (reviewed in ref. 40). Rises in body temperature of persons in response to psychologic stress have also been reported. [57] [69] 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 from the negative studies pertaining to fever--the lack of a positive control. It is essential that the investigators demonstrate that their animals are thermoregulating and that injection of some substance known to elevate body temperature (for example, catecholamines, biogenic amines, opioids, and so on) actually does raise the body temperature of the species being studied. If this drug does elevate body temperature, but a series of doses of putative pyrogens have no effect on body temperature, then this would provide critical evidence that that 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, the maintenance of a 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 a fever is unknown; however, as in endothermic vertebrates, the maintenance of an elevated body temperature will likely also result in an approximately 20% increase in energy consumption. If fever did not have an adaptive function, then it would be unlikely that this energetically expensive phenomenon would have persisted for millions of years in so many groups of organisms.

In addition to the above "economic" argument for a beneficial role for fever in the vertebrates, there have appeared several studies specifically involving the role of fever in disease in reptiles, fishes, and insects, as well as mammals. The results of these investigations are described below.

Correlational Studies

Clinical studies involving human beings generally have shown that the magnitude of the fever is associated with the severity of the infection. [7] As a result, patients with the highest fevers tend to have the highest mortality. The difficulty with the studies involving human beings is that they are completely uncontrolled. Often the results are confounded because some patients receive certain drugs that others do

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not receive. Furthermore, the patients clearly have not been infected with identical doses of pathogens. To properly perform (from a scientific standpoint) survival studies on human beings, one must infect subjects with identical doses of pathogens, administer no drugs, and then compare their resultant fevers with their mortality or morbidity rates. Clearly, these experiments would be totally unethical. Therefore, what is available in the clinical literature tends to be clinical impressions and, as such, it is difficult to assess objectively whether fever has a beneficial role.

In studies that have correlated body temperature with survival rate, several investigators have found that fever is associated with better prognoses during bacterial infections. [12] [32] [56] [90] 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. [23] In studies involving children who had "febrile" convulsions, it was reported that high fevers (above 40°C) were associated with lower incidence of subsequent "febrile" convulsions. [24] [25]

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 there is an increase in survival rate as body temperature is elevated. [41] 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. [84] In this study, ferrets (*Mustela*spp.) were infected with different strains of influenza viruses, 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 the 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 described previously. [81] That is, an elevation in temperature of the cultures decreased the replication of the viruses. Interestingly, the more virulent strain of virus was 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 fever has a beneficial function.

Antipyretic Studies

In several studies, a population of mammals was infected with identical amounts of pathogens and the effects of antipyresis on mortality or morbidity quantified. Some of these studies have combined antipyretic

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drug therapy with the use of other drugs (such as glucocorticoids or antibiotics) and, thus, the results are difficult to interpret (for example, see ref. 36). Others have used "antipyretic" drugs such as aspirin, acetaminophen, or ibuprofen (for example, see ref. 29), but no temperature measurements were noted and, thus, it is impossible to relate morbidity to temperature.

Van Miert et al [85] studied the effects of flurbiprofen, a nonsteroidal anti-inflammatory/antipyretic, on *Trypanosoma vivax* infection in goats. They found that this drug blocked the febrile responses during the acute phase of the infection, with the antipyretic drug alone having no effect on afebrile body temperature. Sixteen of 17 goats given the *T. vivax* without the flurbiprofen had a mild infection. All five infected goats treated with an antipyretic dosage of flurbiprofen died. Vaughn et al [87] studied the effect of administration of an antipyretic drug directly into an area of the brain of rabbits implicated in the control of fever, the preoptic-anterior hypothalamus, on mortality during infection of rabbits with *Pasteurella multocida*. The fevers in the rabbits infused with the antipyretic drug were reduced by about 50%. This group of infected rabbits had a significant increase in mortality compared with the group of infected rabbits infused with control solution. Husseini et al [34] studied the effects of suppression of fever in influenza-injected ferrets using sodium salicylate, and they found that treatment with the antipyretic drug resulted 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 [77] investigated the effects of body temperature on bacterial growth rates in experimental pneumococcal infection in rabbits. Rabbits were injected with *Streptococcus pneumoniae* intracisternally and developed fevers averaging 1.5°C. To lower body temperature, the rabbits were anesthetized with pentobarbital or urethane. Body temperature was controlled by varying ambient temperature. 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° to 41°C) was -0.70 ($P < 0.001$), suggesting that elevated temperatures suppressed growth rate of the bacteria. Kurosawa et al [45] 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 were treated with mefanamic acid or acetylsalicylic acid or were untreated. The antipyretic drugs led to varying

amounts of reduction in body temperature. Treatment with either of these drugs led to increased mortality and slower recovery among the survivors.

Ectothermic vertebrates also have been used to study the role of fever in disease. Bernheim and Kluger [9] studied the effects of sodium salicylate-induced antipyresis on survival of the lizard *Dipsosaurus dorsalis*. Lizards were injected with the 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

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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 about 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 these experiments was not toxic. These data indicated to us that the administration of sodium salicylate to these infected lizards was harmful only when it resulted in a reduction in body temperature to the afebrile level. When sodium salicylate failed to produce antipyresis (as in the five lizards in the simulated desert environment or in the eight lizards maintained in the constant temperature chamber), the survival in infected lizards was not adversely affected by the drug.

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

Hyperthermia and Hypothermia Studies

The subject of the effects of hyperthermia and hypothermia on the course of infection through the year 1960 is discussed in greater detail in Bennett and Nicastri's review. [7] Although it is difficult to draw definitive conclusions concerning the role of fever in disease based on hyperthermia or hypothermia studies, the weight of the evidence supports an adaptive function for fever during infections with certain bacterial or viral pathogens (Table 2).

Klastersky, [36] performed survival studies on rabbits that were made hypothermic by shaving their fur. Klastersky injected these rabbits with pneumococcal bacteria and then treated all of them with penicillin. Those rabbits that were shaved developed considerably lower fevers than did the control rabbits. The mortality rate of the control rabbits was 46% and that of the shaved rabbits only 31%; however, as noted earlier, all the rabbits received the antibiotic drug penicillin, thus making interpretation difficult.

Many other studies that have involved the induction of hypothermia or hyperthermia in pneumococcal-infected animals have led to essentially the opposite results of those reported by Klastersky. For example, in 1909, Strouse [80] demonstrated that the natural resistance of pigeons to pneumococci was related to their normal body temperature of about 41.5°C. When their body temperatures were reduced by ice or by the administration of drugs, they became susceptible to the infection and died. Similar findings were reported by Muschenheim et al [64] for pneumococcal infections in rabbits. These animals were infected with pneumococci, and hypothermia was induced by one of several methods so

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TABLE 2 -- EFFECTS OF LOWERED BODY TEMPERATURE ON MORBIDITY AND MORTALITY TO DISEASE

Species	Pathogen	Effect of Lowered Temperature	Ref. No.
Rabbit	pneumococci	protective	36
Rabbit	pneumococci	harmful	64
Mouse	malaria	protective	20

Mouse	influenza	protective	37
Pigeon	pneumococci	harmful	81
Rabbit	*Pasteurella multocida*	protective	88
Rat	*Salmonella enteritidis*	protective	3, 4
Mouse pups	Coxsackie virus	harmful	82
Dog pups	herpesvirus	harmful	16
Mouse	rabies	harmful	6
Humans	acute rhinitis	harmful	93
Humans	acute rhinitis	protective	53
Lizards	*Aeromonas hydrophilla*	harmful	42
Goldfish	*Aeromonas hydrophila*	harmful	21
Sockeye salmon	sockeye virus	harmful	89
Sockeye salmon	hematopoietic necrosis virus (IHN)	harmful	1
Rainbow trout	hematopoietic necrosis virus (IHN)	harmful	2
Crickets	*Rickettsiella grylli*	harmful	52
Grasshoppers	*Nosema acridophagus*	harmful	10
Bumblebees	conopid fly parasite	protective	63
Guinea pigs	*Escherichia coli*	harmful	75

that the rectal temperatures of these rabbits were maintained between 30°C and 34°C. Control rabbits were infected and had their body temperature 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 was clearly harmful to the infected host, and that the development of fever led to an enhancement of the host defense mechanism.

Vaughn et al [88] found that even though treatment of rabbits with antipyretic drugs increased the mortality from *Pasteurella multocida*, physical cooling of rabbits *decreased* mortality. 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 venae cavae. The cooled rabbits maintained average body temperature at about the normal afebrile temperature for rabbits (38.98°C), and the noncooled 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 they would be activating a variety of heat conservation and production effector responses. The authors of this study suggested that thermoregulatory effector mechanisms involved in cold defense may enhance survival. These data are similar to those of Bane. [3] for rats infected with *Salmonella enteritidis*. In this study, the spinal cord of rats was cooled, resulting in an increased metabolic rate (oxygen uptake) and a survival that was borderline significantly higher than in

infected animals that did not have their spinal cord cooled (P=0.06). Interestingly, there were no differences in core temperatures between the control and experimental rats. Banet [5] then showed that there was a correlation between survival 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 at fevers above 38.7°C. What this might mean, however, is that the sickest animals mounted the greatest febrile responses, and despite any beneficial effect of fever, these animals had a higher mortality. Banet [5] 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.

An area that has received considerable attention is that of the febrile responses of newborns. It has been known for a long time that many newborn mammals have a labile body temperature during their first few days of life. [67] Furthermore, in response to infection, newborn human infants, [30] or other infant mammals such as rabbits, [74] tend to have a limited febrile response. Satinoff et al [74] have shown, however, that newborn rabbits, although not raising their body temperature by physiologic means following an injection of endotoxin, raise their body temperature by behavioral means. When injected with *Pseudomonas* endotoxins and allowed to select a range of environmental temperatures, these rabbits selected a warmer environmental temperature, resulting in an elevation in their body temperatures. Haahr and Mogensen [30] suggested that hyperthermia (or more precisely a rise in body temperature) during certain viral infections was 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 in newborn mice, dogs, and humans. For example, Teisner and Haahr [82] found that when 2- to 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°C to 3°C higher than for control mice held at room temperature of 22°C to 24°C. Those mice that were held at 34°C had a considerably lower mortality than did the control mice. Carmichael et al [16] reported similar findings for 2 to 5-day-old dog pups that were inoculated with canine herpesvirus. When the pups were held at an environmental temperature of 28°C to 30°C, they had a rectal temperature of about 35°C to 37°C; those held at an environmental temperature of 36.7°C to 37.7°C had a rectal temperature of 38.3°C to 39.4°C, approximately normal rectal temperatures for adult dogs. Following inoculation with herpesvirus, those dogs with the lower rectal temperatures died within 8 days, whereas those with the higher rectal temperatures survived 9 days or longer. The authors of this study concluded that the elevation of the body temperature to the adult level was beneficial to the infected pups. Based on these data, Haahr and Mogensen [30] suggested that one of the reasons that generalized herpes simplex infections are greatly over-represented in premature babies

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might be attributable to their restricted temperature regulation and poor febrile response. Thus, although newborns might not be able to develop fevers owing to inadequate metabolic machinery or the ability to behaviorally thermoregulate, allowing them to have an elevated body temperature during infections seems to be protective.

Bell and Moore [6] have found that housing of mice in a warm ambient temperature (35°C) led to decreased mortality owing to inoculation with rabies virus. The average body temperatures of mice in the warm environmental temperature was 2°C higher than those in the control environment (20°C)

Yerushalmi and Lwoff [93] found that treatment of human subjects with local hyperthermia (that is, inhalation of warm humidified air) decreased the magnitude of acute rhinitis ("infective Coryza"). In a follow-up study, however, Macknin et al [53] found a slight improvement in rhinitis in patients provided with cool vapor compared with the warmed air.

Mice infected with influenza develop a regulated hypothermia, rather than a fever. [37] This regulated reduction in body temperature appears to be protective. There is a large literature showing that hypoxia induces a reduction in body temperature that enhances host survival, [92] and unpublished data by Kozak et al support the hypothesis that the reduction in body temperature in the influenza-infected mice is, at least in part, attributable to hypoxia.

There have also been many hypothermia/hyperthermia studies 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°C, 36°C, 38°C, 40°C, and 42°C. [42] Control lizards were inoculated with saline 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°C 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 mortality percentages were 34°C, 100%; 38°C and 36°C, 75% 40° C, 33%; and 42°C, 25%. In 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 deaths occurred within 3 1/2 days in infected lizards maintained at 34°C to 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

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undetermined adverse effect of long-term elevation in body temperature in lizards.

There have been several studies involving the effects of temperature on the mortality of fishes. One of these, by Covert and Reynolds, [21] entailed infecting goldfish with live A. *hydrophila* and monitoring their survival rate over 3 days. These investigators had previously reported that several species of freshwater fishes developed fevers in response to injections with these bacteria. [70] [72] In their survival study, they infected goldfish and then held them at temperatures of 25.5°C, 28.0°C, or 30.5°C. These represented, respectively, hypothermic, normothermic, and febrile temperatures. Goldfish maintained at a febrile temperature of 30.5°C had a survival of 84%; those maintained at 28.0° C had a survival of 64%; those at 25.5°C had a survival of 24%. Another 10 fish were injected with the same dose of live A. *hydrophila* and 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 of goldfish.

There have been several studies involving the effects of elevations in water (= body) temperature on the mortality of various species of freshwater fishes infected with viruses. For example, Watson et al [89] reported that sockeye salmon (*Oncorhynchus nerka*) infected with sockeye salmon virus experienced fewer mortalities when held at a water temperature of 20°C than when held at 15.5°C or lower. In 1970, Amend [1] reported similar findings for sockeye salmon infected with hematopoietic necrosis virus (IHN). The mortality of salmon held between 12°C and 16°C was about 66%, whereas for those held between 18°C and 20°C it was only approximately 30%. Even when there was a delay of up to 24 hours before the infected fishes were placed in the warmer environment, there was still a substantial decrease in the mortality. Similar results were reported for IHN-infected rainbow trout (*Salmo gairdneri*). [2]

One of the difficulties in interpreting these studies is that, because it is unknown whether these fishes develop fevers in response to viral infections, it is unclear whether raising their body temperatures simulates hyperthermia (body temperature exceeding set-point) or fever (an elevated body temperature in which set-point = body temperature). If the fish were simply hyperthermic, then the beneficial effects of raising the body temperatures of these fishes would simply be a form of fever therapy and, therefore, these results would not be applicable to a discussion of the role of fever in disease. Because several species of freshwater fishes develop fevers in response to bacterial infection, it is likely that, given the opportunity, the species of fishes used in the viral studies would also behaviorally select warmer environmental temperatures. If this turns out to be the case, then these results will support the thesis that fever has an adaptive function in fishes.

Louis et al [52] infected crickets (*Gryllus bimaculatus*) with the intracellular parasite *Rickettsiella grylli*. They reared the crickets at different

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ambient temperatures and found that those crickets reared at warmer temperatures (higher than 29°C) survived this infection. When these crickets were infected and allowed to select a preferred body temperature in a temperature gradient, they selected a temperature averaging 33.0°C. The average body temperature of noninfected crickets was 26.6° C.

Boorstein and Ewald [10] 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 enhanced both survival and growth. Infected grasshoppers maintained at febrile temperatures demonstrated increased fecundity, as quantified by numbers of eggs laid, compared with infected grasshoppers maintained at afebrile temperatures.

Highly Regulated Nature of Fever

Much has already been described in earlier articles on the biologic basis of fever. Fevers are triggered by the release of "endogenous pyrogens" from a large number of different types of macrophage-like cells. These endogenous pyrogens include the cytokines interleukin-1 (IL-1), IL-6, and others. They act at the level of the anterior hypothalamus to raise the thermoregulatory set-point, thus initiating a large number of physiologic and behavioral responses, which result in the elevation of body temperature (for example, see ref. 40). In addition to the release of endogenous pyrogens, there are also endogenous antipyretics or cryogens, which act to modulate the febrile rise in body temperature, thus generally preventing body temperature from rising to dangerous levels. Over the past 10 years, investigators have shown that arginine vasopressin, alpha-melanocyte stimulating hormone, glucocorticoids, and, in some cases, tumor necrosis factor may act as endogenous antipyretics. This highly regulated nature of fever, containing endogenous factors that both raise and lower body temperature, also supports the argument that fever has evolved as host defense response.

MECHANISMS OF A PROTECTIVE EFFECT OF FEVER

Enhancing Specific Components of Host Defense

There are numerous examples of increases in specific components of host defenses caused by subtle changes in temperature (Table 3). Because of space limitations, these are simply listed.

TABLE 3 -- SOME EFFECTS OF FEBRILE TEMPERATURES ON HOST DEFENSE RESPONSES

Enhanced neutrophil migration
Increased production of antibacterial substances by neutrophils (eg, superoxide anion)
Increased production of interferon
Increased antiviral and antitumor activity of interferon
Increased T-cell proliferation
Decreased growth of microorganisms in iron-poor environment

*Data from*references 40, 54, and 73

Protecting Against Pathogen-Induced Disturbances in Homeostasis

Recently, Kozak [43] proposed an additional rationale for the protective effect of fever. He hypothesized that in addition to the effect of temperature on various host defense responses (see Table 3), fever also could be considered a homeostatic process in terms of maintenance of a constancy of cell membrane "condition" in the infected organism. The membrane condition is a physical state of the cell surface based on the functional interrelationship of two essential factors: (1) composition of the membrane's lipids, and (2) actual temperature of the membrane. The specific physiologic interplay of these two factors accounts for a dynamic equilibrium of the membrane with its environment and, in consequence, the functioning of the cell. During infection, the structural elements of the membrane undergo changes, mostly due to induction of certain phospholipid degradation by phospholipases and the liberation of arachidonic acid. The resultant release of potent mediators of inflammation and infection, such as eicosanoids and platelet activating factors from the membrane, leads to depletion of double bonds (that is, decreases the unsaturation index) of the membrane. This, in turn, results in phase shifting in the thermodynamic properties of the membrane (that is, phase-transition temperature, viscosity/fluidity) toward higher temperatures. Increasing body temperature during infection is hypothesized to result in a compensation for these disturbances in membrane structure, and it may restore membrane conditions essential for signal transduction, expression of receptors, and the controlled running of metabolic processes, thus maintaining homeostasis.

Thus, an elevation in body temperature may have two types of effects. One attenuates the viability of some pathogenic microorganisms by enhancing specific components of specific and nonspecific immunity. The other is speculated to help to restore disturbances in membrane properties.

CONCLUSION

The results of the studies of the survival value of fever in ectothermic vertebrates indicate that following an infection, a rise in body

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temperature results in a decrease in their mortality and morbidity. These data provide further support for the hypothesis that fever in endotherms is also beneficial, because it is unlikely that fever would be adaptive in insects, fishes, and reptiles and would have become maladaptive in birds and mammals.

Based on the data reviewed here, it can be concluded that fever evolved as a host defense mechanism. But it is also clear that not all fevers are beneficial. Why should this be the case? Mackowiak [55] recently suggested that because some data point toward a beneficial role for fever and others support the hypothesis that fever is maladaptive (for example, in association with hypoglycemia and shock), this apparent paradox can be resolved "if one accepts preservation of the species rather than survival of the individual as the essence of evolution." Mackowiak goes on to state that "the febrile response and its mediators may have evolved both as a mechanism for accelerating the recovery of infected individuals with localized or mild to moderately severe systemic infections and for hastening the demise of hopelessly infected individuals, who pose a threat of epidemic disease to the species." There is an inherent problem with this hypothesis--evolution works on the level of the individual, not the species. With the rare exception of "kin" selection, organisms are not altruistic, sacrificing themselves for the good of the community.

So why should there be circumstances in which there is overproduction of cytokines and other inflammatory mediators (which lead to massive fevers as well as other potentially harmful effects such as vascular leakage)? Does this represent a breakdown in host defenses, and if so, why should this occur? 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, and so on. If we assume that some large percentage of the time (for example, 95%) the acute-phase responses induced by infection, injury, or trauma are beneficial, one can readily see why the stereotyped acute-phase responses would have evolved and been retained (Fig. 1). As long as the cost-benefit ratio is weighted toward the benefit side, fever (and other host defense responses) would be selected for, even if this occasionally leads to increased morbidity and mortality.

Another explanation for the occasional maladaptive role of fever (or other acute-phase responses) is that the evolution of host-pathogen interactions never ceases. As the host evolves new mechanisms for combating infection (such as antibody production, elevation in body temperature, and so on), the pathogen also evolves new mechanisms for successfully parasitizing the host. There undoubtedly develops a symbiotic relationship between the host and its parasite with, in most cases, a balance being achieved. This balance keeps the host immunologically "primed" or prepared in the event it is exposed to some new

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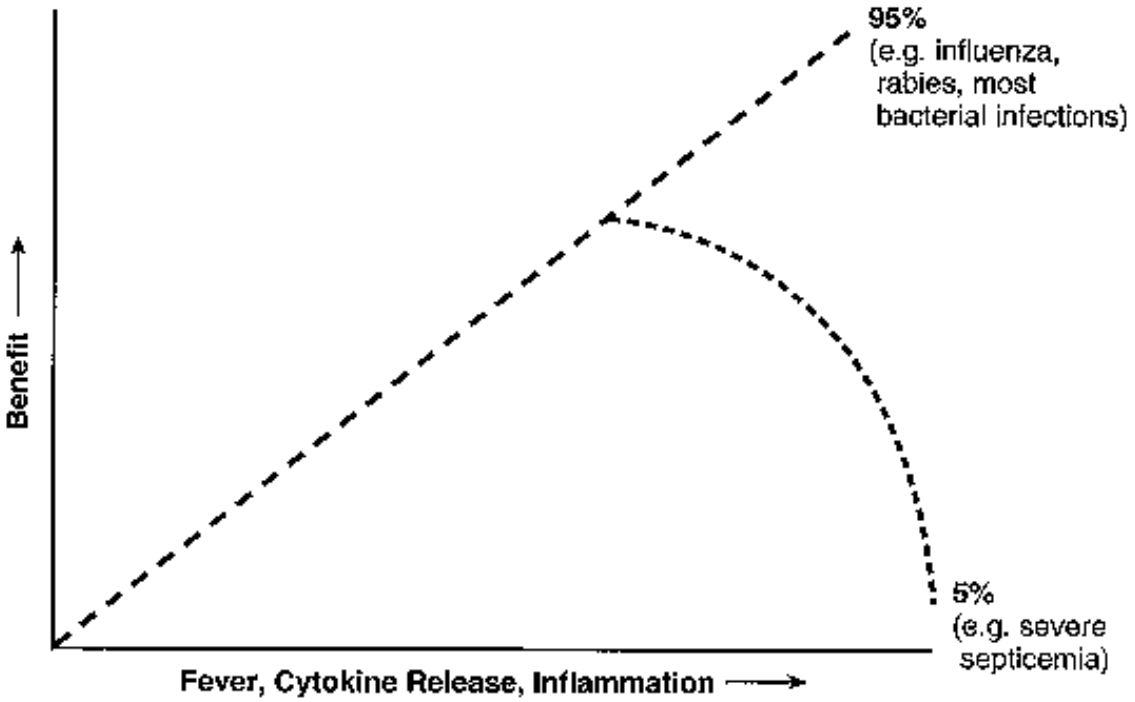

Figure 1. Acute phase responses induced by infection, injury, or trauma.

pathogen. Although we believe that the balance is skewed toward fever being adaptive, there may be occasions in which the "smart" pathogen has developed mechanisms to use the host's elevated temperature to facilitate its own growth or survival.

If fever is, overall, beneficial, then why does the organism not maintain a fever continually, even when not infected? First, there is the metabolic cost of fever. As described earlier, simply elevating and maintaining a body temperature at an elevated level costs considerable energy. Another hypothesis to explain this failure to continually maintain a febrile body temperature was raised by Sohnle and Gambert. [79] They proposed that the maintenance of a body temperature below the optimal temperature for immunologic defenses may be a mechanism to reduce the "contribution of the immune system to aging." The maintenance of a body temperature that reduces overall host defenses would reduce the amount of cytotoxic agents (for example, free radicals) released by neutrophils and macrophages, and thus reduce tissue damage unrelated to fighting infection. They argued that support for their intriguing hypothesis comes from data indicating that fishes living in cooler water live longer than those at higher temperatures, and that dietary restriction in rats and mice was associated with lower body temperatures and greater longevity.

Another possible explanation for fevers to be short acting is that a change in body temperature, itself, may have beneficial value to the host. Most living organisms have had to adapt their structural and biochemical characteristics to a given temperature to function at the lowest possible thermodynamic cost. Invading microorganisms acclimated

to a given ambient temperature may encounter unfavorable conditions if the temperature of the host changes rapidly either upward or downward. The invading microbe may suffer "thermic shock," which might contribute to reduced growth.

Overall, we believe there is overwhelming evidence in favor of fever being an adaptive host response to infection that has persisted throughout the animal kingdom for hundreds of millions of years. As such, it is probable that the use of antipyretic/anti-inflammatory/ analgesic drugs, when they lead to the suppression of fever, results in the increased morbidity and mortality during most infections. The reason that this increased morbidity and mortality may not be readily apparent to most healthcare workers is that we are armed with dozens of host defense responses, with fever being only one of them. Furthermore, most infections are not life-threatening and subtle changes in morbidity are not easily detected, particularly, in "experiments" that are not carefully controlled.

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