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Is Fever Beneficial?

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Fever, the regulation of body temperature at an elevated level, is a common response to infection throughout the vertebrates, as well as in many species of invertebrate animals. It is probable that fever evolved as an adaptive response to infection hundreds of millions of years ago. Many components of the nonspecific and specific host response to infection are enhanced by small elevations in temperature. Perhaps more important, studies of bacterial- and viral-infected animals have shown that, in general, moderate fevers decrease morbidity and increase survival rate.

FEVER

A fever can be defined as an increase in regulated body temperature resulting from an elevation in the thermoregulatory "set-point." This definition makes a clear distinction between fever and elevations in body temperature that may result from passive heating (e.g., sitting in a sauna) or as the result of a breakdown in the ability to regulate body temperature (e.g., during heat stroke or malignant hyperthermia).

For thousands of years it was known that fevers occurred during many illnesses, but studies carried out in Beeson's laboratory in the 1940s [1] were the first to demonstrate that the infected host produces and releases an *endogenous* fever-inducing protein—endogenous or leukocytic pyrogen. This hormone is secreted by many different types of cells, including the macrophage, Kupffer cell, astrocyte and glial cell, the keratinocyte, and others [2]. Endogenous pyrogen is thought to circulate in the blood and to cross the blood-brain barrier, perhaps in the region of the organum vasculosum of the laminae terminalis [3]. The area of greatest sensitivity to endogenous pyrogen is the preoptic-anterior hypothalamus [4–6], and injection of minute amounts of endogenous pyrogen directly into this region of the brain induces high fevers. With the recent data indicating that brain tissue itself produces endogenous pyrogen, it is possible that some fevers are the result of a localized release of this protein [7]. The exact biochemical events that result in the elevated thermoregulatory set-point are still being debated (see the papers by Bernheim, Stitt, Coceani, and Mitchell in this symposium); nevertheless, the "febrile" organism uses behavioral and physiological mechanisms to raise its body temperature to this elevated set-point. It is not until the fever "breaks" that the set-point is returned to normal; then the behavioral and physiological responses are all directed toward returning body temperature to the afebrile level.

HISTORY OF ENDOGENOUS PYROGEN

The evolutionary history of hormones, particularly protein hormones, is fascinating. Many of the same or similar hormones and intercellular mediators are known to exist in life forms from the most primitive invertebrates to the higher mammals. For

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example, the hypothalamic peptide, gonadotropin releasing hormone, is found throughout the vertebrates, and a gonadotropin releasing hormone-like factor is found even in yeast cells [8]. There is evidence that yeast also use this hormone for reproduction, perhaps as a pheromone involved in mating. Opioid peptides, which have many known functions in mammals, including the stimulation of feeding [9], also increase food intake in amebas [10], and insulin-like proteins are found in *E. coli* and in protozoa [11].

Endogenous pyrogen also has a lengthy evolutionary history with multiple functions. Within the past few years it has become apparent that leukocyte endogenous mediator, lymphocyte activating factor, and endogenous pyrogen are the same, or closely related, proteins, now known by the name "interleukin-1" (IL-1). A listing of all the effects of IL-1 are beyond the scope of this review; however, many of them can be found in Table 1. (See the excellent review by Dinarello [2] and the recent proceedings of the symposium "The Physiologic, Metabolic, and Immunologic Actions of Interleukin-1" [12] for more information regarding the sources, molecular biology, and effects of IL-1.) Among its many actions is the initiation of the so-called "acute phase responses" to infection. Interestingly, most of these acute phase responses have a long phylogenetic history—presumably caused by the release of IL-1. For example, the acute phase proteins, C-reactive protein and serum amyloid P, are found throughout the vertebrates, and a C-reactive protein-like molecule has even been found in the horseshoe crab [13].

Fever is also a widespread phenomenon. 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 2). There have been only two reports of ectothermic vertebrates that have failed to develop fever, the lizard *Cordylus cataphractus* [30] to rabbit IL-1 and to heat-killed bacteria, and the teleost fish *Lepomis gibbosus* to endotoxin and to prostaglandin E_1 [31].

IS FEVER BENEFICIAL?

The results of studies of fever in "lower" animals strongly suggest that fever has an ancient phylogenetic history. Fever probably evolved hundreds of millions of years ago, as a means of enhancing host defense responses to infection. Although this may seem like a rash statement, I believe it is improbable that fever would have evolved and been retained throughout the vertebrates and invertebrates without being of benefit to the host. There is a large metabolic cost associated with elevating and then maintaining body temperature even 1 or 2°C above normal. Most biochemical reactions have a Q_{10} of approximately two to three; this means that for every 1°C rise in body temperature, metabolic rate increases about 10 percent or more. It is unlikely that the large increase in energy expenditure associated with fever would have evolved and been retained had it no survival value. Maladaptations, which occasionally occur, are clearly selected against.

Occasionally the argument is made that some host responses to infection are harmful. I have difficulty thinking of any physiological (this includes immunological) response that is, predominantly, maladaptive. Although certain inflammatory responses are thought to be injurious (such as inflammation in knee-joints or allergic reactions to pollen), it is generally agreed that the inflammatory response is essential to survival in a hostile world. Without the movement of phagocytes into a damaged area to destroy or inactivate the pathogens and the subsequent activation of repair

TABLE 1
Some Effect of Interleukin-1
(See [2,12] for references)

Fever
Increased slow-wave sleep
Granulopoiesis
Release of granules from neutrophils
Increased oxidative metabolism by neutrophils
Decreased food appetite
Hypoferremia
Hypozincemia
Hypercupremia
Synthesis of acute phase proteins such as haptoglobin, fibrinogen, C-reactive protein, serum amyloid A, and others
Release of amino acids from proteins
Activation of T lymphocytes
Activation of B lymphocytes
Enhanced natural killer cell activity
Fibroblast proliferation

TABLE 2
Febrile Responses of Ectothermic Vertebrates and Invertebrates

Species	Activator of Fever	Reference
	Reptiles	
Dipsosaurus dorsalis	Bacteria, IL-1	[14,15]
Iguana iguana	Bacteria	[16]
Terrepene carolina	Bacteria	[17]
Chrysemys picta	Bacteria	[17]
	Amphibians	
Hyla cinerea	Bacteria	[18]
Rana pipiens	Bacteria	[19]
Rana catesbeiana	Bacteria	[19]
Rana esculenta	Bacteria, PGE_1, IL-1?	[20]
Necturus maculosus	PGE_1	[21]
	Fishes	
Micropterus salmoides	Bacteria	[22]
Lepomis macrochirus	Endotoxin, bacteria	[22,23]
Carassius auratus	Endotoxin, bacteria	[24,25]
	Invertebrates (Arthropods)	
Cambarus bartoni (crayfish)	Bacteria	[26]
Gromphadorhina portentosa (cockroach)	Endotoxin, bacteria	[27]
Homarus americanus (lobster)	PGE_1	[28]
Penaeus duorarum (shrimp)	PGE_1	[28]
Limulus polyphemus (horseshoe crab)	PGE_1	[28]
Buthus occitanus (scorpion)	PGE_1	[29]
Androctonus australis (scorpion)	PGE_1	[29]

mechanisms, minor breaks in epithelial linings could result in massive infection and death.

Other than the "evolutionary" argument developed above, are there any hard data that fever is beneficial? Within the past decade, numerous studies have demonstrated that small elevations in body temperature, similar to those observed during fever, result in an enhancement of the immune response. Four examples will be briefly discussed. These include increased mobility and activity of white blood cells, stimulation of interferon production and function, activation of T lymphocytes, and the effect of hypoferremia on the growth of pathogens.

Once a potential pathogen breaks through the protective skin or epithelial barriers lining the respiratory or digestive system, the next line of defense is probably the activation of the polymorphonuclear leukocyte or neutrophil. These cells rapidly migrate to the site of infection and then phagocytize the foreign substances. Phagocytosis results in a burst of activity leading to the production of many antibacterial substances, including hydrogen peroxide, superoxide anion, lysozyme, and lactoferrin [32]. Studies from several laboratories have shown that febrile temperatures result in more rapid neutrophil migration [33,34] and secretion of antibacterial chemicals [35,36].

The interferons are a family of proteins which exert potent anti-viral and anti-tumor, as well as anti-bacterial, effects. These actions of interferon are enhanced at febrile temperatures [37,38]. In addition, the *in vivo* production of interferon in the rhesus monkey is increased at febrile temperatures [39]. Not only does the production and activity of interferon increase at febrile temperatures, but interferon, itself, appears to be pyrogenic, perhaps via the production of interleukin-1 [40,41].

As mentioned above, interleukin-1 exerts many effects on host defense mechanisms. Perhaps the most widely studied is its effect on the activation of a group of white blood cells responsible for "cell-mediated" immunity, the T lymphocyte. The "activated" T lymphocyte undergoes proliferation, thus enabling it to exert its anti-viral and anti-tumor actions. This T-cell proliferation is facilitated by fever [42–46].

Another effect of interleukin-1 is to reduce the plasma iron concentration. Several studies have shown that this hypoferremia serves to reduce the growth rate of many species of bacteria (see review in [47]). Although the reduction in plasma iron concentration is independent of the presence of fever [48], there appears to be a synergism between fever and hypoferremia in reducing the growth of bacteria [49–52]. Many species of bacteria are less able to produce iron-chelating proteins at febrile temperatures and therefore are unable to obtain adequate iron for growth.

In addition to the above studies that have focused on the effects of fever on specific immune functions, there have been several investigations involving the effects of fever on mortality and morbidity during bacterial and viral infections. In general, these studies have shown that moderate fevers have a beneficial effect on the outcome of infections. For example, lizards or goldfish infected with bacteria have higher survival rates when febrile [53,54]. Newborn mammals infected with a variety of viruses also have higher survival rates when febrile [55,56]. Suppression of fever using antipyretic drugs results in increased influenza virus in ferrets [57] and increased mortality rate in bacterially infected rabbits [58]. Clinical studies also have shown a correlation between fever and decreased morbidity and mortality rate during a variety of infections [59–61].

CAVEATS

It is important to emphasize that although fever probably evolved as an adaptive host-defense response to infection, not all fevers *must* be beneficial. In terms of evolution, a trait merely needs to have survival value in order to have evolved and been retained. This simply means, as alluded to above, that statistically fever is beneficial. In individual cases, fever may be maladaptive. For example, in people with heart conditions or wasting due to cachexia, fever might pose an unmanageable stress. High fevers during pregnancy might result in an increased incidence of birth defects. But, in most cases, it is likely that moderate fevers serve to rev up host defenses and facilitate the healing process.

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