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 Beeon'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 E1 [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
### THE ADAPTIVE VALUE OF FEVER

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

| Effect                                      |
|---------------------------------------------|
| Fever                                       |
| Increased slow-wave sleep                   |
| Granulopoiesis                              |
| Release of granules from neutrophils        |
| Increased oxidative metabolism by neutrophils |
| Decreased food appetite                      |
| Hypoferrremia                               |
| 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]      |
| Chrysemyx picta                    | Bacteria                         | [17]      |
| **Amphibians**                      |                                  |           |
| Hyla cinerea                        | Bacteria                         | [18]      |
| Rana pipiens                        | Bacteria                         | [19]      |
| Rana catesbeiana                    | Bacteria                         | [19]      |
| Rana esculenta                      | Bacteria, PGE₁, IL-1?            | [20]      |
| Necturus maculosus                 | PGE₁                             | [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)        | PGE₁                             | [28]      |
| Penaeus duorarum (shrimp)           | PGE₁                             | [28]      |
| Limulus polyphemus (horseshoe crab) | PGE₁                             | [28]      |
| Buthus occitanus (scorpion)         | PGE₁                             | [29]      |
| Androctonus australis (scorpion)    | PGE₁                             | [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 hypothermia 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 hypothermia 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 hypothermia 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 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.

REFERENCES

1. Beeson PB: Temperature elevating effect of a substance obtained from polymorphonuclear leukocytes. Clin Invest 27:542, 1948
2. Dinarello CA: Interleukin-1. Reviews of Infectious Diseases 6:51–95, 1984
3. Blatteis CM, Bealer SL, Hunter WS, Llanos-Q J, Ahokas RA, Mashburn TA Jr: Suppression of fever after lesions of the anteroventral third ventricle in guinea pigs. Brain Res Bull 11:519–526, 1983
4. Cooper KE, Cranston WI, Honour AJ: Observations on the site and mode of action of pyrogens in the rabbit brain. J Physiol (Lond) 191:325–337, 1967
5. Jackson DL: A hypothalamic region responsive to localized injection of pyrogens. J Neurophysiol 30:586–602, 1967
6. Rosendorff C, Mooney JJ: Central nervous system site of action of a purified leucocyte pyrogen. Am J Physiol 220:597–603, 1971
7. Fontana A, Weber E, Dayer J-M: Synthesis of interleukin 1/endogenous pyrogen in the brain of endotoxin-treated mice: a step in fever induction? J Immunology 133:1696–1698, 1984
8. Loumaye E, Thorner J, Catt K: Yeast mating pheromone activates mammalian gonadotrophs: evolutionary conservation of a reproductive hormone? Science 218:1323–1325, 1982
9. Yim GKW, Lowy MT: Opioids, feeding and anorexias. Fed Proc 43:2893–2897, 1984
10. Josefsson J-O, Johansson P: Naloxone-reversible effect of opioids on pinocytosis in Amoeba proteus. Nature 282:78–80, 1979
11. Le Roith D, Shiloach J, Berelowitz M, Frohman LA, Liotta AS, Krieger DT, Roth J: Are messenger molecules in microbes the ancestors of the vertebrate hormones and tissue factors? Fed Proc 42:2602–2607, 1983
12. The Physiologic, Metabolic and Immunological Actions of Interleukin-1. In Progress in Leukocyte Biology. Edited by MJ Kluger, JJ Oppenheim, MC Powanda. New York, Alan R. Liss, Inc, 1985, 586 pp
13. Baltz ML, de Beer FC, Feinstein A, Munn EA, Milstein CP, Fletcher TC, March JF, Taylor J, Bruton C, Clamp JR, Davies AJS, Pepys MB: Phylogenetic aspects of C-reactive protein and related proteins. In C-Reactive Proteins and the Plasma Protein Response to Tissue Injury. Edited by I Kushner, JE Volanakis, H Gewurz. Ann NY Acad Sciences 389:49–75, 1982
14. Vaughn LK, Bernheim HA, Kluger MJ: Fever in the lizard Dipsosaurus dorsalis. Nature 252:473–474, 1974
15. Bernheim HA, Kluger MJ: Endogenous pyrogen-like substance produced by reptiles. J Physiol (Lond) 267:659–666, 1977
16. Kluger MJ: The evolution and adaptive value of fever. Am Scientist 66:38–43, 1978
17. Monagas WR, Gatten RE Jr: Behavioural fever in the turtles Terrapene carolina and Chrysemys picta. J Therm Biol 8:285–288, 1983
18. Kluger MJ: Fever in the frog Hyla cinerea. J Therm Biol 2:79–81, 1977
19. Casterlin ME, Reynolds WW: Behavioral fever in anuran amphibian larvae. Life Sci 20:593–596, 1977
20. Myhre KM, Cabanac M, Myhre G: Fever and behavioural temperature regulation in the frog Rana esculenta. Acta Physiol Scand 101:219–229, 1977
21. Hutchison VH, Erskine DJ: Thermal selection and prostaglandin E
fever in the salamander Necturus maculosus. Herpetologica 37:195–198, 1981
22. Reynolds WW, Casterlin ME, Covert JB: Behavioural fever in teleost fishes. Nature 259:41–42, 1976
23. Reynolds WW, Casterlin ME, Covert JB: Febrile responses of bluegill (Lepomis macrochirus) to bacterial pyrogens. J Therm Biol 3:129–130, 1978
24. Reynolds WW, Covert JB: Behavioral fever in aquatic ectothermic vertebrates. In Drugs, Biogenic Amines and Body Temperature. Edited by KE Copper, P Lomax, E Schonbaum. Basel, S Karger, 1977, pp 108–110
25. Reynolds WW, Covert JB, Casterlin ME: Febrile responses of goldfish Carassius auratus to Aeromonas hydrophila and to Escherichia coli endotoxin. J Fish Diseases 1:271–273, 1978
26. Casterlin ME, Reynolds WW: Fever and antipyresis in the crayfish Cambarus bartoni. J Physiol (Lond) 303:417–421, 1980
27. Bronstein SM, Conner WE: Endotoxin-induced behavioural fever in the Madagascar cockroach, Gromphadorhina portentosa. J Physiol 303:327–330, 1984
28. Casterlin ME, Reynolds WW: Fever induced in marine arthropods by prostaglandin E
1. Life Sciences 25:1601–1604, 1979
29. Cabanac M, Guelte LL: Temperature regulation and prostaglandin E
1 fever in scorpions. J Physiol (Lond) 303:365–370, 1980
30. Laburn HP, Mitchell D, Kenedi E, Louw GN: Pyrogens fail to produce fever in cordyloid lizard. Am J Physiol 241:R198–R202, 1981
31. Marx J, Hilbig R, Rahmann H: Endotoxin and prostaglandin E
1 fail to induce fever in a teleost fish. Comp Biochem Physiol 77A:483–487, 1984
32. Davis JM, Gallin JI: The neutrophil. In Cellular Functions in Immunity and Inflammation. Edited by JJ Oppenheim, DL Rosenstreih, M Potter. New York, Elsevier/North Holland, 1981, pp 77–102
33. Bernheim HA, Bodel PT, Askenase PW, Atkins E: Effects of fever on host defense mechanisms after infection in the lizard Dipsosaurus dorsalis. Br J Exp Pathol 59:76–84, 1978
34. Nahas GG, Tannieres ML, Lennon JF: Direct measurement of leukocyte motility: effects of pH and temperature. Proc Soc Exp Biol Med 138:350–352, 1971
35. van Oss CJ, Absalom DR, Moore LL, Park BH, Humbert JR: Effect of temperature on chemotaxis, phagocytic engulfment, digestion and O
2 consumption of human polymorphonuclear leukocytes. J Reticuloendothelial Soc 27:561–565, 1980
36. Johansen KS, Berger EM, Repine JE: Effect of temperature on polymorphonuclear leukocyte function. Acta Path Microbiol Immunol Scand Sect C 91:355–359, 1983
37. Heron I, Berg K: The actions of interferon are potentiated at elevated temperature. Nature 274:508–510, 1980
38. Yerushalmi A, Tovey M, Gresser I: Antitumor effect of combined interferon and hyperthermia in mice. Proc Soc Exp Biol Med 169:413–415, 1982
39. Downing JF, Martinez-Valdez H, Long T, Elizondo R, Taylor MW: In vivo induction of IFN-gamma at febrile temperatures. In The Biology of the Interferon System. Edited by H Kirchner, H Schellekens. Amsterdam, Elsevier Science Pub BV, 1984, pp 429–432
40. Dinarello CA, Bernheim HA, Duff GW, Le HV, Nagabhushan TL, Hamilton NC, Coceani F: Mechanisms of fever induced by recombinant human interferon. J Clin Invest 74:906–913, 1984
41. Feldberg W, Scott GM: Interferon fever in cats. J Physiol (Lond) 355:28P, 1984
42. Roberts NJ Jr, Steigbigel RT: Hyperthermia and human leukocyte functions: effects on response of lymphocytes to mitogen and antigen and bactericidal capacity of monocytes and neutrophils. Infect Immun 18:673–679, 1977
43. Gupta S, Agarwal S: Effect of hyperthermia on in vitro proliferative response of lymphocyte subpopulations. Fed Proc 39(3):916, 1980
44. Duff GW, Durum SK: Fever and immunoregulation: hyperthermia, interleukins 1 and 2, and T-cell proliferation. Yale J Biol Med 55:437–442, 1982
45. Hanson DF, Murphy PA, Silican R, Shin HS: The effect of temperature on the activation of thymocytes by interleukins I and II. J Immunol 130:216–221, 1983
46. Jampel HD, Duff GW, Gershon RK, Atkins EA, Durum SK: Fever immunoregulation: III. Hyperthermia augments the primary in vitro humoral immune response. J Exp Med 157:1229–1238, 1983
47. Weinberg ED: Iron and infection. Microbiol Rev 42:45–66, 1978
48. Tocco RJ, Kahn LL, Kluger MJ, Vander AJ: Relationship of trace metals to fever during infection: are prostaglandins involved? Am J Physiol 244:R368–R373, 1983
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49. Garibaldi JA: Influence of temperature on the biosynthesis of iron transport compounds by Salmonella typhimurium. J Bact 110:262–265, 1972
50. Kochar I: Role of siderophores in nutritional immunity and bacterial parasitism. In Microorganisms and Minerals. Edited by ED Weinberg. New York, M Dekker, 1977, pp 251–288
51. Grieger TA, Kluger MJ: Fever and survival: the role of serum iron. J Physiol (Lond) 279:187–196, 1978
52. Kluger MJ, Rothenburg BA: Fever and reduced iron: their interaction as a host defense response to bacterial infection. Science 188:166–168, 1979
53. Kluger MJ, Ringler DH, Anver MR: Fever and survival. Science 188:166–168, 1975
54. Covert JB, Reynolds WW: Survival value of fever in fish. Nature 267:43–45, 1977
55. Carmichael LE, Barnes FD, Percy DH: Temperature as a factor in resistance of young puppies. J Infect Dis 120:669–678, 1969
56. Haahr S, Mogensen S: Function of fever. Lancet ii:613, 1977
57. Husseini RH, Sweet C, Collie MH, Smith H: Elevation of nasal viral levels by suppression of fever in ferrets infected with influenza viruses of differing virulence. J Infect Dis 145:520–524, 1982
58. Vaughn LK, Veale WL, Cooper KE: Antipyresis: its effect on mortality rate of bacterially infected rabbits. Brain Res Bull 5:69–73, 1980
59. Yerushalmi A, Lwoff A: Traitement du coryza et des rhinites persistantes allergizues par la thermotherapie. C R Acad Sc Paris, t 291 (Series D):857–959, 1980
60. Hoefs J, Sapico FL, Canawati HN, Montgomery JZ: The relationship of white blood cell (WBC) and pyrogenic response to survival in spontaneous bacterial peritonitis (SBP). Gastroenterology 78(5):1308, 1980
61. Weinstein MP, Iannini PB, Stratton CW, Eickhoff TC: Spontaneous bacterial peritonitis. A review of 28 cases with emphasis on improved survival and factors influencing prognosis. Am J Med 64:592–598, 1978