

Physiological Rationale for Suppression of Fever

Philip A. Mackowiak

Medical Care Clinical Center, Veterans Affairs Maryland Health Care System, and Department of Medicine, University of Maryland School of Medicine, Baltimore

Two critical assumptions are made when prescribing antipyretic therapy. One is that fever is, at least in part, noxious, and the other is that suppression of fever will reduce, if not eliminate, the noxious effects of fever. At present, neither assumption has been validated experimentally.

Fever, antipyretic therapy's target, is "a state of elevated core temperature, which is often, but not necessarily, part of the defensive response of multicellular organisms (hosts) to the invasion of live (microorganisms) or inanimate matter recognized as pathogenic or alien by the host" [1]. The febrile response, of which fever is but one component, is a complex physiological reaction to disease involving a cytokine-mediated rise in body core temperature, generation of acute-phase reactants, and activation of numerous physiological, endocrinologic, and immunologic systems [2]. The rise in core temperature during fever is to be distinguished from the unregulated rise that occurs during hyperthermia, in which pyrogenic cytokines are not directly involved and against which standard antipyretics are largely ineffective. Antipyretics are agents capable of blocking or reversing fever's cytokine-mediated rise in core temperature, but they do not affect body temperature in the afebrile state. They are to be distinguished from hypothermia agents (cryogens), which are capable of lowering core temperature even in the absence of fever.

Two critical assumptions are made when prescribing antipyretic therapy. One is that fever is, at least in part, noxious, and the other is that suppression of fever will reduce, if not eliminate, fever's noxious effects. Neither assumption has been validated experimentally. In fact, there is considerable evidence that fever is an important defense mechanism that contributes to the host's ability to resist infection [3, 4].

Evidence of fever's role as a defense mechanism comes from several sources. Studies of the phylogeny of fever have shown the response to be widespread within the animal kingdom (figure 1) [3]. Mammals, reptiles, amphibians, and fish, as well as several invertebrate species, have been shown to manifest fever in response to challenge with microorganisms or other known pyrogens. Moreover, numerous investigations have demonstrated that such animals have enhanced resistance to infection

when increases in body temperature occur within their physiological range [3, 6–8].

In mammalian experimental models, increasing body temperature by artificial means has been shown to enhance the resistance of mice to herpes simplex virus [9], poliovirus [10], Coxsackie B virus [11], rabies virus [12], and *Cryptococcus neoformans* [13], but to decrease resistance to *Streptococcus pneumoniae* [14]. Increased resistance of rabbits to *S. pneumoniae* [15] and *C. neoformans* [16], dogs to herpesvirus [17], piglets to gastroenteritis virus [18], and ferrets to influenza virus [19] has also been observed after induction of artificial fever. Unfortunately, because raising body temperature by artificial means does not duplicate the physiological alterations that occur during fever in homeotherms (and because it entails a number of opposite physiological responses [20]), data obtained by use of mammalian experimental models have been less convincing than those obtained by use of reptile or fish models.

Clinical data supporting an adaptive role for fever, although sparse, include evidence of both the beneficial effects of fever and the adverse effects of antipyretics on the outcome of infection. In a retrospective analysis of 218 patients with gram-negative bacteremia, Bryant et al. [21] reported a positive correlation between maximum temperature on the day of diagnosis of bacteremia and survival. A similar relationship has been observed among patients with polymicrobial sepsis and mild (but not severe) underlying diseases [22]. In an examination of factors influencing the prognosis of spontaneous bacterial peritonitis, Weinstein et al. [23] identified a positive correlation between a temperature $>38^{\circ}\text{C}$ and survival.

Children with chicken pox who are treated with acetaminophen have been reported to have a longer time to total crusting of lesions than that observed for placebo-treated control subjects [24]. Stanley et al. [25] have reported that adults infected with rhinovirus exhibit more nasal viral shedding when given aspirin than when given placebo. Furthermore, Graham et al. [26] have reported a trend toward longer duration of rhinovirus shedding in association with antipyretic therapy, and they have shown that use of aspirin or acetaminophen is associated with suppression of the serum-neutralizing antibody response and with increased nasal symptoms and signs. Such data are subject to several interpretations. They do not prove a causal relation-

Reprints or correspondence: Dr. Philip A. Mackowiak, Director, Medical Care Clinical Center (111), VA Medical Center, 10 N. Greene St., Rm. 5D-143, Baltimore, MD 21201 (Philip.Mackowiak@med.va.gov).

Clinical Infectious Diseases 2000;31(Suppl 5):S185–9
 © 2000 by the Infectious Diseases Society of America. All rights reserved.
 1058-4838/2000/3104S5-0007\$03.00

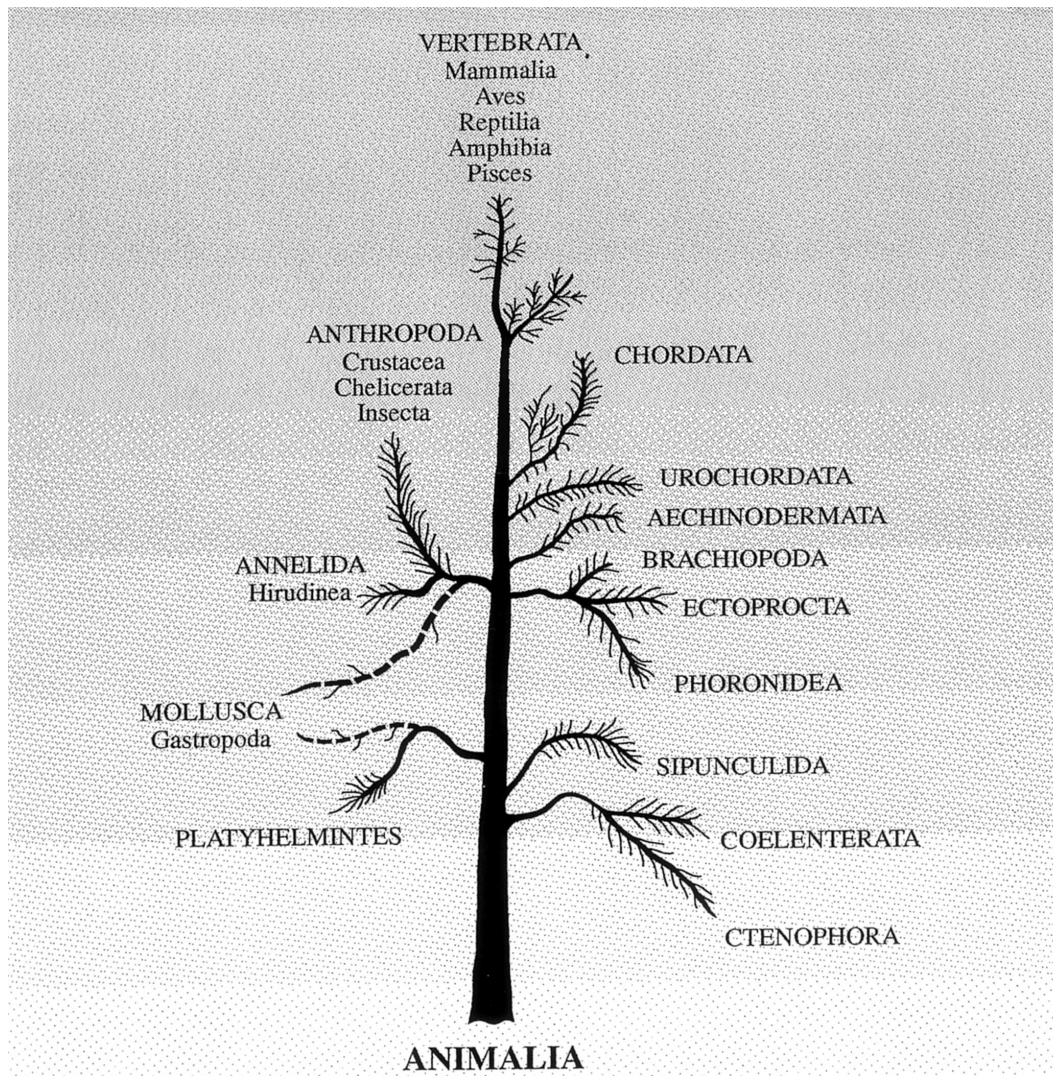


Figure 1. Evolutionary tree of animals. A febrile response has been documented in the phyla Vertebrata, Arthropoda, and Annelida. These observations suggest that the febrile response evolved more than 4 million years ago, at approximately the time when evolutionary lines leading to arthropods and annelids diverged. Reprinted with permission from Mackowiak [5].

ship between fever and improved prognosis during infection. Nevertheless, they are consistent with such a relationship, and when considered in concert with the phylogeny of the febrile response and the animal data summarized above, they constitute strong circumstantial evidence that fever is an adaptive response in most situations.

Whereas the foregoing investigations examined the relationship between elevation of core temperature and outcome of infection, others have considered the endogenous mediators of the febrile response. In such studies, all 4 of the major pyrogenic cytokines have been shown to have immune-potentiating capabilities, which might theoretically enhance resistance to infection [27]. In vitro and in vivo investigations of these cytokines have provided evidence of a protective effect of interferon

(IFN), TNF- α , and/or IL-1 against *Plasmodia* species [28–30], *Toxoplasma gondii* [31], *Leishmania major* [32], *Trypanosoma cruzi* [33], and *Cryptosporidium* species [34].

Several recent reports have also shown pyrogenic cytokines to have enhanced resistance to viral [35–37] and bacterial infections [38, 39]. Treatment of normal and granulocytopenic animals with IL-1 has been shown to prevent the death of some animals with gram-positive and gram-negative bacterial infections [39]. However, IL-1 is effective only if administered an appreciable time (e.g., 24 h) before initiation of infections with rapidly fatal courses. For less acute infections, administration of IL-1 can be delayed until shortly after the infectious challenge. Such observations suggest that the physiological effects of fever that enhance resistance to infection might be limited

to localized infections or systemic infections of only mild to moderate severity.

These data raise the possibility that suppression of fever, at least during infections, might be counterproductive. However, recent reports demonstrating a role for IL-1, TNF- α , IL-6, and IFN in mediating the physiological abnormalities of at least some infections suggest that fever's mediators may, at times, exert a detrimental effect. The most persuasive evidence in this regard derives from studies of gram-negative bacterial sepsis [40]. It has long been suspected that bacterial lipopolysaccharide (LPS) plays a pivotal role in the syndrome. Purified LPS induces a spectrum of physiological abnormalities that are similar to those that occur in patients with gram-negative bacterial sepsis. In experimental animals, challenge with LPS causes TNF- α and IL-1 to be released into the bloodstream coincident with the appearance of signs of sepsis [41]. Furthermore, patients with the septic syndrome have detectable levels of circulatory TNF- α , IL-1, and IL-6, independent of culture-documented infection; such levels correlate inversely with survival [42].

IL-1, alone or in combination with other cytokines, induces many of the same physiological abnormalities (e.g., fever, hypoglycemia, shock, and death) seen after administration of purified LPS [43]. In a murine experimental model for septic shock, IFN administered either before or as long as 4 h after LPS challenge increased mortality, whereas pretreatment with anti-IFN antibody significantly reduced mortality [44]. In several recent investigations, the adverse effects of gram-negative bacterial sepsis, injections of LPS, or both have been attenuated by pretreatment of experimental animals with IL-1 antagonists [45, 46] and monoclonal antibodies directed against TNF- α [47, 48]. Furthermore, animals rendered tolerant to TNF- α by means of repeated injections of the recombinant cytokine were protected against the hypotension, hypothermia, and lethality of gram-negative bacterial sepsis [49].

Taken together, these observations have led to a growing conviction that pyrogenic cytokines are central mediators of the clinical and humoral manifestations of gram-negative bacterial sepsis. These observations have generated intense interest, although, to date, there has been little progress [50] in the clinical application of antagonists of such cytokines. Analysis of similar data suggests that pyrogenic cytokines might mediate at least some of the systemic manifestations and/or local manifestations of sepsis due to gram-positive bacteria [41, 51, 52], AIDS [53], spirochetal infections [54, 55], meningitis [56], adult respiratory distress syndrome [53, 57], suppurative arthritis [58], and mycobacteriosis [59].

With regard to the widely held perception that fever is capable of inducing thermal damage in some situations, the increases in core temperature encountered during fever, which rarely exceed a temperature of 41°C, have never been shown to be harmful per se [60]. Nevertheless, many clinicians believe that, for certain patients, even the relatively modest increases

in core temperature encountered during fever are deleterious and should therefore be suppressed. Children, primarily those between 3 months of age and 5 years of age, are one such category of patients. Among children of this age, the frequency of seizures reported to occur during episodes of fever has ranged from 2% to 5% in the United States and western Europe [61, 62] to as high as 14% in other selected countries [63]. Although most children have temperatures of $\leq 39.0^{\circ}\text{C}$ at the time of their seizure [64], many tolerate even higher fevers later without experiencing convulsions [65]. Unfortunately, antipyretic therapy has not been shown to protect against recurrences of febrile seizure in the few controlled trials that have been conducted to date [66].

It has also been suggested that patients with underlying cardiovascular or pulmonary disorders might be especially susceptible to the adverse effects of fever because of the increased metabolic demands imposed by the elevated temperature [67]. Such demands, which peak during the chill phase (largely as a result of shivering) include increases in sympathetic tone [20], oxygen consumption, respiratory minute volume, and respiratory quotient [68]. Although these have been proffered as prima facie justification for the use of antipyretic therapy for patients with underlying cardiopulmonary disorders, the risk/benefit ratio of such therapy has yet to be determined.

Antipyretic therapy might also be justified, at least in theory, if the metabolic cost of fever exceeded its physiological benefit, if the treatment provided symptomatic relief without adversely affecting the course of the febrile illness, or if the toxicologic costs (i.e., side effects) of the antipyretic regimen were appreciably lower than its beneficial effects. Unfortunately, although clinicians have long argued the validity of each of these propositions as justification for antipyretic therapy, few experimental observations exist to support any of these arguments [69].

References

1. International Union of Physiological Sciences Thermal Commission. Glossary of terms for thermal physiology. 2d ed. *Pflügers Arch* **1987**;410: 567-87.
2. Mackowiak PA, Bartlett JG, Borden EC, et al. Concepts of fever: recent advances and lingering dogma. *Clin Infect Dis* **1997**;25:119-38.
3. Kluger MJ, Kozak W, Conn CA, et al. The adaptive value of fever. In: Mackowiak PA, ed. *Fever: basic mechanisms and management*. 2d ed. Philadelphia: Lippincott-Raven, **1997**:255-66.
4. Mackowiak PA. Fever: blessing or curse? A unifying hypothesis. *Ann Intern Med* **1994**;120:1037-40.
5. Mackowiak PA. Temperature regulation and the pathogenesis of fever. In: Mandell GL, Douglas RG, Bennett JE, eds. *Principles and practice of infectious diseases*. 5th ed. Philadelphia: Churchill Livingstone, **2000**: 604-22.
6. Kluger MJ, Ringler DH, Anver MR. Fever and survival. *Science* **1975**;188: 166-8.
7. Bernheim HA, Kluger MJ. Fever: effect of drug-induced antipyresis on survival. *Science* **1976**;193:237-9.
8. Covert JR, Reynolds WW. Survival value of fever in fish. *Nature* **1977**;267: 43-5.
9. Schmidt JR, Rasmussen AF Jr. The influence of environmental temperature

- on the course of experimental herpes simplex infection. *J Infect Dis* **1960**;107:356–60.
10. Lwoff A. Factors influencing the evolution of viral diseases at the cellular level and in the organism. *Bacteriol Rev* **1959**;23:109–24.
 11. Walker DL, Boring WD. Factors influencing host-virus interactions. III. Further studies on the alteration of Coxsackie virus infection in adult mice by environmental temperature. *J Immunol* **1958**;80:39–44.
 12. Bell JF, Moore GJ. Effects of high ambient temperature on various stages of rabies virus infection in mice. *Infect Immun* **1974**;10:510–5.
 13. Kuhn LR. Effect of elevated body temperature on cryptococcus in mice. *Proc Soc Exp Biol Med* **1949**;71:341–3.
 14. Eiseman B, Mallette WG, Wotkins RS, Summers WB, Tong JL. Prolonged hypothermia in experimental pneumococcal peritonitis. *J Clin Invest* **1956**;35:940–6.
 15. Rich AR, McKee CM. The mechanism of a hitherto unexplained form of native immunity to the type III pneumococcus. *Bull Johns Hopkins Hosp* **1936**;59:171–207.
 16. Kuhn LR. Growth and viability of *Cryptococcus hominis* at mouse and rabbit body temperatures. *Proc Soc Exp Biol Med* **1939**;41:573–4.
 17. Carmichael LE, Barnes FD. Effect of temperature on growth of canine herpes virus in canine kidney cell and macrophage cultures. *J Infect Dis* **1969**;120:664–8.
 18. Furuchi S, Shimizu Y. Effect of ambient temperatures on multiplication of attenuated transmissible gastroenteritis virus in the bodies of newborn piglets. *Infect Immun* **1976**;13:990–2.
 19. Toms GL, Davies JA, Woodward CG, Sweet C, Smith H. The relation of pyrexia and nasal inflammatory response to virus levels in nasal washings of ferrets infected with influenza viruses of differing virulence. *Br J Exp Path* **1977**;58:444–58.
 20. Greisman SE. Cardiovascular alterations during fever. In: Mackowiak PA, ed. *Fever: basic mechanisms and management*. New York: Raven Press, **1991**:143–65.
 21. Bryant RE, Hood AF, Hood CE, Koenig MG. Factors affecting mortality of gram-negative rod bacteremia. *Arch Intern Med* **1971**;127:120–8.
 22. Mackowiak PA, Browne RH, Southern PM Jr, Smith JW. Polymicrobial sepsis; analysis of 184 cases using log linear models. *Am J Med Sci* **1980**;280:73–80.
 23. Weinstein MR, Iannini PB, Staton CW, Eichoff TC. Spontaneous bacterial peritonitis: a review of 28 cases with emphasis on improved survival and factors influencing prognosis. *Am J Med* **1978**;64:592–8.
 24. Dorn TF, DeAngelis C, Baumgardner RA, et al. Acetaminophen: more harm than good for chicken pox? *J Pediatr* **1989**;114:1045–8.
 25. Stanley ED, Jackson GG, Panusarn C, et al. Increased viral shedding with aspirin treatment of rhinovirus infection. *JAMA* **1975**;231:1248–51.
 26. Graham MH, Burrell CJ, Douglas RM, et al. Adverse effects of aspirin, acetaminophen, and ibuprofen on immune function, viral shedding, and clinical status in rhinovirus-infected volunteers. *J Infect Dis* **1990**;162:1277–82.
 27. Dinarello CA. Endogenous pyrogens. The role of cytokines in the pathogenesis of fever. In: Mackowiak PA, ed. *Fever: basic mechanisms and management*. New York: Raven Press, **1991**:23–47.
 28. Mellouk S, Green SJ, Nacy CA, Hoffman SL. IFN- γ inhibits development of *Plasmodium berghei* exoerythrocytic stages in hepatocytes by an L-arginine-dependent effector mechanism. *J Immunol* **1991**;146:3971–6.
 29. Naotunne TS, Karunaweera ND, Del Giudice G, et al. Cytokines kill malaria parasites during infection crisis: extracellular complementary factors are essential. *J Exp Med* **1991**;173:523–9.
 30. Curfs JHAJ, Van Der Meer JWM, Sauerwein RW, Eling WMC. Low dosages of interleukin 1 protect mice against lethal cerebral malaria. *J Exp Med* **1990**;172:1287–91.
 31. Woodman JP, Dimier IH, Bout DT. Human endothelial cells are activated by IFN- γ to inhibit *Toxoplasma gondii* replication: inhibition is due to a different mechanism from that existing in mouse macrophages and human fibroblasts. *J Immunol* **1991**;147:2019–23.
 32. Liew FY, Li Y, Millotts S. Tumor necrosis factor- α synergizes with IFN- γ in mediating killing of *Leishmania major* through the induction of nitric oxide. *J Immunol* **1990**;145:4306–10.
 33. Torrico F, Heremans H, Rivera MT, Van Marck E, Billiau A, Carlier Y. Endogenous IFN- γ is required for resistance to acute *Trypanosoma cruzi* infection in mice. *J Immunol* **1991**;146:3626–32.
 34. Ungar BVP, Kao T-C, Burris JA, Finkelman FD. *Cryptosporidium* infection in an adult mouse model: independent roles for IFN- γ and CD4⁺ T lymphocytes in protective immunity. *J Immunol* **1991**;147:1014–22.
 35. Sambhi SK, Kohonen-Corish MRJ, Ramshaw IA. Local production of tumor necrosis factor encoded by recombinant vaccinia virus is effective in controlling viral replication in vivo. *Proc Natl Acad Sci USA* **1991**;88:4025–9.
 36. Feduchi E, Carrasco L. Mechanism of inhibition of HSV-1 replication by tumor necrosis factor and interferon. *Virology* **1991**;180:822–5.
 37. Striijp HAG, Van Der Tol ME, Miltenburgh LAM, Van Kessel KPM, Verhoff J. Tumor necrosis factor triggers granulocytes to internalize complement-coated virus particles. *Immunology* **1991**;73:77–82.
 38. Hedges S, Anderson P, Lidin-Janson G, Deman P, Svanborg C. Interleukin-6 response to deliberate colonization of the human urinary tract with gram-negative bacteria. *Infect Immun* **1991**;59:421–7.
 39. Vogels MTE, Vander Meer JWM. Use of immune modulators in nonspecific therapy of bacterial infections. *Antimicrob Agents Chemother* **1992**;36:1–5.
 40. Bernheim HA, Bodel T, Askenase PW, Atkins E. Effects of fever on host defense mechanisms after injection of the lizard *Dipsosaurus dorsalis*. *Br J Exp Pathol* **1978**;59:76–84.
 41. Dinarello CA. The proinflammatory cytokines interleukin-1 and tumor necrosis factor and treatment of the septic shock syndrome. *J Infect Dis* **1991**;163:1177–84.
 42. Casey LC, Balk RA, Bone RC. Plasma cytokine and endotoxin levels correlate with survival in patients with the sepsis syndrome. *Ann Intern Med* **1993**;119:771–8.
 43. Johnson J, Brigman KL, Jesmok G, Meyrick B. Morphologic changes in lungs of anesthetized sheep following intravenous infusion of recombinant tumor necrosis factor α . *Am Rev Respir Dis* **1991**;144:179–86.
 44. Heinzel FP. The role of IFN- γ in the pathology of experimental endotoxemia. *J Immunol* **1990**;145:2920–4.
 45. Henricson BE, Neta R, Vogel SN. An interleukin-1 receptor antagonist blocks lipopolysaccharide-induced colony-stimulating factor production and early endotoxin tolerance. *Infect Immun* **1991**;59:1188–91.
 46. Ohlsson K, Björk P, Bergenfeldt M, Hageman R, Thompson RC. Interleukin-1 receptor antagonist reduces mortality from endotoxin shock. *Nature* **1990**;348:550–2.
 47. Opal SM, Cross AS, Sadoff JC, et al. Efficacy of antilipopolysaccharide and anti-tumor necrosis factor monoclonal antibodies in a neutropenic rat model of *Pseudomonas* sepsis. *J Clin Invest* **1991**;88:885–90.
 48. Overbeek BP, Veringa EM. Role of antibodies and antibiotics in aerobic gram-negative septicemia: possible synergism between antimicrobial treatment and immunotherapy. *Rev Infect Dis* **1991**;13:751–60.
 49. Alexander HR, Sheppard BC, Jensen JC, et al. Treatment with recombinant tumor necrosis factor- α protects rats against lethality, hypotension, and hypothermia of gram-negative sepsis. *J Clin Invest* **1991**;88:34–9.
 50. Fisher CJ Jr, Agosti JM, Opal SM, et al. Treatment of septic shock with tumor necrosis factor receptor: Fc fusion protein. *N Engl J Med* **1996**;334:1697–702.
 51. Freudenberg MA, Galanos C. Tumor necrosis factor alpha mediates lethal activity of killed gram-negative and gram-positive bacteria in d-galactosamine-treated mice. *Infect Immun* **1991**;59:2110–5.
 52. Gibson RL, Redding GJ, Henderson WR, Truog WE. Group B streptococcus induces tumor necrosis factor in neonatal piglets: effect of the tumor necrosis factor inhibitor pentoxifylline on hemodynamics and gas exchange. *Am Rev Respir Dis* **1991**;143:598–604.
 53. Birs DL, Redfield RR, Tencer K, Fowler A, Burke DS, Tosato G. Induction

- of interleukin-6 during human immunodeficiency virus infection. *Blood* **1990**;76:2303–10.
54. Radolf JD, Norgard MV, Brandt ME, Isaacs RD, Thompson PA, Beutler B. Lipoproteins of *Borrelia burgdorferi* and *Treponema pallidum* activate cachectin/tumor necrosis factor synthesis: analysis using a CAT reporter construct. *J Immunol* **1991**;147:1968–74.
55. Habicht GS, Katona LI, Benach JL. Cytokines and the pathogenesis of neuroborreliosis: *Borrelia burgdorferi* induces glioma cells to secrete interleukin-6. *J Infect Dis* **1991**;164:568–74.
56. Jacobs RF, Jabor DR. The immunology of sepsis and meningitis-cytokine biology. *Scand J Infect Dis Suppl* **1990**;73:7–15.
57. Jenkins JK, Carey PD, Byrne K, Sugerman HJ, Fowler AA III. Sepsis-induced lung injury and the effects of ibuprofen pretreatment: analysis of early alveolar events via repetitive bronchoalveolar lavage. *Am Rev Respir Dis* **1991**;143:155–61.
58. Saez-Llorens X, Jafara HS, Olsen KD, Nariuchi H, Hansen EJ, McCracken GH. Induction of suppurative arthritis in rabbits by *Haemophilus* endotoxin, tumor necrosis factor- α , and interleukin- 1β . *J Infect Dis* **1991**;163:1267–72.
59. Rook GAW, Al Attiyah R. Cytokines and the Koch phenomenon. *Tubercle* **1991**;72:13–20.
60. Mackowiak PA, Boulant JA. Fever's glass ceiling. *Clin Infect Dis* **1996**;22:525–36.
61. Hirtz DG. Generalized tonic clonic and febrile seizures. *Pediatr Clin North Am* **1989**;36:365–82.
62. Berg AT. Febrile seizures and epilepsy: the contributions of epidemiology. *Pediatr Perinat Epidemiol* **1992**;6:145–52.
63. Lessell S, Torres JM, Kurland LT. Seizure disorders in a Guamanian village. *Arch Neurol* **1962**;7:37–44.
64. Aicardi J. Febrile convulsions. In: Aicardi J, ed. *Epilepsy in children*. 2d ed. New York: Raven Press, **1994**:253–75.
65. Lennox-Buchthal MA. Febrile convulsions: a reappraisal. Amsterdam: Elsevier, **1973**:1–138.
66. Rosman NP. Febrile convulsions. In: Mackowiak PA, ed. *Fever: basic mechanisms and management*. 2d ed. Philadelphia: Lippincott-Raven, **1997**:267–77.
67. Styrt B, Sugarman B. Antipyresis and fever. *Arch Intern Med* **1990**;150:1589–97.
68. Horwath SM, Spurr GB, Hutt BK, Hamilton LH. Metabolic cost of shivering. *J Appl Physiol* **1956**;8:595–602.
69. Mackowiak PA, Plaisance KI. The benefits and risks of antipyretic therapy. *Ann N Y Acad Sci* **1998**;856:214–23.