Physiological Rationale for Suppression of Fever

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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. pneumonia* [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°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-

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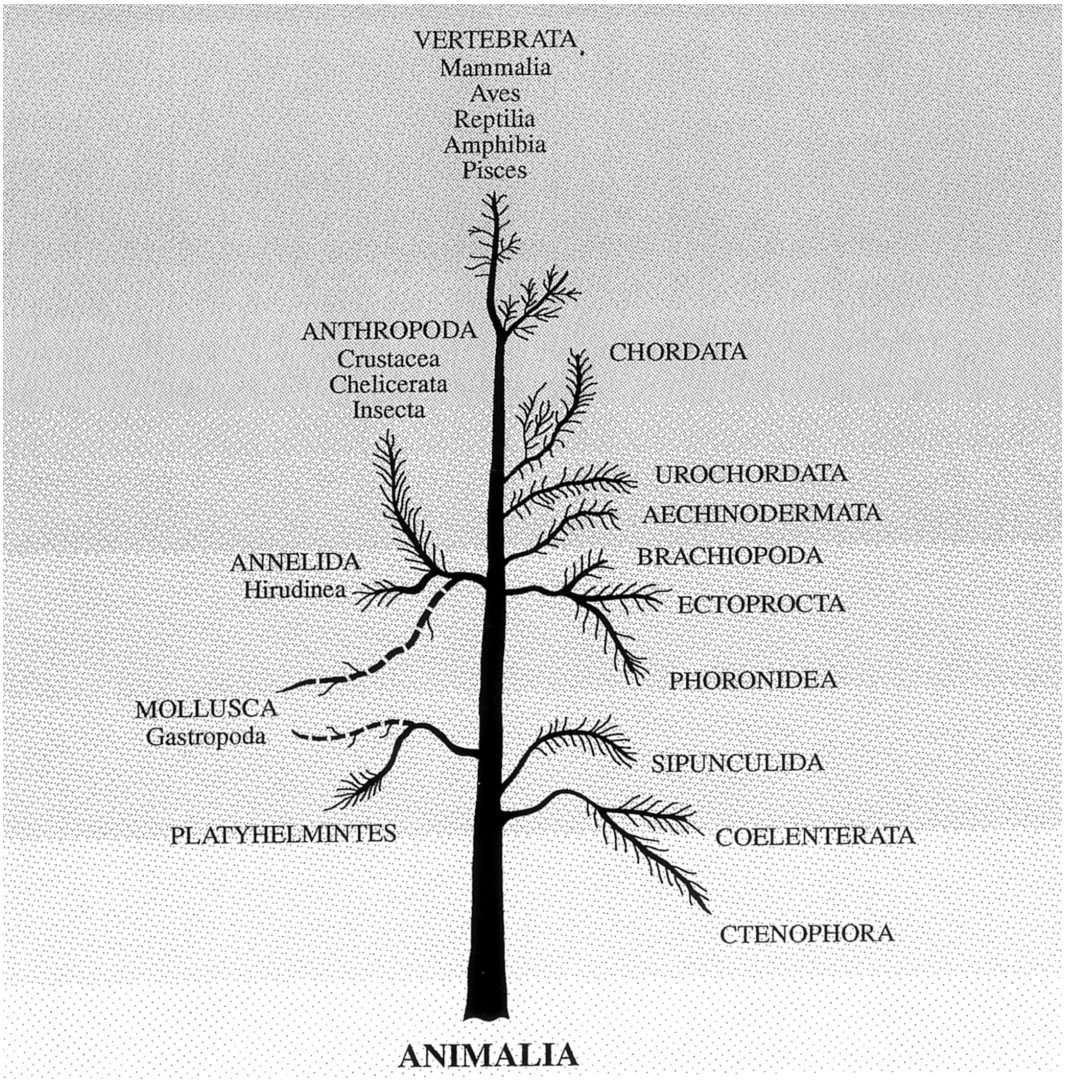

Figure 1. Evolutionary tree of animals. A febrile response has been documented in the phyla Vertebrata, Arthropoda, and Annelida. These observations suggest that the febrile response evolved more than 4 million years ago, at approximately the time when evolutionary lines leading to arthropods and annelids 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 $\leqslant$39.0°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].

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