response that is conserved highly in all mammals (*1*). That fever, despite high metabolic and nutritional costs, is conserved so highly argues forcefully for its evolutionary value, as does the endogenous nature of its mechanism, which requires a complex series of steps and interactions. Recent work on the biology of cytokines has enabled the effects of individual components of this response — all of which are beneficial to the host — to be examined. It is reasonable to argue on the basis on the many similarities in the febrile response and its mechanism among different vertebral classes, that fever is an adaptive benefit to the host — despite the fact that it is an energy-expensive phenomenon. Our inability to demonstrate directly the beneficial effects of fever in the intact vertebral host because of the diverse metabolic effects of antipyresis means that this evolutionary evidence is probably the best we have.

Some support for fever comes from comparative biology. Cold-blooded animals such as lizards lack a mechanism to produce fever when they become infected. A "heat-seeking" instinct has been described in these creatures, however; this allows them to raise their body temperature by *external* means: the animals find the warmest spot in the environment and remain there while their body temperature increases in response to the external stimulus. The survival value of such behaviour has been shown clearly in the laboratory.

A question often raised about the evolutionary argument is why fever would be beneficial in mild to moderately severe infections but demonstrably deleterious in fulminant disease (*2*). Such a difference can be explained by the fact that evolution has no interest in the preservation of the individual, only in preserving the species: recovery of many individuals with mild to moderately severe infections is far more important than the survival of the occasional case of fulminant illness.

As Russell et al. point out, it has proved difficult to show an unequivocal effect from reducing fever as part of the treatment of infection. As mentioned, to undertake such studies is a daunting task — because a beneficial effect predictably would be found primarily in mild to moderately severe disease, end-points are impossible to select. Obviously the duration of fever cannot be one endpoint, but what other sign or symptom can be objectively and quantitatively measured in a reproducible manner? Hundreds and probably thousands of patients would have to be enrolled in double-blind, placebo-controlled studies and followed in exquisite detail. This is why so little clinical data are available, and it seems unlikely that more will be obtained. The information summarized by Russell et al., however, does seem to support the conclusion that reducing fever in mild infection can adversely influence the course of at least some illnesses.

On the other hand, good evidence supports the view that the high fevers encountered in septic states are deleterious to the host and that their suppression is helpful in assuring survival (*2*). As pointed out earlier, these instances are comparatively rare, and from an evolutionary perspective all of the affected individuals would have died.

In addition to the probability that antipyretics may prolong the course of mild to moderate infectious illnesses, what other deleterious effects might they have? Russell et al. point out that little is known about the pharmacokinetics of these drugs in poorly or malnourished children. Even in developed countries, all available methods of antipyresis must be treated with respect. Warning labels became required for paracetamol recently and for aspirin in the more distant past. In addition to acute poisoning, the former has been implicated in the development of chronic renal disease, and perhaps liver failure, when repeatedly administered over prolonged periods of time (*3*). Perhaps more important is the fact that antipyretics mask symptoms or signs; children with pneumonia, for example, may not receive a proper diagnosis because their respiratory rate decreases (*4*) or because, when the body temperature starts to fall, the child may be considered to be on the way to recovery and thus needing no further observation. Finally, of course, the costs may consume a significant amount of resources that, in developing countries, could be better devoted to specific diagnosis and therapy.

Other potential benefits of reducing fever are sometimes cited to justify the use of antipyresis. A common assumption is that these drugs make patients feel better, but no clear evidence shows that this is so. Parents and physicians consistently cannot distinguish between the effects of placebo and paracetamol in most circumstances (*5*). Perhaps the exceptions are conditions accompanied by pain, for which the analgesic effects of the medication provide the benefit. When fevers rise above 39.5 °C, a reduction in body temperature is sometimes accompanied by an improvement in subjective symptoms, but this is inconstant, with young children seeming to benefit more than older children (*6*).

The major problem when evaluating the subjective effects of antipyretics is that they have an enormous placebo value — as various studies have shown (*5, 6*). Despite the firm belief in the effects of antipyretics, children do not feel any better, eat better, or become more active after their use than they do after they receive placebo. The argument that the use of antipyretics reduces the occurrence of febrile seizures also is not based on evidence: no studies have shown this to be true. Even in children with previous febrile seizures, the use of antipyretics has not been helpful (*7*). Some physicians believe that the response to antipyretics can be used to differentiate between bacterial and viral infections, with the latter responding more completely and promptly. Numerous studies have shown this to be a fallacy (*8, 9*).

In summary, what does the evidence seem to indicate? Fever represents a universal, ancient, and usually beneficial response to infection, and its suppression under most circumstances has few, if any, demonstrable benefits. On the other hand, some harmful effects have been shown to occur as a result of suppressing fever: in most individuals, these are slight, but when translated to millions of people, they may result in an increase in morbidity and perhaps the occurrence of occasional mortality. It is clear, therefore, that widespread use of antipyretics should not be encouraged either in developing countries or in industrial societies. Unfortunately though, just as fever represents an ancient biological response, an emotional effect is embedded deeply. Through the ages, parents have seen that when fever begins to diminish and disappears, the child feels better and recovers from the illness — whatever it was. Thus, the fever has become synonymous with the illness. This flaw in logic has persisted in parents' and physicians' minds, and they are seduced by the thought that if they "make the fever go away, the patient will be well." No amount of scientific discourse will change this attitude, and antipyresis will continue to be used in children with low-grade fevers, or even no fevers, in the home as well as the hospital. A reasonable evidence-based approach is to discourage the use of antipyretics in fevers <39 °C, reserving them for patients with higher temperatures. ■

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