

Is Fever Beneficial to the Host: A Clinical Perspective

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Received August 15, 1985

Fever is a phylogenetically ancient host response to infection, being found in fish and lizards, and conserved, with all its metabolic costs, in the higher mammals, including man. The conservation of the fever response in evolution is used as an argument for its survival value and, indeed, in experiments with cold-blooded animals "behavioral fever" has been demonstrated to reduce mortality associated with infection. Recent advances in the biology of interleukin-1 and other cytokines have allowed the testing, *in vitro*, of components of mammalian host defense (such as immune cell function) at temperatures typical of fever, and marked effects have been found. It remains to be demonstrated, however, that the hyperthermia of fever has survival value in man, and though it might be predicted that fever would be beneficial in infections, it is quite possible that in some circumstances even mild fever could be construed as harmful. In autoimmunity, for example, increased T-cell activation at febrile temperatures may well accelerate disease progress.

With the heart rate, respiratory rate, and blood pressure, the body temperature of most hospital patients is recorded at least once daily. The universal recognition of the value of fever as a clinical sign is, of course, ancient [1], and in the past the presence of fever was often regarded as favorable to the patient's survival prospects. However, in the late nineteenth century aspirin became available and was greatly used by physicians who could now relieve their patients of the discomforts associated with inflammation. Undoubtedly, the popularity of aspirin derived from pain reduction, the antipyretic effect being of secondary interest. Nevertheless, the indiscriminate reduction of fever became common medical practice—the immediate symptomatic gains apparently outweighing any imponderable risk of pathogenic penalties.

Interest in the favorable aspects of fever revived in the 1920s with the use of artificial fever induction to combat intractable chronic infections, but this was soon overshadowed by the discovery of antibacterial drugs, although not before curiosity in the pathogenesis of fever and its role in host defense had been aroused.

Today we recognize that fever is a regulated rise in body temperature under central nervous control [2]. The central nervous adjustments that lead to fever are stimulated by a pyrogenic polypeptide released from activated host blood or tissue cells such as macrophages. Originally, the host-derived mediator of fever was known as endogenous or leucocytic pyrogen (EP, LP) [3], and it is now clear that fever induction is but one of many activities of endogenous pyrogen [4]. Conversely, other cytokines, of which alpha interferon is an example, have been shown to possess pyrogenic activity seemingly independent of EP. Despite this, EP remains the model—if eventually perhaps not the only—host mediator of fever.

In the 1970s, two key observations in the biology of fever were made by contributors to this symposium: definite survival value of fever in infected lizards was demonstrated

by Kluger and his colleagues [5]; Dinarello and others [6,7] showed that endogenous pyrogen was probably identical with the immunopotentiating monokine, lymphocyte activating factor (LAF). This EP/LAF cytokine, now referred to as interleukin-1 (IL-1) was soon credited with a formidable range of biological effects potentially relevant to host defense and maintenance of tissue structure. Recent gene sequencing indicates that what we call IL-1 is probably not a single gene product but several distinct polypeptides derived from a multi-gene family.

These advances have set the stage for a level of understanding of the biology of fever that was hitherto unthinkable. From the clinician's viewpoint, however, it seems that the role of fever for good or ill in many circumstances will remain unclear at least for some time to come. In human disease the issue is difficult to resolve for two broad reasons: first, a direct test of survival value in the whole animal is hard to design since, in homeotherms, it is impossible to isolate temperature as a single manipulated variable; second, the value of information obtained from applying febrile temperatures to components of host defense systems *in vitro* depends on an understanding of their role in the course of a particular disease. Clearly, some ostensibly defensive systems—notably immune responses—may themselves contribute to the morbidity and mortality associated with a number of human diseases. The interrelation of fever and immune cell function is, itself, complicated and merits fuller discussion in this debate.

FEVER AND IMMUNITY

The association of fever with the immune response through their shared endogenous mediator, IL-1, led to the question of how these two effects of IL-1, a brain-mediated elevation in temperature and augmentation of lymphocyte activation, might be related. To test if the pyrogenic action of IL-1 created an optimal temperature environment for its own lymphostimulatory action, murine thymocytes were exposed to IL-1 both at 37°C and at a fever temperature, 39°C. T-cell proliferation measured after a three-day culture was found to be greatly increased at the higher temperature—often as much as tenfold [8]. This thermal enhancement of IL-1-driven T-cell proliferation did not seem a general property of lymphocyte mitogenesis, since B cells responded less well to the polyclonal mitogen lipopolysaccharide at the higher temperature. It was confirmed *in vivo* that the IL-1 used in these experiments was pyrogenic for the mouse strain used as thymocyte donors [9]. Average mouse temperature rose from 37.2°C to 38.59°C (range, 0.4–1.9°C) following intravenous injection of IL-1.

These studies were extended to test the effect of febrile temperature on the primary, *in vitro*, humoral immune response of murine spleen cells to sheep red blood cells. In this system a whole population of spleen cells responds to the antigenic stimulus by generating activated B cells that secrete specific antibody. This occurs under T-cell control during a five-day culture. Initial experiments showed that the number of antibody-producing B cells obtained from these cultures could be increased by two- to twentyfold (average, tenfold) by exposure of the spleen cells to febrile temperatures [10]. Furthermore, optimal effects occurred with exposure to hyperthermia restricted to the first 24 hours of culture, and if cells were held at 37°C for the first 48 hours and then exposed to hyperthermia for the subsequent three days, no thermal augmentation was detected.

The immune response studied was the outcome of a series of interactions involving different lymphocyte populations. Studies with isolated cell populations that were exposed individually to hyperthermia and then added back to re-constitute the whole

spleen cell culture demonstrated that the generation of T helper cells was greatly increased at the higher temperature, while B-cell function was not and T suppressor generation and function were not influenced [10].

It is noteworthy that T cells are highly sensitive to temperature change from about 32°C—typical of the body periphery—up to deep-body temperature levels that occur during fever [11].

The molecular basis of thermally augmented T-cell function is still not clear, but it is of interest that hyperthermic conditions that lead to the appearance of “heat-shock proteins” [12] or “stress proteins” also stimulate immune function when applied for one hour at a critical time during the first day of a five-day culture. Conversely, reversible blocking of protein synthesis during thermal exposure prevents both the appearance of heat-shock proteins and the subsequent augmentation of immune function measured five days later [13]. Though thermally enhanced T-cell function was independent of any change in accessory cell function brought about by heat-shock conditions in these experiments, other investigators have reported that monocyte IL-1 production is actually reduced by sustained exposure to fever temperatures, suggesting a possible negative feedback influence of IL-1 on its own release [14].

The recent finding [15] that recombinant human alpha interferon also had pyrogenic properties led to the testing in mice of the immunoregulatory and the antiviral properties of interferon at febrile temperatures. At 39°C, interferon completely blocked the generation of suppressor cells *in vitro* and, *in vivo*, augmented both delayed-type hypersensitivity and antibody responses [16]. Additionally, fibroblasts treated with interferon at febrile temperatures were significantly more resistant to subsequent viral challenge than those treated with interferon at 37°C.

The results of these and similar experiments suggest that fever may have survival value through increased immune responsiveness at higher temperature. However, it is important to stress that others have found, for example, that natural killer activity of human mononuclear cells incubated for 18 hours at 39°C was significantly reduced, as was the production of interleukin-1, interleukin-2, and granulocyte-macrophage colony-stimulating factor [Dinarello CA: personal communication].

IMMUNITY AND FEVER

Apart from the effects that the hyperthermia of fever may have on the function of the immune system, it is well established that fever is, itself, generated during the course of immune responses. In the case of cellular immunity, Atkins et al. [17,18] have demonstrated that antigen reacts with specifically sensitized lymphocytes, leading to the release of transferable factors that can stimulate EP production in mononuclear phagocytes. EP-inducing lymphokines are also released following allogeneic responses [19] and lectin stimulation of lymphocytes [20]. Recently, Atkins and Francis showed that desensitization of hypersensitive guinea pigs is associated with increased cell-mediated suppression of lymphokine-stimulated EP release [21]. Collectively, these results provide an explanation for the occurrence of fever during delayed-type hypersensitivity reactions.

While lymphokine-mediated EP release may explain fever during cellular immune responses, it is thought that antigen:antibody immune complexes are responsible for the occurrence of fever in humoral immune responses. In naive animals treated with antiserum, fever occurs following injection of antigen [22], and pre-formed antigen-antibody complexes are pyrogenic in normal animals [23]. A role for the complement

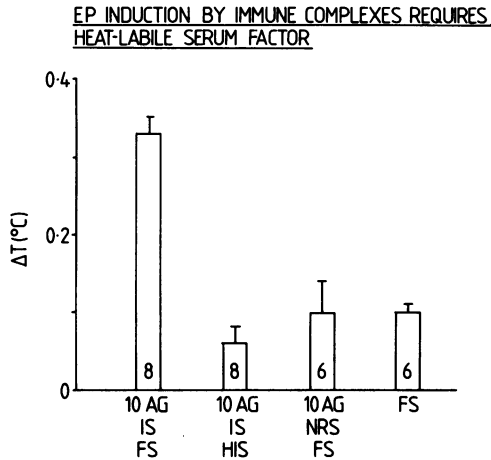


FIG. 1. The equivalence point of rabbit immune serum (IS) to ovalbumin (AG) was found by immunoprecipitation. Soluble immune complexes were prepared *in vitro* at 10× antigen excess (10 AG) by mixing AG and IS in the cold. Controls consisted of mixtures of 10 AG with normal rabbit serum (NRS). The complexes and control mixtures were incubated with rabbit blood leukocytes (standardized for monocyte content) in the presence of either fresh serum (FS) or heat-inactivated serum (HIS) overnight at 37°C. The EP contents of supernatants from 2×10^6 monocyte aliquots were tested in the rabbit pyrogen test [27]. EP content is shown on the vertical axis as the maximum induced temperature change. Means and standard errors for the number of experiments shown in the bars are given.

system in immune complex fever has also been documented [24]. Work from Atkins's laboratory has demonstrated directly that immune complexes in antigen excess will stimulate the release of EP from blood leukocytes *in vitro* [25]. In this study also, as shown in Fig. 1, a heat-labile cofactor (presumably complement) was required for this activity [26]. There is therefore good evidence that both cellular and humoral immune responses can result in the generation of EP/IL-1 with the development of fever in the host.

FEVER IN CLINICAL PRACTICE

Laboratory studies such as those discussed previously do suggest that, in mammals, mild to moderate fever (up to about 39°C) may be protective in cases where increased T-cell activation would favor the host. Presumably, immune responses to most infectious pathogens would fall into this category. But even with this limitation it must be remembered that other aspects of accessory and immune cell function, such as the production of interleukins, may be inhibited at febrile temperatures. Since IL-1 activities affect a wide range of tissues, and IL-1-induced hyperthermia reduces subsequent IL-1 release, many potentially host-defensive responses might be impaired over and above the loss of the stimulus for fever. Even if it is accepted that fever temperatures may have a beneficial effect on the immune response against pathogens, a significant problem arises when we consider the occurrence of fever in sterile inflammation. Fever in the absence of detectable infection is a common finding in clinical practice. For example, in a retrospective study of patients on a coronary care unit, 51 consecutive patients with myocardial infarction by electrocardiographic and enzyme-release criteria had a mean temperature of 37.47°C on the second day, while 45 consecutive patients from the same unit with chest pain but who did not meet the criteria of a myocardial infarction had a mean temperature of 36.9°C on the second day after the onset of chest pain [Orpin M, Duff GW: personal observations]. At present, the pathogenesis of this small but consistent fever following myocardial damage, like the fever associated with pulmonary embolism and similar conditions, is unknown. Whether these might be beneficial or detrimental to the patient is impossible to judge.

On the other hand, in diseases such as systemic lupus erythematosus and rheumatoid

arthritis, where there is well-documented evidence of pathogenic autoimmune activation, it might be expected that the facilitating effect of fever temperature on immune responsiveness would be harmful. It may of course be argued by those who support a beneficial role for fever that in cases of autoimmunity the fever occurs as a result of the breakdown of normal control mechanisms and is therefore not comparable with fever in the setting of a "normal" host defense system. In response, the view could be expressed that over the course of evolution host defense systems have become more complicated and therefore have more ways of going wrong—and that fever in reptiles is not comparable to fever in humans.

In crystal-deposition diseases such as gout, fever also occurs and urate crystals have been shown to stimulate EP release from human monocytes *in vitro* [28], but it is difficult to imagine any beneficial role of fever temperature in gout. Perhaps in this disease fever is the price the host must pay for the biological effects of IL-1 which may contribute to the containment or removal of urate crystals in the tissues.

Most physicians take the view that mild fevers are best left alone while higher fevers should be reduced, especially in infants and individuals with known organ impairment. The more important issue is to define the etiology of the fever so that specific therapy, if it exists, can be instituted. As far as the human host is concerned, the answer to the question "Is fever beneficial?" must surely be qualified by the conditions in which fever occurs. In the words of Robert Louis Stevenson, "the full truth of this odd matter is what the world has long been looking for" [29].

ACKNOWLEDGEMENT

This essay is dedicated to Professor Elisha Atkins on his retirement from Yale University School of Medicine.

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