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Fever: Its History, Cause, and Function

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Concepts of fever from Hippocrates to the present are briefly outlined and compared with current ideas of the pathogenesis of fever. Evidence is presented that endogenous pyrogen, the hormone that elevates body temperature, is identical with lymphocyte-activating factor, a monokine that stimulates lymphocyte proliferation and function.

It now appears that inflammation and fever are closely interrelated phenomena that are modulated by a single hormone and that have been selected by evolution to protect the host against infection.

Since the beginning of recorded history, fever has been a hallmark of disease. Akkadian cuneiform inscriptions of the sixth century B.C. appear to have adapted an ancient Sumerian pictographic symbol of a flaming brazier to denote in a single ideogram both fever and the local warmth accompanying inflammation [1]. The four cardinal features of inflammation—heat, redness, swelling, and pain—were first enunciated by Celsus, a physician of the early Roman Empire. Though Celsus's observations reappeared in a tenth-century manuscript and have remained a central dogma of pathology learned by every medical student to the present, it was not until the mid-nineteenth century that specific experiments were done to investigate the possible causal relation between inflammation and fever. Impressed no doubt by his clinical observations, the German surgeon, Billroth, induced his pupil, Frese, to inject filtrates of autogenous pus into cats. In his notes, Frese observed that fevers promptly developed after each of several intravenous injections into the same cat, but, unfortunately, the possible role of contaminating bacterial pyrogens, unknown at that time, makes uncertain the interpretation of these abortive but creative experiments [2].

In the Hippocratic writings that form the cornerstone of our science of medicine, there are many marvelously precise descriptions of febrile diseases—so accurate, indeed, that it is possible to recognize such entities as malaria (in its various forms) and bacterial pneumonias as well as enteric fevers. The characteristic fluctuations in body temperature occurring in these diseases—the sustained fevers of pneumonia, the intermittent (tertian or quartan) fevers of malaria, and, in particular, the stepwise rise in temperature with the onset of typhoid fever—are all unequivocally described, although we remain uncertain how such observations were made long before the advent of the clinical thermometer in the eighteenth century. With the chill that heralds the onset of many fevers, the temperature of the skin, of course, is

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actually cooled as the internal temperature rises so that the correlation of internal and external temperatures at this time is actually an inverse one. Perhaps some of these subtle changes in body temperature were inferred to be correlated with observed changes in pulse, although there appears to be no explicit reference to this until the works of Hierophilus in the third century B.C.

Unfortunately, the Greeks, with their love of hypothesis and symmetry, "tried to explain Nature," as someone has said, "while shutting their eyes." Hence, the Hippocratic legacy of the doctrine of four humors: blood, phlegm, black bile, and yellow bile, which fitted neatly with the four corresponding elements: air, water, earth, and fire, respectively, and their four intersecting qualities: wet, cold, dry, and hot. Disease, in Hippocratic terms, resulted from an imbalance of these humors, with fever due to an excess of yellow bile which, like fire, was hot and dry. The humoral theory, embellished by Galen in the second century A.D., dominated medical thinking well into the seventeenth century. After the publication in 1628 of Harvey's momentous discovery of the circulation of the blood, physicians in the seventeenth century became aligned in two opposing camps: the iatrophysicists and the iatrochemists. The iatrophysicists, impressed no doubt with the forcefulness of the febrile patient's pulse, saw fever in terms of increased friction of blood coursing through the system, a process which was believed ordinarily to maintain animal heat. Other modifications of this theory asserted that "the heart and arteries are the instruments which excite this heat; but this is not done by the Friction caused by the Circulation of the Humours, but only the intestine Motion, which the Circulation gives to the several Particles which constitute the Mass of animal Fluids." The iatrochemists, on the other hand, believed that heat was produced in fluids by fermentation and putrefaction. "Man's Body, of which he is so vain, is little better than a smoking Dunghill," declared Stevenson, one of the iatrochemical proponents. Fever, then, was simply a hyperfermentation taking place in the blood, presumably chiefly in the veins since there was said to be three or four times more blood in the veins than in the arteries. Stevenson's theory, as Mendelsohn has noted in *Heat and Life*, a monograph reviewing the development of the theory of animal heat, "emerges as a strange mixture of late 17th Century chemistry and vitalism, and, for all its attempts to explain a wide range of animal functions, it remains 'merely another hypothesis' with little basis in experiment" [3].

In the eighteenth century, an era of classification developed in regard to fevers, with one author listing as many as 103 different kinds, identified by such quaint terms as putrid, malign, ataxic, or synochus, all based, presumably, on various external manifestations of the patient such as his appearance, character of the pulse, etc. With the development of postmortem examination of diseased tissues, some physicians of this era still continued to use these lesions simply as additional markers for the identification of already established different kinds of fever. Fevers with obvious sites of inflammation were known as "symptomatic"; those in which no lesion could be found were called "essential." This tide of nosology was quietly turned by several remarkable works in the early eighteenth century by a French physician, Broussais, who attempted to correlate different manifestations of febrile illnesses with corresponding changes in the tissues seen in postmortem pathology. By postulating an irritating (or inflammatory) agent as the initiating cause of the pathologic changes seen in various tissues, he constructed an anatomopathological "web of causality" which, as Foucault has pointed out, replaced the old nosology with its confusing terms and, in effect, created a new physiology of disease [4]. Thus, the concept of pathogenicity was born, although the actual discovery of the

microbial agents of disease was to await the scientific genius of Pasteur and Koch more than 50 years later. However, inflammation as a pathologic process was again clearly linked with one of its chief manifestations, fever, in disease.

It was not until the late nineteenth century that the role of the central nervous system was established in regulating normal body temperature as well as the elevated temperatures occurring in fever. In 1876, the great French physiologist, Claude Bernard, recognizing the discoveries of Lavoisier and Liebig that the sources of animal heat resided in metabolic processes of the body, defined the role of the autonomic nervous system in modifying heat loss through regulating the flow of blood to the surface [5]. The thermoregulation of warm-blooded creatures thus became identified as one of the major manifestations of his theory of homeostasis—namely, that dynamic mechanisms operate in life to maintain the constancy of the "milieu interieur." In 1875, the year before Bernard's studies on animal heat appeared, von Liebermeister had postulated in his handbook of the pathology and therapy of fevers that fever results from a disorder that "sets" body temperature at a new higher level. Thirteen years later, in 1888, William H. Welch, Professor of Pathology and colleague of Sir William Osler at Johns Hopkins University, wrote an extraordinary, detailed treatise on fever based in large part on his own experiments as both a pathologist and bacteriologist [6]. This classic work defined the mechanisms for heat production and loss in the body and demonstrated the balance that ordinarily exists between them. He then hypothesized that the central nervous system regulates body temperature in health as well as in fever and summarized evidence from his own and other experiments that the thermoregulatory center was located in subcortical areas of the brain near the thalamus. Animals with a lower cervical cord transection or given curare to block nervous impulses to the muscles failed to respond with fever when given a pyrogenic agent intravenously. He further postulated that certain tissue ferments (in non-infectious disease) as well as toxins from microbes (both virulent and avirulent) produce fever indirectly by a common mechanism, perhaps by releasing a ferment from the host's leukocytes. In other experiments, in which he subjected rabbits to prolonged periods of hyperthermia in hot boxes, he separated the effect of increased body temperature per se (which produced only minimal pathologic changes on postmortem examination) from other, clearly harmful consequences of infection clinically. On the basis of these findings, he suggested, in conclusion, that fever itself might indeed have a beneficial effect, either directly by destroying microbes or, indirectly, by increasing the host's resistance to infection.

Thus, the modern theory of the pathogenesis of fever was born and the main lines of future investigations were clearly drawn 50 years or more before others were to show that leukocytes in inflammatory lesions and exudates contain an agent that produces fever when given intravenously.

The wheel had come full circle; the two processes of inflammation and fever were joined again, as in the single word, "ummu," in the ancient Akkadian text, nearly 2,500 years ago.

Recent studies on the pathogenesis of fever originated 40 years ago with the independent observations by Menkin, and somewhat later by Bennett and Beeson, that a pyrogenic material could be extracted from sterile inflammatory exudates. Although it seems likely that Menkin's material was contaminated with extraneous bacterial pyrogens, Bennett and Beeson clearly established in a subsequent study in rabbits that leukocytes derived from exudates, blood, or various inflammatory lesions were sources of an endogenous pyrogen (EP) [7].

Initially EP was thought to be derived only from granulocytes; later, monocytes

or macrophages from various sites (blood, lung, liver, or peritoneal exudates) were shown to be potent sources of EP. Using phagocytosis of staphylococci as a stimulus, Murphy and his associates have recently shown that EP production in mixed populations of blood cells can be entirely attributed to their monocyte content. When sufficiently purified, granulocytes, though functioning normally in other ways, do not generate detectable amounts of EP *in vitro* [8].

Among the microbial agents that have been shown to evoke release of EP, both *in vivo* and *in vitro*, are the lipopolysaccharides that form part of the cell wall of the gram-negative bacteria (so called "endotoxins") as well as various gram-positive bacteria, pathogenic fungi and viruses, and some of their soluble products. The mechanisms by which these agents activate cells to release pyrogen are multiple and, though not well known, probably include certain particulate stimuli (including phagocytosis), as well as chemical stimulation, presumably of the cell membrane. Studies of rabbits with fever accompanying peritoneal infections with pneumococci have shown that pyrogen is rapidly liberated by cells in the inflammatory exudate and subsequently reaches the blood by way of the thoracic duct lymph. Experimentally induced fevers resulting from the injection of both microbial and nonmicrobial antigens into specifically sensitized animals appear to be caused by a circulating EP, although its cellular source (cells in the blood or RES) has not been conclusively demonstrated. In mixed lymphocyte reactions with human cells or in experimental states of delayed hypersensitivity, lymphocytes activated by specific antigen(s) produce a lymphokine that stimulates blood or exudate monocytes to produce EP. Lymphocytes themselves, however, do not appear capable of producing EP directly.

In all these experimental situations it seems clear that an intermediary pyrogen, liberated from tissues of the host, plays a major role in producing the febrile response (reviewed in [9]). Endogenous pyrogen derived from both rabbit and human leukocytes has now been purified to a considerable extent and appears to consist of several molecular species of proteins with a molecular weight of 13–15,000. Collectively, EP can be clearly differentiated on a number of grounds, both biochemical and biological, from all known exogenous pyrogens, including endotoxins, which are lipopolysaccharides with much larger molecular weights in their natural aggregated state.

Studies by several investigators on the mechanism of EP production *in vitro* have shown that it is an active metabolic process, dependent upon temperature and intact cellular structure, and may be blocked by certain enzyme inhibitors during an early critical period after addition of the activator [10,11]. After this initial period, production of EP continues despite addition of various inhibitors of DNA synthesis or of aerobic or anaerobic metabolism. Production of pyrogen is suppressed, however, by inhibitors of protein synthesis long after the initial period required for activation of the cell, suggesting that it is an active synthetic process—an inference that has been confirmed by the finding that radioactively labeled amino acids are incorporated in the synthesis of new EP *in vitro*.

More recent studies in a number of different animals have implicated two additional classes of agents in the brain that may be important, both in normal thermoregulation and in the pathogenesis of fever. Feldberg, Myers, and their associates [12,13] have shown that intracerebral injection of several monoamines—catecholamines and serotonin, both of which occur normally in high concentration in the region of the third ventricle—produces profound effects on the body temperature of various conscious animals. The change in temperature (whether rise

or fall) varies with different species, but clearly, marked elevations in body temperature may be produced in this manner.

Similarly, certain prostaglandins (especially PGE_1), long-chain fatty acids of endogenous origin, produce immediate high fevers when injected in minute amounts directly into the thermoregulatory center of a number of animals [14]. Unlike the effects of EP when given intracerebrally, the pyrogenic action of PGE_1 is not suppressed by aspirin. Since various exogenous pyrogens given intravenously produce increased prostaglandin levels in the brain, and since aspirin is known to block the synthesis of prostaglandins, these findings suggest that other pyrogenic agents may indeed activate the cells in the hypothalamus by synthesizing prostaglandin or other derivatives of arachidonic acid metabolism which, in turn, would function as the "final common pathway" in the pathogenesis of fever. At present, however, the actual sequence of events in the brain that mediate fever is still uncertain.

It is apparent that many questions concerning the pathogenesis of fever remain unanswered. Are there other as yet undiscovered types of endogenous pyrogen? Are monocytes and tissue macrophages the only source of EP? Although EP seems to be the chief factor in producing fever of microbial origin, little is known about the cause of fever in patients with malignant tumors, lymphomas, collagen diseases, or certain metabolic diseases such as acute gout and porphyria. In some of these conditions, factors known to contribute to fever in various infectious diseases, such as inflammation and hypersensitivity, may play a role. As yet, there is no known endogenous agent or component of the inflammatory response that is, by itself, capable of activating cells to produce EP, although the pyrogenicity of synthetic double-stranded RNA, Poly I:C, suggests an intriguing analogy with endogenous RNA and/or DNA. The discovery of such an agent would provide an explanation for fevers in diseases where tissue damage and inflammation are unaccompanied by infection or hypersensitivity (e.g., acute myocardial or pulmonary infarction or thrombophlebitis).

Also, little is known of the location or precursors of EP in the cell or of the specific mechanisms by which EP is activated or disposed of in the body although a metabolite of radioactively labeled EP has been found in the urine.

An exciting new development has been the discovery that EP is, in all probability, identical to lymphocyte-activating factor (LAF), a monokine (now known as interleukin-1, IL-1) that potentiates the mitogenic effect of antigen and mitogens (e.g., concanavalin A) on thymus-derived lymphocytes [15,16]. Since the mitogenic assay for LAF is about a thousandfold more sensitive than is the pyrogenic assay for EP in rabbits, it is likely that other new functions of this substance will be discovered in the near future. A partial radioimmune assay for human EP has been recently described, an advance that should facilitate study of the intracellular synthesis of EP as well as its presence in various tissues during clinical fever [17]. EP derived from clinical exudates or human blood leukocytes activated *in vitro* can be readily detected by pyrogenic assay in humans, rabbits, and, in much smaller amounts, in mice. However, it is much more difficult to measure EP in the circulation of humans with fever than in most experimental models in animals.

It is often said that fever assists the host in combating infection. There is no question of the value of fever therapy that was once used in the treatment of neurosyphilis. It has also been observed that failure to develop fever in the presence of a severe infection signifies a grave prognosis. However, in most of these instances the absence of fever is probably related to circulatory failure, and death is due to this

complication rather than to the lack of benefit conferred by a febrile response, per se, to the infected host.

Under natural circumstances of infection, it seems unlikely that the increase in body temperature itself directly affects the invading microorganism [18]. Thermolabile microbes, like treponemes, rarely induce in the host high temperatures that would destroy themselves. On the other hand, those microbes that do evoke high fevers, like the malaria parasite, are clearly unaffected by these temperatures. However, it has long seemed probable from the evolutionary standpoint that fever is somehow beneficial to the host, and might indirectly modify the virulence of the invading microorganism by accelerating or enhancing some aspect of host resistance to infection, such as the inflammatory and/or immune responses. A study in lizards [19] was the first to show conclusively that the ability to develop fever in infection is clearly correlated with survival. Reptiles, being poikilotherms, regulate their body temperature by behavioral means. When infected with a gram-negative bacterium, they developed a 2°C fever (to 40°C) by selecting an appropriately warm environment. Lizards kept at this febrile temperature after infection survived significantly better than did those maintained at low or neutral temperatures (34°C or 38°C, respectively). In a later study with the same species of lizard, Bernheim et al. showed that the febrile temperature was correlated with the development of an early inflammatory response at the site of infection and a dramatic reduction in the number of bacteria in various organs [20]. More recent studies in rabbits given antipyretics have confirmed that moderate (but not extreme) fevers are associated with decreased mortality in experimental infection [21].

The finding mentioned previously that EP and LAF are presumably identical and that inflammation as well as lymphocyte proliferation and function are increased at febrile temperatures [22] provide powerful evolutionary arguments for the usefulness of fever. Recently, Duff in our laboratory has adduced direct evidence that the mitogenic and functional effects of IL-1 itself are markedly increased at febrile temperatures. Furthermore, it seems likely that EP is also the same as a substance known as leukocyte endogenous mediator (LEM) which produces a number of bodily defense reactions including lowering serum iron (necessary for bacterial metabolism) and promoting synthesis of acute phase proteins, as well as increasing the number of circulating granulocytes and (under the guise of "purified EP") activating certain of their bactericidal mechanisms (reviewed in [23]).

In conclusion, it now appears that fever and inflammation are two ancient and profoundly interrelated responses that are modulated by a single mononuclear cell product—responses that have been devised in the long process of evolution to protect the host against infection. In this light, one can do no better than reiterate the sonorous and prescient conclusion of Thomas Sydenham, one of the greatest British physicians of the seventeenth century, that "Fever is a mighty engine which Nature brings into the world for the conquest of her enemies."

REFERENCES

1. Majno G: The Healing Hand: Man and Wound in the Ancient World. Cambridge, MA, Harvard University Press, 1975, p 56
2. Frese JB: Experimentelle Beiträge zur Aetiologie des Fiebers. Universität zu Dorpat, 1866. Quoted in Wood WB Jr: Studies on the cause of fever. New Eng J Med 258:1023, 1958
3. Mendelsohn E: Heat and Life: The Development of the Theory of Animal Heat. Cambridge, MA, Harvard University Press, 1964

4. Foucault M: The Birth of the Clinic: An Archeology of Medical Perception. New York, Vintage Books, 1975, pp 174–194
5. Bernard C: Leçons sur la Chaleur Animale. Paris, Baillière, 1876, p 121
6. Welch WH: The Cartwright lectures on the general pathology of fever. Med News (Philadelphia) 52:365, 393, 539, 565, 1888
7. Bennett IL Jr, Beeson PB: Studies on the pathogenesis of fever. I. The effect of the injection of extracts and suspensions of uninfected rabbit tissues upon the body temperature of normal rabbits. J Exp Med 98:477, 1953
8. Hanson DF, Murphy PA, Windle BE: Failure of rabbit neutrophils to secrete endogenous pyrogen when stimulated with staphylococci. J Exp Med 151:1360, 1980
9. Bernheim HA, Block LH, Atkins E: Fever: pathogenesis, pathophysiology, and purpose. Ann Int Med 91:261, 1979
10. Nordlund JJ, Root RK, Wolff SM: Studies on the origin of human leukocytic pyrogen. J Exp Med 131:727, 1970
11. Bodel P: Studies on the mechanism of endogenous pyrogen production. I. Investigation of new protein synthesis in stimulated human blood leucocytes. Yale J Biol Med 43:145, 1970
12. Feldberg W, Myers RD: Effects on temperature of amines injected into the cerebral ventricles. A new concept of temperature regulation. J Physiol 173:226, 1964
13. Myers RD, Yaksh TL: Control of body temperature in the unanaesthetized monkey by cholinergic and aminergic systems in the hypothalamus. J Physiol 202:483, 1969
14. Milton AS, Wendlandt S: Effects on body temperature of prostaglandins of the A, E and F series on injection into the third ventricle of unanaesthetized cats and rabbits. J Physiol 218:325, 1971
15. Rosenwasser LJ, Dinarello CA, Rosenthal AS: Adherent cell function in murine T-lymphocyte antigen recognition IV. Enhancement of murine T-cell antigen recognition by human leukocytic pyrogen. J Exp Med 150:709, 1979
16. Murphy PA, Simon PL, Willoughby WF: Endogenous pyrogens made by rabbit peritoneal exudate cells are identical with lymphocyte-activating factors made by rabbit alveolar macrophages. J Immunol 124:2498, 1980
17. Dinarello CA, Renfer L, Wolff SM: Human leukocytic pyrogen: Purification and development of a radioimmunoassay. Proc Natl Acad Sci USA 74:4624, 1977
18. Bennett IL Jr, Nicastri A: Fever as a mechanism of resistance. Bact Rev 24:16, 1960
19. Kluger MJ, Ringler DH, Anver MR: Fever and survival. Science 188:166, 1975
20. Bernheim HA, Bodel PT, Askenase PW, et al: Effects of fever on host defence mechanisms after infection in the lizard *Dipsosaurus dorsalis*. Brit J Exp Path 59:76, 1978
21. Kluger MJ, Vaughn LK: Fever and survival in rabbits infected with *Pasteurella multocida*. J Physiol 282:243, 1978
22. Roberts NJ Jr: Temperature and host defense. Microbiol Rev 43:241, 1979
23. Dinarello CA: Human pyrogen: a monocyte product mediating host defenses. In Advances in Host Defense Mechanisms. Vol 1. Edited by JI Gallin, AS Fauci. New York, Raven Press, 1982, pp 57–74