REVIEW ARTICLE

Concepts of Fever

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If asked to define fever, most physicians would offer a thermal definition, such as "fever is a temperature greater than. . . ." In offering their definition, many would ignore the importance of the anatomic site at which temperature measurements are taken, as well as the diurnal oscillations that characterize body temperature.[1] If queried about the history of clinical thermometry, few physicians could identify the source or explain the pertinacity of the belief that 98.6°F (37.0°C) has special meaning vis-à-vis normal body temperature. Fewer still could cite the origin of the thermometer or trace the evolution of modern concepts of clinical thermometry. Although many would have some knowledge of the fundamentals of thermoregulation and the role played by exogenous and endogenous pyrogens in the induction of fever, few would have more than a superficial knowledge of the broad biological activities of pyrogenic cytokines or know of the existence of an equally complex and important system of endogenous cryogens. A distinct minority would appreciate the obvious paradoxes inherent in an enlarging body of data concerned with the question of fever's adaptive value. The present review considers many of these issues in the light of current data.

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The oldest known written reference to fever exists in Akkadian cuneiform inscriptions from the sixth century BC, which seem to have been derived from an ancient Sumerian pictogram of a flaming brazier that symbolized fever and the local warmth of inflammation.[2] Theoretical constructs concerned with the pathogenesis of fever did not emerge until several centuries later, when Hippocratic physicians proposed that body temperature, and physiologic harmony in general, involved a delicate balance among 4 corporeal humors—blood, phlegm, black bile, and yellow bile.[3] Fever, it was believed, resulted from an excess of yellow bile, a concept consistent with the fact that many infections of that era were associated with fever and jaundice. During the Middle Ages, demonic possession was added to the list of mechanisms believed responsible for fever. By the 18th century, Harvey's discovery of the circulation of blood and the birth of microbiology led iatrophysicists and iatrochemists to hypothesize, alternatively, that body heat and fever result from friction associated with the flow of blood through the vascular system and from fermentation and putrefaction occurring in the blood and intestines.[4] Ultimately, thanks to the work of the great French physiologist, Claude Bernard, the metabolic processes occurring within the body finally came to be recognized as the source of body heat. Subsequent work established that body temperature is tightly controlled within a narrow range by mechanisms regulating the rate at which such heat is allowed to dissipate from the body.

The origin of the practice of monitoring body temperature as an aid to diagnosis is shrouded in uncertainty. The oldest known references to devices used

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to measure temperature date to the first or second century BC, when Philo of Byzantium and Hero of Alexandria are believed to have invented several such devices.[5] It is reasonably certain that Galileo manufactured a primitive (air) thermometer at about the time he assumed the chair in mathematics at Padua in 1592.[6] However, thermometry was not fully assimilated into medical practice until 1868, when Carl Reinhold August Wunderlich published a magnum opus entitled *Das Verhalten der Eigenwärme in Krankenheiten (The Course of Temperature in Diseases)*.[7]

Through *Das Verhalten der Eigenwärme in Krankenheiten,* Wunderlich gave 98.6°F (37.0°C) its special meaning for normal body temperature.[8] He described diurnal variation of body temperature and, in the process, alerted clinicians to the fact that "normal body temperature" is actually a temperature range rather than a specific temperature. In an analysis of a series of clinical thermometric measurements, the size of which has never been equaled (estimated to have included some 1 million observations in as many as 25 000 subjects), Wunderlich established 100.4°F (38.0°C) as the upper limit of the normal range and, in so doing, proffered one of the first quantitative definitions of fever.

Despite the fact that Wunderlich's work was published more than a century ago and was based primarily on axillary measurements generally taken no more often than twice daily, it has survived almost verbatim in modern day concepts of clinical thermometry. Interestingly, recent tests conducted with one of Wunderlich's thermometers suggest that his instruments may have been calibrated by as much as 1.4°C to 2.2°C (2.6°F-4.0°F) higher than today's instruments.[8] As a result, at least some of Wunderlich's cherished dictums about body temperature (eg, the special significance of 98.6°F [37.0°C]) have required revision.[9]

DEFINITIONS

Fever has been defined as "a state of elevated core temperature, which is often, but not necessarily, part of the defensive responses of multicellular organisms (host) to the invasion of live (microorganisms) or inanimate matter recognized as pathogenic or alien by the host."[10] The febrile response (of which fever is a component) is a complex physiologic reaction to disease, involving a cytokine-mediated rise in core temperature, generation of acute phase reactants, and activation of numerous physiologic, endocrinologic, and immunologic systems. The rise in temperature during fever is to be distinguished from that occurring during episodes of hyperthermia. Unlike fever, hyperthermia involves an unregulated rise in body temperature in which pyrogenic cytokines are not directly involved and against which standard antipyretics are ineffective. It represents a failure of thermoregulatory homeostasis, in which there is uncontrolled heat production, inadequate heat dissipation, or defective hypothalamic thermoregulation.

In the clinical setting, fever is typically defined as a pyrogen-mediated rise in body temperature above the normal range. Although useful as a descriptor for the febrile patient, the definition ignores the fact that a rise in body temperature is but one component of this multifaceted response. This standard clinical definition is further flawed, because it implies that "body temperature" is a single entity, when in fact, it is a pastiche of many different temperatures, each representative of a particular body part and each varying throughout the day in response to the activities of daily living and the influence of endogenous diurnal rhythms.

THERMOREGULATION

Heat is derived from biochemical reactions occurring in all living cells.[11] At the mitochondrial level, energy derived from the catabolism of metabolites, such as glucose, is used in oxidative phosphorylation to convert adenosine diphosphate to adenosine triphosphate. At rest, more than half of the body's heat is generated as a result of the inefficiency of the biochemical processes that convert food energy into the free energy pool (eg, adenosine triphosphate). When no external work is performed, the remainder of the body's heat (approximately 45%) is derived from the internal work involved in maintaining the structural and functional integrity of the body (ie, the use and resynthesis of adenosine triphosphate). When external work is performed, a portion of the latter heat (up to 25%) is generated by skeletal muscle contractions.

In adult humans and most other large mammals, shivering is the primary means by which heat production is enhanced. Nonshivering thermogenesis is more important in smaller mammals, newborns (including humans), and cold-acclimated mammals.[11,12] Although several tissues (eg, the heart, respiratory muscles, and adipose tissue) may be involved, brown adipose tissue has been associated most closely with nonshivering thermogenesis. This highly specialized form of adipose tissue located near the shoulder blades, neck, adrenal glands, and deep blood vessels is characterized by its brownish color, a profuse vascular system, and an abundance of mitochondria.[11,13]

Heat, generated primarily by vital organs lying deep within the body core, is distributed throughout the body by the circulatory system. In response to input from the nervous system, the circulatory system determines the temperature of the various body parts and the rate at which heat is lost from body surfaces to the environment (via conduction, convection, radiation, and evaporation).[14] In a warm environment or in response to an elevation in core temperature due to exercise, cutaneous blood flow increases so that heat is transported from the core to be dissipated at the skin surface. In anesthetized animals, although discrete hypothalamic warming increases such cutaneous blood flow, blood pressure is maintained because of a concomitant reduction in gastrointestinal blood flow.[15] In a cold environment or in response to a decrease in core temperature, cutaneous blood flow normally decreases as a means of retaining heat within the body core.[14]

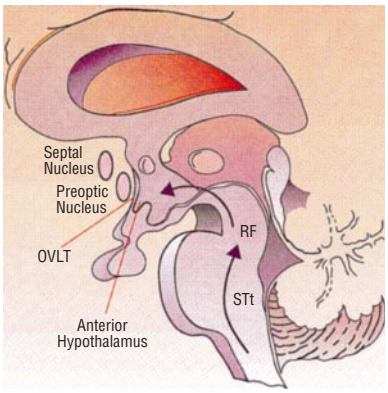

Figure 1. *Sagittal view of the brain and upper spinal cord showing the multisynaptic pathway of skin and spinal thermoreceptors through the spinothalamic tract (STt) and reticular formation (RF) to the anterior hypothalamus, preoptic region, and the septum. OVLT indicates organum vasculosum laminae terminalis. Adapted from Mackowiak and Boulant.[16]*

No single center within the nervous system controls body temperature. Rather, thermoregulation is a process that involves a continuum of neural structures and connections extending from the hypothalamus and limbic system through the lower brainstem and reticular formation to the spinal cord and sympathetic ganglia (**Figure 1**).[16] Nevertheless, an area of the brain located in and near the rostral hypothalamus seems to have a pivotal role in the process of thermoregulation. Although generally referred to as the *preoptic region,* it actually includes the medial and lateral aspects of the preoptic area, anterior hypothalamus, and septum. Numerous studies extending more than 60 years have established that neurons located in this region are thermosensitive and exert at least partial control over physiologic and behavioral thermoregulatory responses.[14,17]

Many, although not all, thermophysiologists believe that the temperature-sensitive preoptic region "regulates" body temperature by integrating thermal input signals from thermosensors in the skin and core areas (including the central nervous system).[18] One of the more widely held theories is that such integration involves a designated thermal set point for the preoptic region that is maintained via a system of negative feedback. According to this theory, if the preoptic temperature rises above its set point for whatever reason (eg, during exercise), heat loss responses are activated to lower body temperature and return the temperature of the preoptic region to the thermal set point (eg, 37.0°C).[19] The thermal set point of a particular heat loss response is thus the maximum temperature tolerated by the preoptic region before the response is evoked. If, on the other hand, the preoptic temperature falls below its thermal set point (eg, as a result of cold exposure), various heat retention and heat production responses are activated to raise body temperature and with it the temperature of the preoptic region to its thermal set point. The thermal set point of a particular heat production response is thus the minimum temperature tolerated by the preoptic region before the response is evoked.

Although useful in explaining the elevation of the thermal set point that occurs during fever, the concept of a single central set point temperature is regarded by many thermal physiologists as oversimplified. At least some of these physiologists prefer to think of body temperature as regulated within a narrow range of temperatures by a composite set point of several thermosensitive areas and several different thermoregulatory responses.[20,21]

A variety of endogenous substances and drugs seem to affect temperature regulation by altering the activity of hypothalamic neurons. Perhaps the best examples of such substances are the pyrogenic cytokines in the next section. These are released by phagocytic leukocytes in response to a wide array of stimuli and have the capacity to raise the thermoregulatory center's thermal set point. Whether they cross the blood-brain barrier to do so[22,23] or act by causing the release of other mediators (eg, prostaglandin E_2) in circumventricular organs, such as the organum vasculosum laminae terminalis[22] is, as yet, uncertain. Whatever the precise endogenous mediators of fever, their primary effect seems to be to decrease the firing rate of preoptic warm-sensitive neurons, leading to activation of responses designed to decrease heat loss and increase heat production.

ENDOGENOUS PYROGENS

Pyrogens traditionally have been divided into 2 general categories: those that originate outside the body (exogenous pyrogens) and those derived from host cells (endogenous pyrogens). Exogenous pyrogens are, for the most part, microbes, toxins, or other products of microbial origin,[24] whereas endogenous pyrogens are host cell–derived (pyrogenic) cytokines that are the principal central mediators of the febrile response. According to current concepts, exogenous pyrogens, regardless of physicochemical structure, initiate fever by inducing host cells (primarily macrophages) to produce endogenous pyrogens. Such concepts notwithstanding, certain endogenous molecules also have the capacity to induce endogenous pyrogens. These include, among others, antigen-antibody complexes in the presence of complement,[25,26] certain androgenic corticosteroid metabolites,[27-29] inflammatory bile acids,[30] complement,[31] and various lymphocyte-derived molecules.[32-34]

Complete understanding of the function of individual pyrogenic cytokines has been hampered by the fact that one cytokine often influences expression of other cytokines and/or their receptors and also may induce more distal comediators of cytokine-related bioactivities (eg, prostaglandins and platelet-aggregating factor).[35] In short, cytokines function within a complex regulatory network in which information is conveyed to cells by combinations and, perhaps, sequences of a host of cytokines and other hormones.[36] Like the words of human communication, individual cytokines are basic units of information. On occasion, a single cytokine, like a single word, may communicate a complete message. More often, however, complete messages received by cells probably resemble sentences, in which combinations and sequences of cytokines convey information. Because of such interactions, it has been difficult to ascertain the direct in vivo bioactivities of particular cytokines. Nevertheless, several cytokines have in common the capacity to induce fe-

Table 1. Biological Characteristics of the Principal Pyrogenic Cytokines*

Pyrogenic Cytokine	Aliases	Cell Source	Expression		Effect on Other Pyrogenic Cytokines	Biological Activities
			Up-regulated by	Down-regulated by		
IL-1	Endogenous pyrogen Leukocyte endogenous pyrogen Lymphocyte-activating factor Mononuclear factor Catabolin Osteoclast-activating factor Hematopoietin-1 Melanoma growth inhibition factor Tumor inhibitory factor-2	Astrocytes Endothelial cells Keratinocytes Monocytes Macrophages Dendrites Fibroblasts	TNF IFN-γ GM-CSF Zymosan LPS IL-1 C5a Leukotrienes PMA	IL-4 IL-6 IL-10 TGF-β Corticosteroids PGE_2 Retinoic acid	↑ IL-6 ↑ TNF ↑ IL-1	IL-2 and IL-2R induction Thymocyte costimulation Fibroblast activation Induce acute phase response T-cell activation Costimulation of B-cell proliferation and differentiation Augment CTL, LAK induction Induce endothelial adhesion molecules Enhance phagocyte microbial killing Accelerate wound healing
TNF-α	Cachectin	Monocytes Macrophages Eosinophils Neutrophils Lymphocytes Astrocytes Endothelial cells Mast cells Kupffer cells NK cells Certain tumors	Bacteria Viruses Fungi Protozoa LPS Staph TSSTI IL-1 IL-2 TNF IFNs GM-CSF PAF Substance P Anti-TCR Tumor cells PMA	Corticosteroids Cyclosporine PGE_2 IL-4 IL-6 IL-10 TGF-β Vitamin D_3	↑ TNF ↑ IL-1 ↑ IL-6	Septic shock Enhance phagocyte microbial killing Tumor necrosis Cachexia Anorexia Endothelial and epithelial MHC, adhesion molecule induction Osteoclast activation B-cell differentiation CTL induction
IL-6	Interferon beta-2 B-cell stimulatory factor-2 Hybridoma or plasmacytoma growth factor Hepatocyte-stimulating factor Cytotoxic T-cell differentiation factor Macrophage granulocyte-inducing factor 2A	Monocytes Macrophages Lymphocytes Fibroblasts Endothelial cells Epithelial cells Keratinocytes Bone marrow stroma Certain tumors	LPS IL-1 TNF IFN-β Calcium ionophore Mitogenic lectin and PMA Viruses	Corticosteroids Estrogens	↓ TNF ↓ IL-1	B-cell growth, differentiation, and IgG synthesis Myeloma proliferation CTL induction Acute phase response Thymocyte costimulation Weak antiviral activity Megakaryocyte maturation Neuronal differentiation Enhance IL-3–dependent stem cell proliferation
IFN-γ	Type II interferon Immune interferon	T cells NK cells	Mitogenic lectins IL-1 IL-2	Corticosteriods Cyclosporine Vitamin D_3	↑ TNF ↑ IL-1	Macrophage priming Antiviral activity Enhance TNF activity MHC induction Enhance NK activity Enhance endothelial ICAM-1 expression Inhibit IL-4–induced B-cell responses B-cell differentiation and IgG2a secretion

**IL indicates interleukin; TNF, tumor necrosis factor; IFN, interferon; GM-CSF; granulocyte-macrophage colony-stimulating factor; LPS, lipopolysaccharide; C5a, complement component C5a; PMA, phorbol myristate acetate; TGF-β, transforming growth factor β; PGE_2, prostaglandin E_2; CTL, cytotoxic T lymphocytes; LAK, lymphocyte-activated killer; NK, natural killer; Staph TSSTI, staphylococcal toxic shock syndrome toxin-1; PAF, platelet-activating factor; TCR, T-cell receptor; MHC, major histocompatibility complex; and ICAM, intercellular adhesion molecule. An upward arrow indicates enhanced expression; a downward arrow, reduced expression. Adapted from Hasday and Goldblum cited in Mackowiak et al.*[35]

ver. Based on this characteristic, they have been codified as so-called pyrogenic cytokines.

The list of currently recognized pyrogenic cytokines includes, among others, interleukin (IL)–1 (IL-1α and IL-1β), tumor necrosis factor α (TNF-α), IL-6, and interferon gamma (IFN-γ) (**Table 1**).[37-45] Even among these few cytokines, complex relationships exist, with certain members up-regulating expression of other members or their receptors under certain conditions and down-regulating them under other conditions.[35] The 4 pyrogenic cytokines have monomeric molecular weights that range from 17 to 30 kd. Undetectable under basal conditions in healthy subjects, they are produced by many different tissues in response to appropriate stimuli. Once released, pyrogenic cytokines have short intravascular half-lives. They are pleiotropic: they interact with receptors present on many different host cells. They are active in picomolar quantities, induce maximal cellular responses

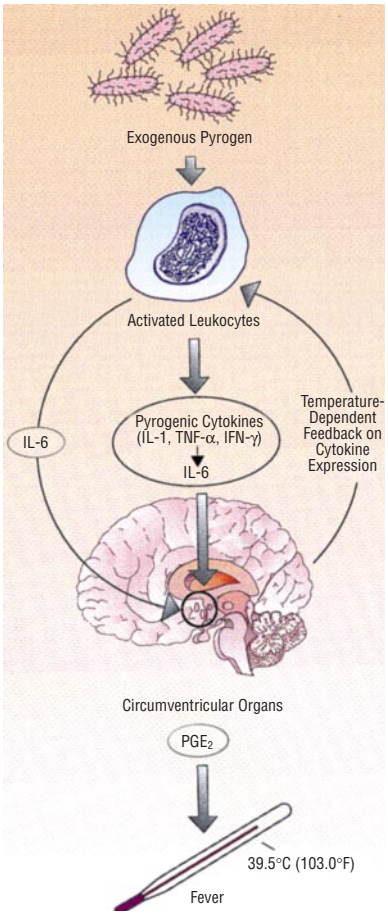

Figure 2. *Hypothetical model for the febrile response. IL indicates interleukin; TNF, tumor necrosis factor; IFN, interferon; and PGE_2, prostaglandin E_2.*

even at low receptor occupancy, and exert local (autocrine or paracrine) and systemic (endocrine) effects.[35]

It has been theorized, although not proved, that interaction between pyrogenic cytokines and their receptors in the preoptic region of the anterior hypothalamus activates phospholipase A_2, liberating plasma membrane arachidonic acid as substrate for the cyclooxygenase pathway. Some cytokines might do so by increasing cyclooxygenase expression directly, causing liberation of the arachidonate metabolite, prostaglandin E_2. Because this small lipid molecule easily diffuses across the blood-brain barrier, it might be the local mediator that actually activates thermosensitive neurons. Although not discussed in this article, recent studies indicate that thermal information involved in the febrile response also might be transmitted from the periphery to the thermoregulatory center via peripheral nerves.[46]

Table 2. The Acute Phase Proteins (ACPs)*

Positive ACPs†
C-reactive protein
Serum amyloid A
Haptoglobin
α_1-Acid glycoprotein
α_1-Protease inhibitor
Fibrinogen
Ceruloplasmin
Complement (C3 and C4)
C1 esterase inhibitor
C4b binding protein
α_2-Macroglobulin
Ferritin
Phospholipase A_2
Plasminogen activator inhibitor-1
Fibronectin
Hemopexin
Pancreatic secretory trypsin inhibitor
Inter-α protease inhibitor
Manose binding protein
Negative ACPs‡
Albumin
Transthyretin
Transferrin
α_2-HS glycoprotein

**Adapted from Kushner and Rzewnicki.[36]*
†Proteins exhibiting increased plasma concentrations during the acute phase response.
‡Proteins exhibiting decreased plasma concentrations during the acute phase response.

Extensive work with pyrogenic cytokines during the last 2 decades has provided a hypothetical model for the febrile response (**Figure 2**). Nevertheless, our understanding of this process remains incomplete and largely speculative. As indicated, several issues remain unresolved: (1) whether circulating cytokines cross the blood-brain barrier or have to be produced within the central nervous system to activate thermosensitive neurons; (2) whether each of the pyrogenic cytokines is capable of raising the thermoregulatory set point independently or must exert this effect through some common pathway (eg, IL-6, as suggested by Dinarello[24]; Figure 2); (3) whether prostaglandin E_2 or other local mediators are a sine qua non of the febrile response; (4) what determines the magnitude of expression of individual cytokines in response to various stimuli; and (5) how the upper limit of the febrile range is set.[35]

Tumor necrosis factor α and IL-1 have pivotal roles during the induction phase of the febrile response[47] but also are expressed throughout the response.[48] A small but growing body of data suggests that temperatures near the upper end of the febrile range influence production of such cytokines.[49-60] However, such effects are highly dependent on experimental conditions.

THE ACUTE PHASE RESPONSE

As noted, a cytokine-mediated rise in core temperature is but one of many features of the febrile response. Numerous other physiologic reactions, collectively referred to as the *acute phase response,* are mediated by members of the same group of pyrogenic cytokines that activate the thermal response of fever.[36] Such reactions include somnolence, anorexia, changes in plasma protein synthesis, and altered synthesis of hormones such as corticotropin-releasing hormone, glucagon, insulin, corticotropin, hydrocortisone, adrenal catecholamines, growth hormone, thyrotropin, thyroxine, aldosterone, and arginine vasopressin. Inhibition of bone formation, negative nitrogen balance, gluconeogenesis, and altered lipid metabolism also are seen during the acute phase response, as are decreased serum concentrations of zinc and iron and increased serum concentrations of copper. Hematologic alterations[61] include leukocytosis, thrombocytosis, and decreased erythropoiesis (resulting in an "anemia of chronic inflammation"[62]). Stimuli capable of inducing an acute phase response include bacterial and, to a lesser extent, viral infection, trauma, malignant neoplasms, burns, tissue infarction, immunologically mediated and crystal-induced inflammatory states, strenuous exercise,[63] and childbirth. Recent data also suggest that major depression,[64] schizophrenia,[65] and psychological stress[66] are capable of inducing an acute phase response.

Traditionally, the phrase *acute phase response* has been used to denote changes in plasma concentrations of a number of secretory proteins derived from hepatocytes. *Acute*

phase proteins, of which there are many (**Table 2**),[36] exhibit increased synthesis (positive acute phase proteins) or decreased synthesis (negative acute phase proteins) during the acute phase response.

Many of the acute phase proteins are believed to modulate inflammation and tissue repair.[67] A major function of C-reactive protein (CRP), for example, is presumed to involve binding of phosphocholine on pathogenic microorganisms, as well as phospholipid constituents on damaged or necrotic host cells. Through such binding, CRP might activate the complement system and promote phagocyte adherence, thereby initiating the process by which pathogenic microbes or necrotic cells are eliminated from the host. Such activities are most likely potentiated by CRP-induced production of inflammatory cytokines[68] and tissue factor[69] by monocytes. Nevertheless, the ultimate function of CRP is uncertain; several in vivo studies have shown it to have anti-inflammatory properties.[70-72]

The other major human acute phase protein, serum amyloid A, recently has been reported to potentiate adhesiveness and chemotaxis of phagocytic cells and lymphocytes.[73] There also is evidence that macrophages bear specific binding sites for serum amyloid A, that serum amyloid A–rich, high-density lipoproteins mediate transfer of cholesterol to macrophages at sites of inflammation,[74] and that serum amyloid A enhances low-density lipoprotein oxidation in arterial walls.[75]

Complement components, many of which are acute phase reactants, modulate chemotaxis, opsonization, vascular permeability, and vascular dilatation and have cytotoxic effects as well.[36] Haptoglobin, hemopexin, and ceruloplasmin all are antioxidants. It is, therefore, reasonable to assume that, like the antiproteases, α_1-antichymotrypsin and C1 esterase inhibitor, they have important roles in modulating inflammation. However, the functional capacity of such proteins is broad.

Although closely associated with fever, the acute phase response is not an invariable component of the febrile response.[36] Some febrile patients (eg, those with certain viral infections) have normal blood levels of CRP. Moreover, patients with elevated blood levels of CRP are not always febrile. The acute phase response, like the febrile response, is a complex response consisting of numerous integrated but separately regulated components. The particular components expressed in response to a given disease process more than likely reflects the specific cytokines induced by the disease.

ENDOGENOUS CRYOGENS

Hippocrates maintained that "Heat is the immortal substance of life endowed with intelligence. . . . However, heat must also be refrigerated by respiration and kept within bounds if the source or principle of life is to persist; for if refrigeration is not provided, the heat will consume itself."[76] Modern day clinicians also generally subscribe to the notion that the febrile range has an upper limit,[1] but do not agree on a precise temperature defining this limit. The lack of a consensus in this regard is understandable, owing to the fact that "body" temperature profiles exhibit considerable individual, anatomic, and diurnal variability. For this reason, the upper limit of the febrile range cannot be defined as a single temperature applicable to all body sites of all people at all times during the day. Nevertheless, the febrile response is a regulated physiologic response, in which temperature is maintained within certain carefully controlled limits, the upper limit of which almost never exceeds 41.0°C, regardless of the cause of the fever or site at which temperature measurements are taken.[77] The physiologic necessity of this upper limit is supported by considerable experimental data demonstrating adverse physiologic effects of core temperatures greater than 41.0°C or 42.0°C.[16]

The mechanisms regulating fever's upper limit have yet to be fully defined. They could lie with the intrinsic properties of the neurons themselves or involve the release of endogenous antipyretic substances that antagonize the effects of pyrogens on thermosensitive neurons. For the former possibility, plots of the firing rates of neurons coordinating thermoregulatory responses and heat production tend to converge at 42.0°C (**Figure 3**).[16] At this temperature, the long-term or extended firing rates of warm-sensitive neurons reach their zenith and cannot be increased further in response to higher temperatures. Similarly, the firing rates of cold-sensitive neurons reach their nadir at 42.0°C and cannot decrease further even if temperature increases further. Thus, regardless of pyrogen concentration, thermosensitive neurons seem to be incapable of providing additional thermoregulatory signals once the temperature reaches 42.0°C.

These same thermosensitive neurons are influenced by a variety of endogenous substances, at least some of which seem to function as endogenous cryogens.[16] Studies by numerous investigators using a variety of animal models have established that arginine vasopressin is present in the fibers and terminals of the ventral septal area of the hypothalamus, is released into the ventral septal area during fever, and reduces fever via its action at type 1 vasopressin receptors when introduced into the ventral septal area and, when inhibited, prolongs fever.[78-80]

α-Melanocyte-stimulating hormone (α-MSH) is another neuropeptide exhibiting endogenous antipyretic activity.[81] Unlike some other antipyretic peptides, α-MSH has not been identified in fibers projecting into the ventral septal area.[82] It does, nevertheless, reduce pyrogen-induced fever when administered to experimental animals in doses below those having an effect on afebrile body temperature.[83-87] When given centrally, α-MSH is more than 25 000 times more potent as an antipyretic than acetaminophen.[81] Repeated central administration of α-MSH does not induce tolerance to its antipyretic effect.[88] In addition, injection of anti–α-MSH antiserum into the cerebral ventricles augments the febrile response of experimental animals to IL-1.[89]

Numerous neurochemicals seem to have the capacity to influ-

ence hypothalamic control of body temperature. Because some lower body temperature even in the absence of fever, they are more appropriately termed *hypothermic* agents than *antipyretic* agents. In some of the earliest work in this area, Feldberg and Meyers[90] observed that intracerebroventricular injections of epinephrine and norepinephrine in cats cause a fall in body temperature, whereas injections of serotonin cause temperature to rise. Based on these observations, they proposed that regulation of body temperature involves a balance between the release of catecholamines (inducing heat loss) and serotonin (activating heat production) in the anterior hypothalamus. More recent data, including those considered in the present article, suggest that the basis of set-point determination by the thermoregulatory network is considerably more complex.[91]

Glucocorticoids and their inducers (corticotropin-releasing hormone and corticotropin) inhibit synthesis of pyrogenic cytokines such as IL-6 and TNF-α.[92-94] Through such effects, they are believed to exert inhibitory feedback on lipopolysaccharide (LPS)–induced fever.[95] Lipocortin 1, a putative mediator of glucocorticoid function, also has been shown to inhibit the pyrogenic actions of IL-1 and IFN.[96] Corticotropin-releasing hormone injected into the third ventricle of experimental animals produces similar antipyretic effects.[97]

Thyroliberin,[98] gastric inhibitory polypeptide,[99] neuropeptide Y,[100] and bombesin,[101] likewise, exhibit cryogenic properties under appropriate conditions. Of these, bombesin is probably the most potent, because it consistently produces hypothermia associated with changes in heat dissipation and heat production when injected into the preoptic area/anterior hypothalamus of conscious goats and rabbits.[101-103] Bombesin is believed to exert its hypothermic effect by increasing the temperature sensitivity of warm-sensitive neurons.[102]

Pyrogenic cytokines, the mediators of the febrile response, might themselves have a direct role in determining fever's upper limit. There

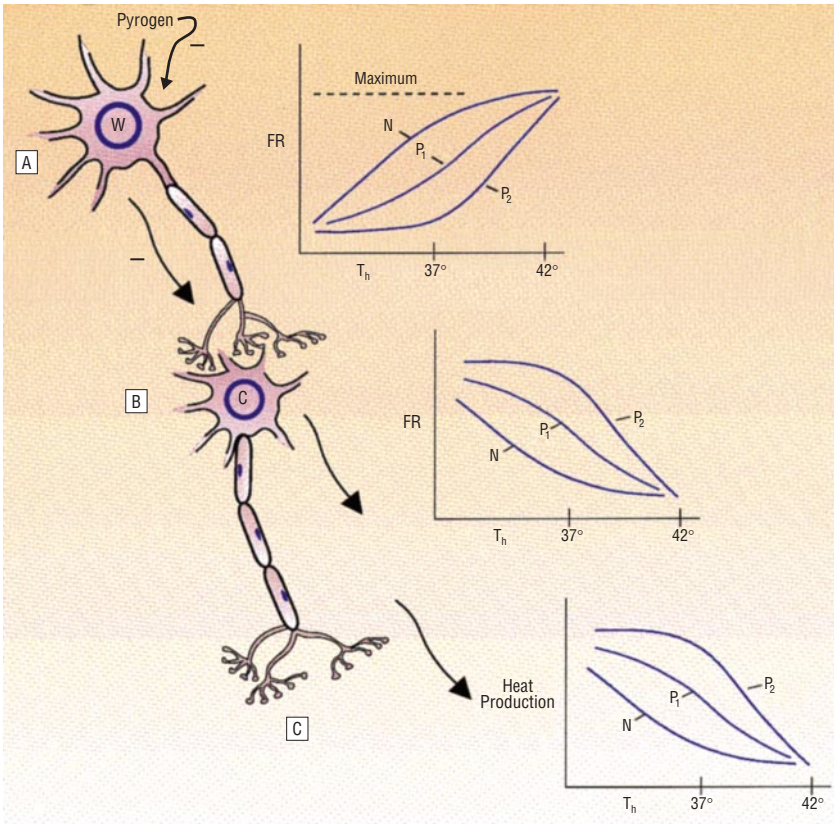

Figure 3. *Model showing responses (A and B) of neuronal firing rates (FR) in the preoptic region and anterior hypothalamus and whole-body metabolic heat production (C) during changes in hypothalamic temperature (T_h). Thermosensitivity is reflected by the slope of each plot. The letters inside the cells indicate a warm-sensitive (w) neuron and a cold-sensitive (c) neuron. With increases in T_h, warm-sensitive neurons raise their FRs, and heat production decreases. Pyrogens inhibit (-) the FRs of warm-sensitive neurons, thereby resulting in accelerated FRs of cold-sensitive neurons and increased heat production. The plots show FR and heat production responses during normal conditions in the absence of pyrogens (N) and in the presence of low concentrations (P_1) and high concentrations (P_2) of pyrogens. The temperatures are given in degrees Celsius. Adapted from Mackowiak and Boulant.[16]*

is, for instance, experimental evidence indicating that under certain conditions TNF-α lowers, rather than raises, body temperature.[104,105] Thus, it is possible that, at certain concentrations or in the appropriate physiologic milieu (eg, at 41.0°-42.0°C), pyrogenic cytokines function paradoxically as endogenous cryogens.

A growing body of literature indicates that release of pyrogenic cytokines, such as IL-1, is followed by increased shedding of soluble receptors for such cytokines, which function as endogenous inhibitors of these pyrogens.[106] In the case of IL-1, a 22- to 25-kd molecule identified in supernatants of human monocytes blocks binding of IL-1 to its receptors.[107] The IL-1 receptor antagonist is structurally related to IL-1α and IL-1β[108] and binds to type I and type II receptors on various target cells without inducing a specific biological response.[109,110] Shedding of soluble circulating receptors of TNF-α that bind to circulating TNF-α and thereby inhibit binding to cell-associated receptors also has been described.[111-115] The precise biological function of such circulating receptor antagonists and soluble receptors is unknown. However, it is possible, that 1 function is to serve as a natural braking system for the febrile response.

RISK-BENEFIT CONSIDERATIONS

Questions about fever's risk-benefit quotient have generated considerable controversy in recent years.[116] The controversy arises because of substantial data indicating potentiating *and* inhibitory effects of the response on resistance to infection. As a result, there is no consensus about the appropriate clinical

situations (if any) in which fever or its mediators should be suppressed.

Data illustrating fever's beneficial effects originate from several sources. Studies of the phylogeny of fever have shown the response to be widespread within the animal kingdom.[117] With few exceptions, 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. This fact has been viewed as some of the strongest evidence that fever is an adaptive response, based on the argument that the metabolically expensive increase in body temperature that accompanies the febrile response would not have evolved and been so faithfully preserved within the animal kingdom unless fever had some net benefit to the host.

Further evidence of fever's beneficial effects can be found in numerous studies demonstrating enhanced resistance of animals to infection with increases in body temperature within the physiologic range.[117] In classic studies involving experimental infection of the reptile *Dipsosaurus dorsalis* with *Aeromonas hydrophila,* Kluger et al[118] and Bernheim and Kluger[119] demonstrated a direct correlation between body temperature and survival. Bernheim and Kluger[119] also showed that suppression of the febrile response with sodium salicylate results in a substantial increase in mortality. Covert and Reynolds[120] corroborated these findings in an experimental model involving goldfish.

In mammalian experimental models, increasing body temperature by artificial means has been reported to enhance resistance of mice to herpes simplex virus,[121] poliovirus,[122] coxsackie B virus,[123] rabies virus,[124] and *Cryptococcus neoformans,*[125] but to decrease resistance to *Streptococcus pneumoniae.*[126] Increased resistance of rabbits to *S pneumoniae*[127] and *C neoformans,*[128] dogs to herpesvirus,[129] piglets to gastroenteritis virus,[130] and ferrets to influenza virus[131] also has been observed after induction of artificial fever. Unfortunately, because raising body temperature by artificial means does not duplicate the physiologic alterations that occur during fever in homeotherms (and, indeed, entails a number of opposite physiologic responses[132]), data obtained using mammalian experimental models have been less convincing than those obtained using reptiles or fish.

Clinical data supporting an adaptive role for fever have accumulated slowly. Like animal data, clinical data include evidence of beneficial effects of fever and adverse effects of antipyretics on the outcome of infections. In a retrospective analysis of 218 patients with gram-negative bacteremia, Bryant et al[133] reported a positive correlation between maximum temperature on the day of bacteremia and survival. A similar relationship has been observed in patients with polymicrobial sepsis and mild (but not severe) underlying diseases.[134] In an examination of factors influencing the prognosis of spontaneous bacterial peritonitis, Weinstein et al[135] identified a positive correlation between a temperature reading of more than 38°C and survival.

It has been reported that children with chicken pox who are treated with acetaminophen have a longer time to total crusting of lesions than placebo-treated control subjects.[136] Stanley et al[137] reported that adults infected with rhinovirus exhibit more nasal viral shedding when they receive aspirin than when given placebo. Furthermore, Graham and colleagues[138] reported a trend toward longer duration of rhinovirus shedding in association with antipyretic therapy and showed that the use of aspirin or acetaminophen is associated with suppression of the serum neutralizing antibody response and with increased nasal symptoms and signs. These data, like those reviewed in the preceding paragraph, are subject to several interpretations and do not prove a causal relationship 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 herein, they constitute strong circumstantial evidence that fever is an adaptive response in most situations.

Whereas the foregoing studies focused on the relationship between elevation of core temperature and the 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 that might theoretically enhance resistance to infection (Table 1).[139] In vitro and in vivo studies of these cytokines have provided evidence of a protective effect of IFN, TNF-α, and/or IL-1 against *Plasmodium* organisms,[140-142] *Toxoplasma gondii,*[143] *Leishmania major,*[144] *Trypanosoma cruzi,*[145] and *Cryptosporidium* organisms.[146]

Several recent reports also have shown enhancement of resistance to viral[147-149] and bacterial[150,151] infections by pyrogenic cytokines. Treatment of healthy and granulocytopenic animals with IL-1 has been shown to prevent death in some gram-positive and gram-negative bacterial infections.[151] However, IL-1 is effective only if administered an appreciable time (eg, 24 hours) before initiation of infections having rapidly fatal courses. In less acute infections, IL-1 administration can be delayed until shortly after the infectious challenge. Such observations suggest that the physiologic effects of fever that enhance resistance to infection might be limited to localized infections or systemic infections of only mild to moderate severity.

The potential of the febrile response for harm is reflected in a recent flurry of reports suggesting that IL-1, TNF-α, IL-6, and IFN mediate the physiological abnormalities of certain infections. Although proof of an adverse effect of fever on the clinical outcome of these infections has yet to be established, the implication is that if pyrogenic cytokines contribute to the pathophysiologic burden of infections, the mediators themselves and the febrile response are potentially deleterious.

The most persuasive evidence derives from studies of gram-negative bacterial sepsis.[152] It has long been suspected that bacterial LPS has a pivotal role in the syndrome. Puri-

fied LPS induces a spectrum of physiological abnormalities that are similar to those occurring 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.[153] Furthermore, patients with the septic syndrome have detectable levels of circulatory TNF-α, IL-1, and IL-6 independent of culture-documented infection, and such levels correlate inversely with survival.[154] Interleukin 1, alone or in combination with other cytokines, induces many of the same physiological abnormalities (eg, fever, hypoglycemia, shock, and death) seen after administration of purified LPS.[155] In a murine experimental model for septic shock, IFN administered before or as long as 4 hours after LPS challenge increases mortality, whereas pretreatment with anti-IFN antibody substantially reduces mortality.[156] In several recent studies, the adverse effects of gram-negative bacterial sepsis, LPS injections, or both have been attenuated by pretreating experimental animals with IL-1 antagonists[157,158] and monoclonal antibodies directed against TNF-α.[159,160] Furthermore, animals rendered tolerant to TNF-α by repeated injections of the recombinant cytokine are protected against the hypotension, hypothermia, and lethality of gram-negative bacterial sepsis.[161]

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 and have generated intense interest, although little progress,[162] in the clinical application of antagonists of such cytokines. Similar data suggest that pyrogenic cytokines might mediate at least some of the systemic and local manifestations of sepsis due to gram-positive bacteria,[153,163,164] AIDS,[165] spirochetal infections,[166,167] meningitis,[168] the adult respiratory distress syndrome,[165,169] suppurative arthritis,[170] and mycobacteriosis.[171]

CONCLUSIONS

To fully appreciate the clinical implications of fever, one must take a broad view that encompasses the febrile response in its entirety. Fever is mediated by a host of cytokines that not only cause the body's thermoregulatory set point to rise, but also simultaneously stimulate production of a panoply of acute phase reactants (although, apparently not invariably) and activate numerous metabolic, endocrinologic, and immunologic systems. For these reasons, fever cannot be equated with hyperthermia. More important, experimental models of "fever" in which body temperature is elevated by external means or by agents that markedly increase heat production by uncoupling oxidative phosphorylation must be recognized as having limited value in the study of this physiologic response. Only if one views fever from the perspective of its relationship with the febrile response, can one begin to explain the apparent paradox inherent in reports demonstrating beneficial effects of therapy with pyrogenic cytokines and their antagonists and, through such understanding, take maximum advantage of the response to alleviate the burden of human disease.

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