REVIEW ARTICLES

Fever's Glass Ceiling

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The importance of an upper limit of the febrile response has been recognized since the time of Hippocrates. Although the precise temperature defining this limit varies according to the site at which body temperature is measured, human core temperature is almost never permitted to rise above 41°C–42°C during fever. There are compelling physiological reasons for such an upper limit of regulated body temperature. The mechanisms by which the limit is maintained are most likely complex and involve special properties of thermoregulatory neurons themselves, circulating endogenous antipyretics (such as arginine vasopressin and α-melanocyte-stimulating hormone), and soluble receptors for the (pyrogenic) cytokine mediators of the febrile response.

"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."

Hippocrates [1]

Although the importance of limiting the accumulation of body heat has been recognized since the time of Hippocrates [1], the upper limit of the febrile range has received scant attention in the clinical literature since 1949, when DuBois [2] published a provocative paper entitled "Why Are Fever Temperatures over 106°F Rare?" In fact, textbooks of physiology and medicine rarely consider the matter worthy of even a passing comment. Nevertheless, experimental data confirming the existence of an upper limit of the febrile range and stressing the importance of this limit to life have accumulated in recent years. The present review summarizes these data as they pertain to the nature of fever's ceiling in humans, the physiological necessity for such a ceiling, and the mechanisms by which it is maintained.

Fever's Upper Limit

Clinicians generally subscribe to the notion that the febrile range has an upper limit [3]. However, there is no agreement

as to the precise temperature defining this limit. The lack of a consensus in this regard is understandable, owing to the fact that profiles of body temperature in homeotherms vary considerably. Most mammals have temperatures between 36.1°C and 38.8°C, with upper safe limits of 41.6°C to 43.3°C. Birds, however, have higher and more labile normal temperatures, with an upper safe limit of 45°C [4]. Furthermore, the upper limit of the febrile range varies according to disease, with some infections (such as malaria) inducing notoriously high fevers and others (e.g., HIV infection) eliciting little if any detectable fever (Wheeler D, Call S, Wasserman SS, Ingram J, Mackowiak PA, unpublished data). Basal temperature exhibits considerable individual variability [6], and it is likely that the same holds true for the febrile range. In addition, clinical readings vary depending on the site (oral, rectal, or tympanic membrane) at which temperature measurements are obtained [7]. Finally, no systematic study of the question of fever's upper limit has been published since the report by DuBois [2] in 1949.

In his report, DuBois [2] placed fever's upper limit between 41°C and 42°C (105.8°F and 107.6°F). He based this conclusion on a survey of 1,761 (axillary and rectal) temperature readings in 357 patients with diseases characterized by high fever. Only 4.3% of the readings exceeded 41.1°C (106°F), and none were above 42°C (107.6°F). As illustrated in one of the figures included in his report (figure 1), fevers rarely reach this upper limit, even when rectal temperatures are monitored in patients with especially severe febrile infections.

DuBois [2] conducted his survey before the advent of antibiotic therapy. In today's setting one rarely sees temperature
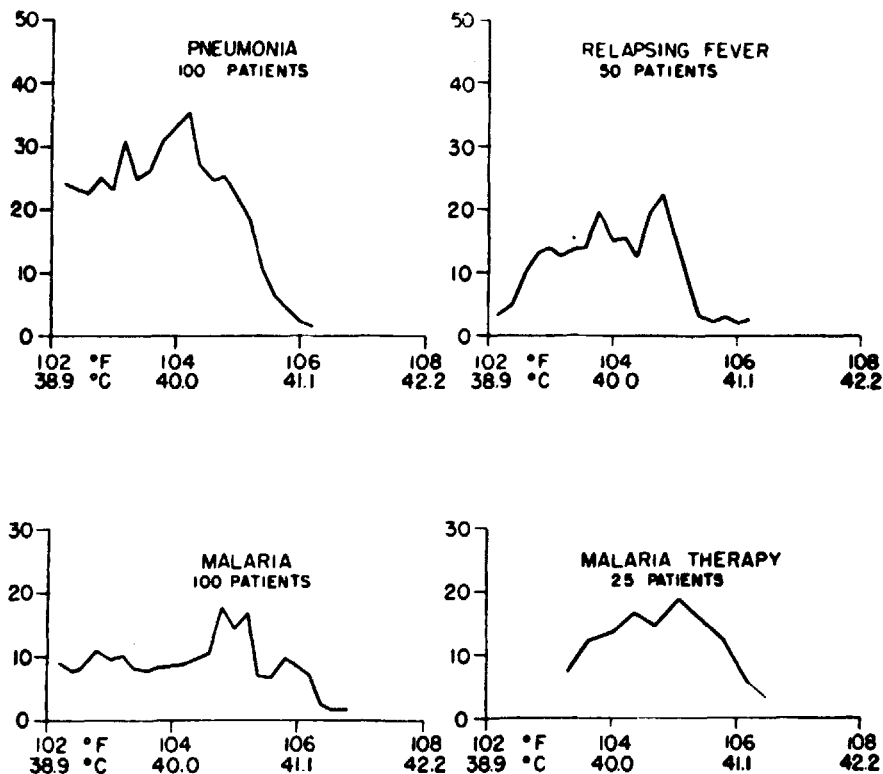
Figure 1. Rectal temperature readings during four different febrile illnesses. Ordinates give the number of readings at each level of temperature. Reprinted with permission from the *American Journal of the Medical Sciences* [2].

readings of >40°C (104°F) in adults, even during the most intensely febrile infections (figure 2). This rarity is, in part, because of the fact that today effective antimicrobial therapy and antipyretic medications are given to such patients but also because oral rather than rectal temperatures are most often monitored in today's clinical setting.

In view of the many variables affecting fever's ceiling, it is not appropriate to view the upper limit of the febrile range as a single temperature applicable to all body sites of all people at all times during the day. Nevertheless, the febrile response — unlike the hyperthermia of the neuroleptic malignant syndrome, malignant hyperthermia, or heat stroke—is a regulated physiological response in which temperature is maintained within certain carefully controlled limits. The upper limit almost never exceeds 42°C [2]—unless there is failure of thermoregulatory mechanisms—regardless of the type of infection, underlying disease, or site at which temperature measurements are taken.

Physiological Necessity of Fever's Ceiling

From a physiological standpoint, at neutral ambient temperatures, it should be only slightly more difficult to raise body temperature from 40°C to 43°C than from 37°C to 40°C [8]. However, temperatures in the former range are rarely seen, even during the most severe infections. The fact that febrile temperatures rarely rise above 40°C and are almost never above 42°C suggests a fortiori that the adverse consequences of body

temperatures above the upper limit of the febrile range outweigh any potential benefits to the human host.

Experimental evidence supporting this conclusion has been provided by Kluger et al. [9], Bernheim and Kluger [10], and Bernheim et al. [11]. In a model involving infection of the lizard *Dipsosaurus dorsalis* with one of its natural pathogens, *Aeromonas hydrophila*, Kluger et al. [9] demonstrated a positive correlation between temperature and survival when temperature of the experimental poikilotherm was raised by physical means from 34°C to 40°C. However, when temperature was increased to 42°C, the highest temperature studied, deaths were observed for the first time in uninfected control animals. It is interesting that, whereas the doubling time of *A. hydrophila* was constant in vitro between 34°C and 40°C, it began to decrease rapidly at incubation temperatures of ⩾42°C. Thus, in the model of Kluger and associates, a body temperature of ⩾42°C, while deleterious to pathogenic microorganisms, was also harmful to the host.

The specific adverse consequences of increases in body temperature above 41°C–42°C cannot be reliably ascertained by studying subjects with infections or other classical febrile disorders, because such disorders are so rarely associated with temperatures of this magnitude and because, in cases of fatal febrile conditions, it is impossible to separate the morphological and physiological effects of fever from those of the underlying disease. To ascertain such effects one must examine fatal cases of heat stroke or fever therapy. In the former instance, body temperature may exceed the upper limit of the febrile range
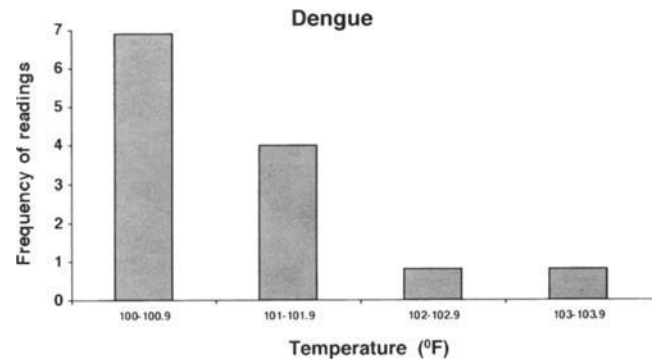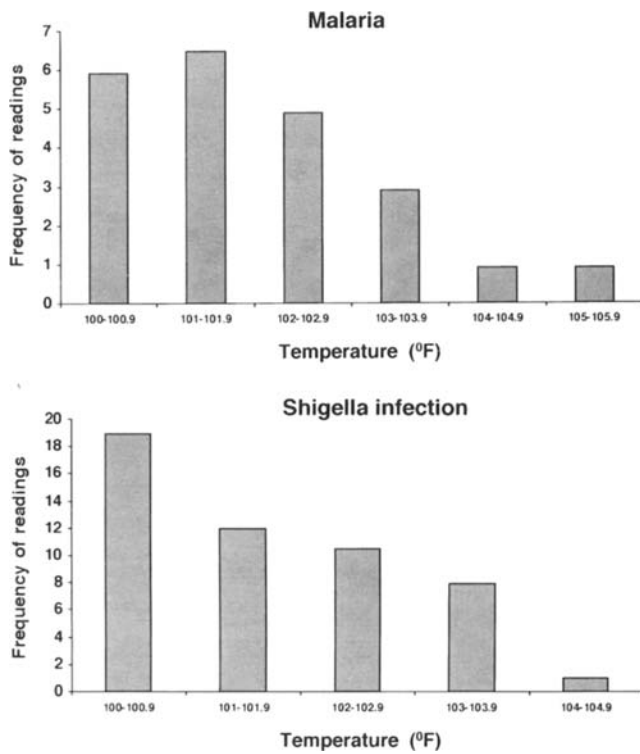
Figure 2. Maximum oral temperature readings (°F) in volunteers with malaria (A), dengue (B), and shigella infection (C). Ordinates give the number of readings at each level of temperature. At the time of the temperature measurements, subjects were participating in clinical trials conducted at the Center for Vaccine Development at the University of Maryland School of Medicine (Baltimore). Temperatures of >101°F were generally treated promptly with specific antimicrobial agents (not available in the case of dengue) and acetaminophen.

because of failure of thermoregulatory systems; in the latter instance, body temperature may exceed the upper limit of the febrile range because such systems are overridden by physical means.

The cardinal features of classical heat stroke are a core temperature of ≥40.5°C (105°F); hot, flushed, and dry skin; and CNS dysfunction [12]. In cases associated with physical exertion (exertional heat stroke), persistence of sweating may obscure the diagnosis, because cooling of the skin by vaporization masks a markedly elevated core temperature. Acid-base abnormalities are common and are due, at least in part, to the fact that simple heating of healthy subjects leads to hyperventilation and respiratory alkalosis. Hypokalemia, hypernatremia, hypophosphatemia, and hyperphosphatemia are also seen in some cases [13]. If circulatory failure and shock supervene, lactic acidosis tends to complicate the acid-base abnormalities. Disseminated intravascular coagulation with thrombocytopenia and elevated fibrinolytic split products in plasma and urine are also features of severe cases of heat stroke.

These protean biological abnormalities reflect the widespread organ dysfunction that occurs at body temperatures of >41°C–42°C. The pathological picture is characterized by cellular swelling and degeneration and by widespread hemorrhages varying from petechiae to massive bleeding [14]. As a result, affected organs such as the brain, kidneys, and liver are congested or edematous, with increased weights and swollen cells. Not all organs are equally susceptible to this form of injury. For instance, the pancreas and adrenal glands are often

spared, even when there are severe abnormalities in organs such as the brain, liver, and kidney [14].

Similar morphological abnormalities and associated physiological dysfunction are also occasionally seen in patients subjected to whole-body hyperthermia in devices such as the Kettering Hyperthem Cabinet [15]. The earliest abnormalities occurring in the course of such therapy are visceral congestion and disseminated focal hemorrhages in internal organs [16–19]. The subendocardium is especially susceptible in this regard; however, the brain, lungs, liver, and kidney are also commonly affected in fatal cases.

The precise explanation for the widespread abnormalities occurring when body temperature rises above the upper limit of the febrile range is uncertain. Thermal sensitivity of the brain, but not other vital organs, has been attributed to the unique susceptibility of its polyribosomes to thermal injury [20]. At 40°C–42°C, these polyribosomes begin to disaggregate; above 41°C, irreversible destruction of cerebral mitochondria occurs [21, 22]. However, in most animals thermal death occurs well below temperatures causing coagulation of proteins or denaturation of enzymes [23]. In experimental animals both immunization against endotoxin and administration of antibiotics before heating sharply reduce mortality due to hyperthermia, thus suggesting that pyrogens of intestinal origin mediate at least some of the deleterious effects of heat stroke [12].

In one of the earliest theories concerning mechanisms responsible for the adverse effect of hyperthermia itself on cell function, Hartman [24] proposed that anoxia was the prime

(but not necessarily the sole) factor responsible for such effects. Hartman theorized that the morphological abnormalities of hyperpyrexia, which share many features in common with those of prolonged asphyxia, are due in large part to alterations in oxygen supply and delivery. Central to his theory was the observation that both the metabolic rate and oxygen utilization increase with temperature, whereas physiological mechanisms for furnishing oxygen to tissues decrease at body temperatures of >41°C–42°C [25–27]. He suggested that the respiratory alkalosis that invariably accompanies hyperpyrexia leads to increased stability of oxyhemoglobin, thereby impairing release of oxygen to tissues—the latter effect being at least partially offset by the hyperthermia itself—which decreases oxyhemoglobin stability.

Although numerous more contemporary theories have sought to explain these same abnormalities, none are generally accepted as valid. Hubbard and Armstrong [28] have proposed an "energy depletion model" to explain hyperthermia-induced cellular dysfunction. According to their model, the increased morbidity and mortality due to exercise-induced hyperthermia (as compared with equivalent heat loads in the absence of physical effort) derives from a thermally driven energy drain superimposed on the energy lost as a result of exhaustive physical work. These investigators believe that during heat-induced cellular dysfunction, a vicious cycle of increasing cellular activity, increasing energy consumption, and decreasing steady-state energy levels results in dissipative ionic fluxes, adverse metabolic cascades, and other reactions leading to irreversible cell damage. In this model, as in all of the models thus far proposed, the ultimate adverse consequences of hyperthermia on cell function depend on the duration, intensity, and rate of heating as well as on variations in regional and local circulation within the affected tissue.

Lepock and Kruuv [29], for their part, have proposed that protein denaturation is the most likely initial rate-limiting event in hyperthermia-induced cytotoxicity. They offer as support for their theory a wide array of data demonstrating protein denaturation during exposure of mammalian cells to temperatures in excess of 40°C; these investigators estimate that 5%–10% of denaturation occurs during 15- to 30-minute exposures to 45°C. However, the critical target affected by such denaturation has not been identified, nor has the target been localized to any particular organ or cellular component.

Yatvin and Cramp [30] have recently concluded from their own work and a review of the literature that, rather than protein denaturation per se, alterations in the fluidity of cell membranes that result from an increase in the content of cholesterol, phospholipids, and protein is the critical cellular derangement induced by hyperthermia. Other researchers have pointed to degradation of DNA, inhibition of DNA synthesis, induction of chromosomal aberrations [31–34], inhibition of protein synthesis [35, 36], protein denaturation [37], increased protein phosphorylation [38], increased lysosomal enzyme activity [39–41], alterations in cytoskeletal and structural proteins [42–47],
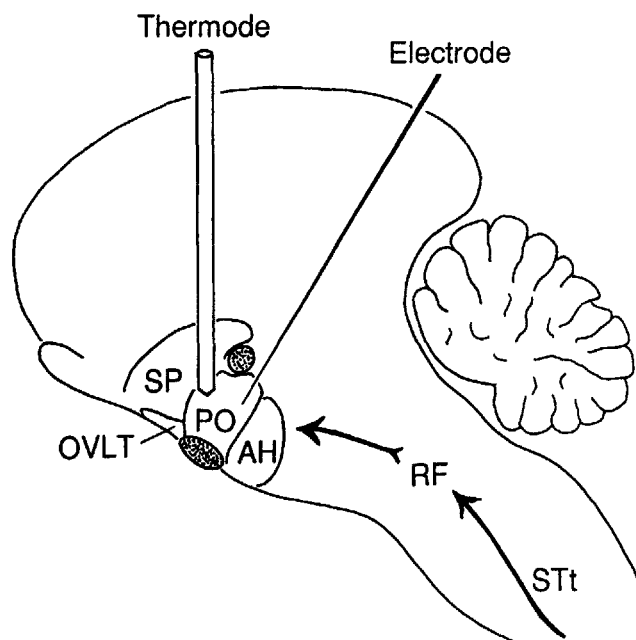

Figure 3. Sagittal view of a mammalian brain showing an implanted thermode for altering hypothalamic temperature and a microelectrode for recording firing rates of individual neurons. AH = anterior hypothalamus; OVLT = organum vasculosum lamina terminalis; PO = preoptic region; RF = reticular formation; SP = septum; STt = spinothalamic tract. A multisynaptic pathway of skin and spinal thermoreceptors through the STt and RF to the AH, PO, and SP is shown (arrows).

and increases in intracellular free calcium in association with relocation of kinase C [48–51] as events contributing to the adverse effects of hyperthermia. More than likely, multiple adverse cellular events are triggered simultaneously by temperatures of >42°C, and together these events mediate the cellular dysfunction and death due to hyperthermia.

Mechanisms Regulating Fever's Upper Limit

The foregoing evidence supporting an upper limit of the febrile range infers the existence of regulatory mechanisms involved in fever that prevent body temperature from rising above 41°C–42°C (105.8°F–107.6°F). Since body temperature and fever are controlled by neural structures near the rostral hypothalamus, it is likely that fever's upper limit is controlled by neurons in this area. The mechanisms involved in such regulation might lie in the intrinsic properties of the neurons themselves or in the release of endogenous antipyretic substances that antagonize the effects of pyrogens on the neurons.

Neuronal Properties

Neurons coordinating thermoregulatory responses are located in the preoptic region and anterior hypothalamus (PO/AH) and in adjacent septal areas. As shown in figure 3, these

structures are located near the organum vasculosum of the lamina terminalis (OVLT), a circumventricular region thought to be the site at which cytokines or other pyrogenic mediators enter the brain from the blood [52, 53]. The importance of the PO/AH in thermoregulation is best illustrated in studies of animals with implanted thermodes that induce localized hypothalamic warming and cooling (figure 3). All physiological and behavioral thermoregulatory responses can be elicited in these animals simply by changing hypothalamic temperature with the implanted thermode [54]. Each thermoregulatory response has its own hypothalamic set-point temperature, such that the response is evoked when the PO/AH is either warmed or cooled beyond this set point. PO/AH warming evokes heat loss responses, like panting [55–57] or sweating [58], whereas PO/AH cooling evokes heat production responses, such as shivering [55, 59] or nonshivering thermogenesis [60, 61]. In addition, more moderate changes in PO/AH temperature elicit changes in blood flow in the skin [62] and a variety of thermoregulatory behaviors [63, 64].

When hypothalamic temperature is changed and microelectrodes record neuronal activity, three cell types are recognized: temperature-insensitive neurons, warm-sensitive neurons, and cold-sensitive neurons. Electrophysiological studies have been conducted, both in vivo (in anesthetized and unanesthetized animals) and in vitro (in hypothalamic tissue slices and cultures); most studies find similar ratios of these neurons in the PO/AH and septum as well as throughout the diencephalon [54, 65, 66]. Approximately 60% of the neurons are classified as temperature-insensitive, since they show little or no change in their firing rates when hypothalamic temperature is changed.

Warm-sensitive neurons account for >30% of PO/AH neurons and exhibit increased firing rates during hypothalamic warming or decreased firing rates during hypothalamic cooling. By comparison, <10% of PO/AH neurons are considered cold-sensitive, with firing rates that increase during cooling or decrease during warming. Within each of these three cell populations, there are neurons that also respond to various nonthermal stimuli, such as changes in glucose concentration, osmolality, and reproductive hormones [67–69]. Since these nonthermal stimuli can alter the activity of thermoregulatory neurons, they might have a role in regulating fever's upper limit, which would be particularly important if these nonthermal stimuli are altered by elevated temperatures or other conditions associated with fever.

In the PO/AH and septum, warm-sensitive and cold-sensitive neurons also receive afferent input from thermoreceptors in the skin and spinal cord [70–72]. As shown in figure 3, it is likely that much of this afferent information arrives over multisynaptic pathways from the spinothalamic tract to the reticular formation in the brain stem and the hypothalamus [73]. In the PO/AH and septum, this afferent input rarely affects temperature-insensitive neurons; however, most warm-sensitive and cold-sensitive neurons respond to changes in skin or spinal cord temperature [72]. Thus, the thermosensitive neurons integrate
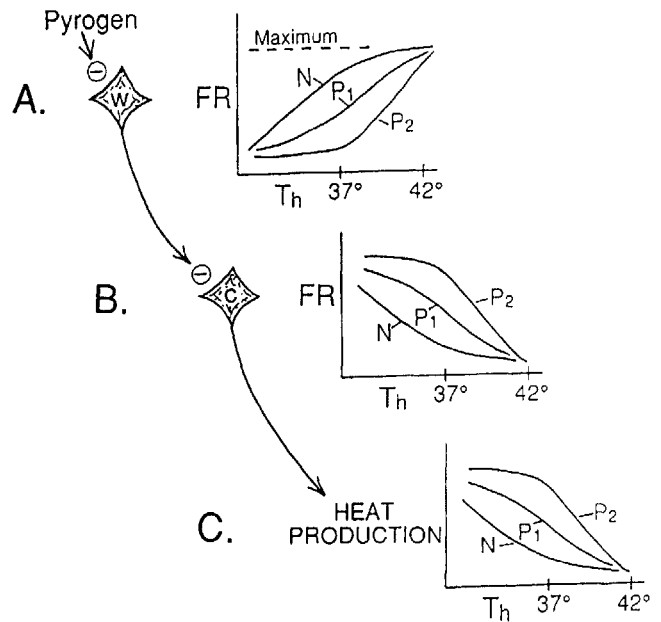

Figure 4. Model showing responses (*A* and *B*) of neuronal firing rates (FR) in the preoptic region and anterior hypothalamus and whole-body metabolic heat production (*C*) during changes in hypothalamic temperature (T_h). Thermosensitivity is reflected by the slope of each plot. The letters inside the cells indicate a warm-sensitive (w) neuron and a cold-sensitive (c) neuron. During increases in T_h, warm-sensitive neurons increase their FRs, and some warm-sensitive neurons synaptically inhibit (−) other neurons, thus causing the other neurons to appear cold-sensitive. During decreases in T_h, cold-sensitive neurons increase their FRs, and heat production increases. Pyrogens inhibit (−) the FRs of warm-sensitive neurons, thereby resulting in increased FRs of cold-sensitive neurons and increased heat production. The plots show FR and heat production responses during normal conditions without pyrogens (N) and during low concentrations (P_1) and high concentrations (P_2) of pyrogens.

thermal information derived from both central and peripheral sources.

Warm-sensitive neurons in the PO/AH are intrinsically thermosensitive and retain their thermosensitivity even when their synaptic input is experimentally blocked [74, 75]. Intracellular recordings from these neurons indicate that the mechanism responsible for their warm sensitivity is a temperature-dependent depolarizing prepotential that precedes each action potential [76]. In contrast to warm-sensitive neurons, cold-sensitive neurons in the PO/AH do not appear to be intrinsically thermosensitive. The activity of cold-sensitive neurons is much more dependent on excitatory and inhibitory postsynaptic potentials [76], and neuronal cold sensitivity usually disappears during synaptic blockade [74, 75].

Experimental data summarized in figure 4 suggest that neuronal cold sensitivity is due to synaptic inhibition from adjacent warm-sensitive neurons. At 37°C, populations of warm-sensitive neurons display a wide range of spontaneous firing rates, and these firing rates often correlate with the neurons' range of thermosensitivity [54, 73, 76–78]. Warm-sensitive neurons

with low firing rates usually express their greatest thermosensi-tivity above 37°C, thus suggesting that such neurons participate in heat loss responses that are elicited in the hyperthermic range. By contrast, warm-sensitive neurons with high firing rates often display their maximum firing rates when the hypo-thalamic temperature is near 37°C.

Figure 4A shows a warm-sensitive neuron with a high firing rate under normal conditions (N) in the absence of pyrogens. Hypothalamic warming above 37°C has little effect on the firing rate of this neuron; however, cooling below 37°C causes the firing rate to decrease markedly. As shown in figure 4B, some warm-sensitive neurons synaptically inhibit adjacent spontaneously firing neurons, thereby causing the inhibited neurons to appear to be cold-sensitive. Hypothalamic cooling decreases the firing rate of warm-sensitive neurons and, there-fore, decreases the synaptic inhibition of cold-sensitive neu-rons. This causes cold-sensitive neurons to increase their firing rate as the hypothalamus is cooled below 37°C. Thus, the firing rate of cold-sensitive neurons is a mirror image of the firing rate of warm-sensitive neurons. If some cold-sensitive neurons control shivering and nonshivering thermogenesis as shown in figure 4C, heat production should increase when the hypotha-lamic temperature is cooled below 37°C.

Fever develops when pyrogens alter the activity of hypotha-lamic neurons that control body temperature [79]. In response to exogenous pyrogens, such as bacterial lipopolysaccharides, leukocytes and macrophages produce an array of endogenous pyrogens that include IL-1, IL-6, TNF, and IFN. Some investi-gators believe that circulating endogenous pyrogens cause me-diators, such as prostaglandin E, to be released at the OVLT (figure 3) [80, 81]. Other researchers suggest that there are fragments of endogenous pyrogens small enough to cross the blood-brain barrier or that endogenous pyrogens in the circula-tion trigger elevations in a separate pool of endogenous pyro-gens within the brain [82–84]. Several studies have shown that fever is produced in response to PO/AH or OVLT injections of prostaglandin E and endogenous pyrogens, such as IL-1 [85, 86]. During infections, concentrations of these substances often increase within the brain [84, 87].

Some electrophysiological studies indicate that pyrogenic substances inhibit warm-sensitive neurons, excite cold-sensi-tive neurons, and have either mixed or little effect on tempera-ture-insensitive neurons [88, 89]. Figure 4 shows how pyrogens might act on PO/AH neurons to generate fever through in-creased heat production. The predictive effects of a low concen-tration of pyrogen (P_1) and a high concentration of pyrogen (P_2) on the activity of hypothalamic neurons controlling shiv-ering and nonshivering thermogenesis are illustrated. These predictive effects are based on previous studies that correlate the spontaneous firing rate at 37°C and thermosensitivity (i.e., the slope of the firing rate plotted as a function of temperature) [54, 71–73, 77, 78]. Often, in the hyperthermic range, increases in thermosensitivity occur when warm-sensitive neurons de-crease their spontaneous firing rate (figure 4A) or when cold-

sensitive neurons increase their spontaneous firing rate (figure 4B). As a result, thermoresponse curves of both warm-sensitive and cold-sensitive neurons tend to converge at hypothalamic temperatures near 42°C—fever's upper limit.

Figure 4A illustrates the change in activity of a warm-sensitive neuron during inhibition by low and high concentra-tions of pyrogen. While low concentrations of pyrogen par-tially reduce the firing rate at 37°C, the neuron also becomes sensitive over a wider range of temperatures. High concentra-tions of pyrogen reduce the firing rate to minimal levels at 37°C so that the neuron is only sensitive to temperatures in the hyperthermic range. Since neuronal cold sensitivity is determined by synaptic inhibition from warm-sensitive neu-rons, the thermoresponse curves in figure 4B are the mirror images of those in figure 4A.

If cold-sensitive neurons regulate thermogenesis, then simi-lar responses might be expected for heat production (figure 4C). In the presence of low concentrations of pyrogen, heat production should increase, even when body temperature is 37°C. This heat production eventually raises body temperature and is equivalent to the chill phase of fever. Heat production gradually diminishes as body temperature rises to a new ele-vated level, and regulation around the new elevated set-point temperature is equivalent to the plateau phase of fever. High concentrations of pyrogen maximally inhibit warm-sensitive neurons and, in this way, allow cold-sensitive neurons to spon-taneously fire at their highest levels. As shown in figure 4C, this causes maximal heat production at 37°C; however, when body temperature rises, heat production quickly decreases as the temperature approaches the febrile set point.

As illustrated in figure 4, the plots of neuronal firing rates and heat production tend to converge as body temperature approaches 42°C. At 42°C the firing rates of warm-sensitive neurons reach their zenith and cannot be increased further in response to temperatures of >42°C. Similarly, the firing rates of cold-sensitive neurons reach their nadir at 42°C and cannot decrease further if temperatures increase above 42°C. Thus, regardless of the pyrogen concentration, thermosensitive neu-rons may be incapable of providing additional neural signals to finely regulate body temperature once the temperature reaches 42°C. Regulated increases in body temperature (i.e., fever) above 42°C, therefore, might not be possible because thermo-regulatory neurons are incapable of responding appropriately to temperatures of >42°C.

Endogenous Antipyretics

As indicated above, thermosensitive neurons in the PO/AH are influenced by a variety of endogenous substances [67–69]. At least some of these substances appear to function as endogenous antipyretic agents that might have a role in regulat-ing fever's upper limit.

Arginine vasopressin (AVP). The search for endogenous antipyretics responsible for limiting the height of the febrile

response began in earnest with studies of the temporarily blunted febrile response of periparturient ewes and newborn lambs to challenges with iv endotoxin [90]. Unable to identify a thermoregulatory defect or an inability of such animals to synthesize and release endogenous pyrogens, Kasting et al. [91] hypothesized the existence of an endogenous antipyretic agent responsible for the state of pyrogen unresponsiveness. AVP emerged as a likely candidate for such an endogenous antipyretic, after several groups of investigators [92–94] showed that the low-molecular-weight neuropeptide was present in increased concentrations in the circulation of pregnant ewes at the time of their diminished responsiveness to challenge with fever-inducing agents. More importantly, it was shown that if AVP is perfused into discrete areas of the brain of the nonpregnant ewe via a push-pull cannula system, application to the ventral septal area (but not other areas) reduces endotoxin-induced fever in a dose-dependent manner [95].

Subsequent studies by numerous investigators using a variety of animal models have established that AVP is present in the fibers and terminals of the ventral septal area, that it is released into the ventral septal area during fever, that it reduces fever via its action at V_1 receptors when introduced into the ventral septal area, and that it prolongs fever when inhibited [96]. The means by which AVP brings about a reduction in body temperature are not yet clear [97]. Its action appears to be mediated by V_1-type receptors [98]. AVP can interfere with glutamate-induced excitation of neurons [99], but the importance of this action to its antipyretic effect is not known. It apparently does not specifically impair thermogenesis [99]. Rather, it appears to prevent or reduce fever through a receptor-mediated action that has no effect on normal body temperature [100].

Evidence against the role of AVP as a physiologically important endogenous antipyretic agent comes from work involving the Brattleboro rat. This genetic variant of the Long-Evans rat possesses a recessive autosomal allele expressing AVP deficiency. Although animals homozygous for the allele are profoundly deficient in AVP, they do not exhibit an exaggerated febrile response to challenges with endogenous pyrogens or to prostaglandin E or endotoxin [101–104]. Nevertheless, it has been suggested that such conflicting evidence, rather than obviating a role for AVP in setting the upper limit of the febrile response, indicates that, like the febrile response itself, endogenous antipyresis most likely involves several peptidergic systems [20] (vide infra).

α-Melanocyte-stimulating hormone (α-MSH). Another central peptide exhibiting endogenous antipyretic activity is the neuropeptide α-MSH [105]. This relatively small molecule shares the 1–13 amino acid sequence with adrenocorticotropic hormone. Unlike some antipyretic peptides, α-MSH has not been identified in fibers projecting into the septum [106]. It does, nevertheless, reduce pyrogen-induced fever when administered (intragastrically, iv, intracerebroventricularly, or into the septal region of the brain) to experimental animals in doses

below those having an effect on afebrile temperature [107–111]. When given centrally, α-MSH is >25,000 times more potent as an antipyretic than is acetaminophen [105]. Repeated central administration of α-MSH does not induce tolerance to its antipyretic effect [112]. In addition, injection of antiserum to α-MSH into the cerebral ventricles augments the febrile response of experimental animals to IL-1 [113].

The greatest increases in central concentrations of α-MSH have been shown to occur during the chill phase of fever, when the temperature is rising rapidly, rather than during the plateau or defervescence phases [114]. No such increase in septal α-MSH concentrations occurs when the core temperature is raised by physical means [105]. Whereas large iv doses of α-MSH inhibit fever, they have no demonstrable effect on other aspects of the acute-phase response [115].

The biochemical pathway through which α-MSH exerts its antipyretic effect is not yet known. In fact, little can be said currently of its specific mechanism of action other than that α-MSH does not inhibit prostaglandin synthesis [116] and does not act as a receptor antagonist of IL-1 [117]. In addition, it is not known whether α-MSH exerts its antipyretic effect in concert with AVP. Nevertheless, from the data reviewed above, it is clear that it is a potent endogenous antipyretic agent and, like AVP, might have some role in setting fever's upper limit.

Miscellaneous antipyretic neurochemicals. Numerous neurochemicals appear to have the capacity to influence the hypothalamic control of body temperature. Depending on the environmental temperature, hypothalamic injections of these substances can often increase or decrease body temperature. Although antipyretic agents lower body temperature only when fever is present (i.e., in the presence of endogenous pyrogens), some of the agents considered below are more appropriately viewed as hypothermic agents because they have the capacity to lower body temperature even in the absence of fever. Theoretically, either type of neurochemical might be involved in setting fever's upper limit; however, proof of such involvement remains to be established for any of these agents.

Feldberg and Myers [118], in some of the earliest work in this area, observed that intracerebroventricular injections of epinephrine and norepinephrine cause a fall in body temperature in cats, whereas injections of serotonin cause body temperature to rise. On the basis of these observations, they proposed that regulation of body temperature depends on the balance between the release of catecholamines (inducing heat loss) and serotonin (activating heat production) in the anterior hypothalmus. More recent data, including those considered in the present review, suggest that the basis of set-point determination by the thermoregulatory network is considerably more complex [119].

Glucocorticoids and their inducers (corticotropin-releasing factor and adrenocorticotropic hormone) exhibit striking antipyretic properties under certain conditions. For example, there are numerous in vitro studies showing inhibition of production of pyrogenic cytokines such as IL-6 and TNF by glucocorti-

coids [120–122]. Through such effects, glucocorticoids exert inhibitory feedback on lipopolysaccharide-induced fever [94]. Lipocortin, a proposed mediator of glucocorticoid function, has also been shown to inhibit the pyrogenic actions of IL-1 and IFN [123]. Corticotropin-releasing factor injected into the third ventricle produces similar antipyretic effects [124], which are most likely mediated by the associated rise in blood levels of glucocorticoids [20].

Thyrotropin-releasing hormone [125], gastric inhibitory peptide [126], neuropeptide Y [127], and bombesin [128] are additional neuropeptides exhibiting hypothermic properties under certain conditions. Of these neuropeptides, bombesin is probably the most potent because it constantly produces hyperthermia associated with changes of heat dissipation and heat production when injected into the PO/AH of conscious goats and rabbits [128–130]. Bombesin is believed to exert its hypothermic effect by increasing the temperature sensitivity of warm-sensitive and temperature-insensitive neurons [129].

Endogenous Pyrogens and Their Receptors

Pyrogenic cytokines, the mediators of the febrile response, might themselves play a direct role in determining fever's upper limit. For instance, there is experimental evidence indicating that under certain conditions these cytokines act to lower, rather than raise, body temperature [113, 131]. Thus, it is possible that at certain concentrations or in the appropriate physiological milieu (e.g., at 41°C–42°C), pyrogenic cytokines might function paradoxically as endogenous antipyretic agents.

The febrile response might also peak at 41°C–42°C, because such temperatures inhibit the production of pyrogenic cytokines by inflammatory cells, inhibit the capacity of effector systems to respond to such cytokines, or might promote the elimination of pyrogenic cytokines. With regard to the first possibility, Ensor et al. [132, 133] have recently demonstrated that temperatures within the febrile range (40°C) cause degradation of TNF mRNA in macrophage-like cells in vitro, inhibit TNF-α release, and inhibit total protein synthesis by lipopolysaccharide-stimulated human macrophages but do not inhibit IL-6 expression (figure 5). Several other group of researchers have reported similar temperature-dependent inhibition of expression of various pyrogenic cytokines [134–137]. The specific effects of temperatures at the upper end of the febrile range on responsiveness of effector cells to endogenous pyrogens or on the elimination of such cytokines are not yet known.

A growing body of literature indicates that the release of pyrogenic cytokines such as IL-1 is followed by increased shedding of soluble receptors for such cytokines that function as endogenous inhibitors of such pyrogens [138]. In the case of IL-1, a 22- to 25-kD molecule that blocks binding of IL-1 to its receptors has been identified in supernatants of human monocytes [139]. The receptor antagonist of IL-1 is structurally related to IL-1α and IL-1β [140] and binds to both type I and type II receptors on various target cells without inducing a
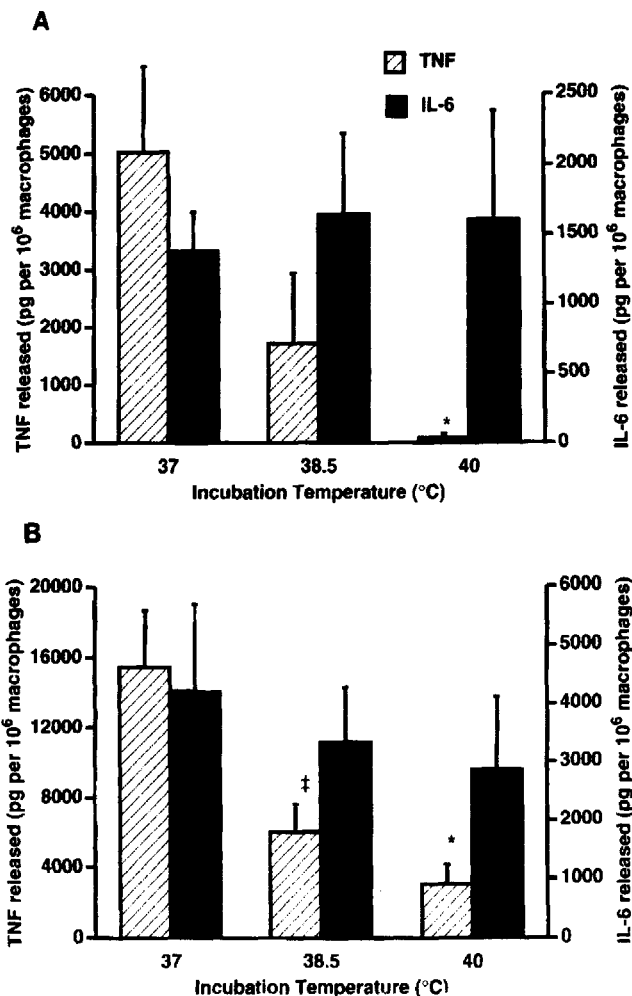

Figure 5. Effect of incubation temperature on TNF-α and IL-6 secretion by lipopolysaccharide-stimulated human monocyte-derived macrophages (HuMoM⊖). Data are expressed as means ± SE; * = $P < .01$; ‡ = $P < .05$ (compared with 37°C). Reprinted with permission from the *American Journal of Physiology* [133].

specific biological response [141, 142]. Similar receptor antagonists of TNF-α have been described [143–147]. The precise biological function of such receptor antagonists is not known. However, it is possible that one such function is to serve as a natural braking system for the febrile response.

Conclusion

Extensive clinical experience and the above-reviewed experimental data affirm the existence of an upper limit of the febrile response. Although the precise temperature defining this limit varies according to the site at which body temperature is measured, it is clear that human core temperature is almost never permitted to rise higher than 41°C–42°C during the regulated increase in temperature that characterizes fever. Recent investigations have identified several mechanisms by which fever's ceiling might be set. The upper limit of the febrile range might

be determined simply by the maximum and minimum firing rates of hypothalamic neurons that regulate body temperature. It is also possible that antipyretic substances that antagonize the actions of endogenous pyrogens play a pivotal role in this process. In all likelihood several different mechanisms are involved simultaneously in the process of endogenous "refrigeration" that prevents body heat from "consuming itself" during the febrile response.

Acknowledgments

References

1. Galen. Galen on the usefulness of the parts of the body. Ithaca, New York: Cornell University Press, 1968:50–3.
2. DuBois EF. Why are fever temperatures over 106°F rare? Am J Med Sci 1949;217:361–8.
3. Mackowiak PA, Wasserman SS. Physicians' perceptions regarding body temperature in health and disease. South Med J 1995;88:934–8.
4. Lee DHK. Heat and cold. Annu Rev Physiol 1948;10:365–86.
5. Deleted in proof.
6. Mackowiak PA, Wasserman SS, Levine MM. A critical appraisal of 98.6°F, the upper limit of the normal body temperature, and other legacies of Carl Reinhold August Wunderlich. JAMA 1992;268: 1578–80.
7. Rabinowitz RP, Cookson SL, Wasserman SS, Mackowiak PA. Study of the effects of anatomic site, oral stimulation and body position on estimates of body temperature. Arch Intern Med 1996 (in press).
8. DuBois EF. Fever and the regulation of body temperature. Springfiled, Illinois: CC Thomas, 1948:3–61.
9. Kluger MJ, Ringler DH, Anver MR. Fever and survival. Science 1975;188:166–8.
10. Bernheim HA, Kluger MJ. Fever: effect of drug-induced antipyresis on survival. Science 1976;193:237–9.
11. Bernheim HA, Bodel PT, Askenase PW, Atkins E. Effects of fever on host defense mechanisms after infection in the lizard *Dipsosaurus dorsalis*. Br J Exp Pathol 1978;59:76–84.
12. Goodman EL, Knochel JP. Heat stroke and other forms of hyperthermia. In: Mackowiak PA, ed. Fever: basic mechanisms and management. New York: Raven Press, 1991:267–87.
13. Knochel JP, Reed G. Disorders of heat regulation. In: Maxwell MH, Kleeman CR, Narins RG, eds. Clinical disorders of fluid and electrolyte metabolism. 4th ed. New York: McGraw-Hill, 1987:1197–232.
14. Shibolet S, Lancaster MC, Danon Y. Heat stroke: a review. Aviat Space Environ Med 1976;280–301.
15. Gore I, Visaacson N. The pathology of hyperpyrexia. Observations at autopsy in 17 cases of fever therapy. Am J Pathol 1949;25:1029–59.
16. Moritz AR, Henriques FC Jr, Dutra FR, Weisiger JR. Studies of thermal injury. IV and V. Arch Pathol 1947;43:466–502.
17. Hall WW, Wakefield EG. A study of experimental heat-stroke. JAMA 1927;89:77–182.
18. Jacobsen VC, Hosoi K. The morphologic changes in animal tissues due to heating by ultrahigh frequency oscillator. Arch Pathol 1931;2: 744–59.
19. Baldwin WM, Nelson WC. The histologic effects produced in albino rats by high frequency currents. Proc Soc Exp Biol Med 1928;26:588–90.
20. Moltz H. Fever: causes and consequences. Neurosci Biobehav Rev 1993;17:237–69.
21. Caputa M. Selective brain cooling: an important component of thermal physiology. In: Szelenyi Z, Szekely M, eds. Contributions to thermal physiology: satellite symposium of 28th International Congress of Physiological Science. Elmsford, New York: Pergamon, 1981: 183–92.
22. Murdock LL, Berlow S, Colwell RE, Siegel FL. The effects of hyperthermia on polyribosomes and amino acid levels in infant rat brain. Neuroscience 1978;3:349–57.
23. Schmidt-Nielsen K. Desert animals; physiological problems of heat and water. Oxford, England: Clarendon, 1964:238.
24. Hartman FW. Lesions of the brain following fever therapy; etiology and pathogenesis. JAMA 1937;109:2116–21.
25. Barr DP, Cecil RL, DuBois EF. Clinical calorimetry. XXXII. Temperature regulation after the intravenous injection of proteose and thyroid vaccine. Arch Intern Med 1922;19:608–34.
26. Bazett HC. Studies on the effects of baths on man. I. Relationship between the effect produced and the temperature of the bath. Am J Physiol 1924;70:412–29.
27. Landis EM, Long WL, Dunn JW, Jackson CL, Meyer U. Studies on the effect of baths on man. III. Effects of hot baths on respiration, blood and urine. Am J Physiol 1926;76:35–48.
28. Hubbard RN, Armstrong LE. The heat illnesses: biochemical, ultrastructural, and fluid-electrolyte considerations. In: Pandolf KB, Sawtia MN, Gonzalez RR, eds. Human performance physiology and environmental medicine at terrestrial extremes. Indianapolis: Benchmark Press, 1988:305–59.
29. Lepock JR, Kruuv J. Mechanisms of thermal cytotoxicity. In: Gerner EW, Cetas TC, eds. Hyperthermic oncology 1992. Vol 2 (Library of Congress no. 1021-9625). Tucson: Arizona Board of Regents, 1993: 9–16.
30. Yatvin MB, Cramp WA. Role of cellular membranes in hyperthermia: some observations and theories reviewed. Int J Hyperthermia 1993;9:165–85.
31. Jorritsma JB, Konings AW. The occurrence of DNA strand breaks after hyperthermic treatment of mammalian cells with and without radiation. Radiat Res 1984;98:198–208.
32. Warters RL, Brizgys LM. Apurinic site induction in the DNA of cells heated at hyperthermic temperatures. J Cell Physiol 1987;133: 144–50.
33. Vilenchik MM. Studies in DNA damage and repair of thermal- and radiation-induced lesions in human cells. Int J Radiat Biol 1989;56:5685–9.
34. Harmon BV, Corder AM, Collins RJ, et al. Cell death induced in murine mastocytoma by 42–47°C heating in vitro: evidence that the form of death changes from apoptosis to necrosis above a critical heat load. Int J Radiat Biol 1990;58:845–58.
35. Mondovi B, Finazzi Agro A, Rotilio G, Strom R, Moricca G, Ross Fanelli A. The biochemical mechanism of selective heat sensitivity of cancer cells. II. Studies on nucleic acids and protein synthesis. Eur J Cancer 1969;5:137–46.
36. Henle KJ, Leeper DB. Effects of hyperthermia (45°) on macromolecular synthesis in Chinese hamster ovary cells. Cancer Res 1979;39: 2665–74.
37. Massicote-Nolan P, Glocheski DJ, Kruuv J, Lepcock JR. Relationship between hyperthermic cell killing and protein denaturation by alcohol. Radiat Res 1981;87:284–99.
38. Bagi C, Hidvegi EJ. Protein phosphorylation and kinase activities in tumor cells after hyperthermia. Int J Radiat Biol 1990;58:633–50.
39. Barratt GH, Wills ED. The effect of hyperthermia and radiation on lysosomal enzyme activity of mouse mammary tumors. Eur J Cancer 1979;15:243–50.

40. Keech ML, Wills ED. The effect of hyperthermia on activation of lysosomal enzymes in HeLa cells. Eur J Cancer 1979;15:1025–31.

41. Dickson JA, Calderwood SK. Thermosensitivity of neoplastic tissues in vivo. In: Storm FK, ed. Hyperthermia and cancer therapy. Boston: Hall Medical Publishers, 1983:63–140.

42. Lin PS, Turi A, Kwock L, Lu RC. Hyperthermia effect on microtubule organization. National Cancer Institute Monograph 1982;61:57–60.

43. van Berger en Henegomen PM, Jordi WJR, van Dongen G, Ramaekers FC, Amesz H, Linnemans WA. Studies on a possible relationship between alterations in the cytoskeleton and induction of heat shock protein synthesis in mammalian cells. Int J Hyperthermia 1985;1: 69–83.

44. Welch WJ, Suhan JP. Morphological study of the mammalian stress response: characterization of the changes in cytoplasmic organelles, cytoskeleton, and nucleoli, and appearance of intranuclear actin filaments in rat fibroblasts after heat-shock treatment. J Cell Biol 1985;101:1198–211.

45. Glass JR, DeWitt RG, Cress AE. Rapid loss of stress fibers in Chinese hamster ovary cells after hyperthermia. Cancer Res 1985;45:258–62.

46. Coakley WT. Hyperthermia effects on the cytoskeleton and on cell morphology. In: Bowler K, Fuller BJ, eds. S. E. B. Symposium XLI: temperature and animal cells, Cambridge, England: Company of Biologists, 1987:187–212.

47. Hofer KG, Mivechi NF, Jofer MG. Effect of membrane and cytoskeleton modification of the heat response of BP-8 murine sarcoma cells. Protoplasma 1989;150:117–23.

48. Coss RA, Dewey WC. Mechanism of heat sensitization of G1- and S-phase cells by procaine HC1. In: Broese JJ, Barendson GW, Kal HB, Vander Kogel AJ, eds. Tumor biology and therapy. Amsterdam: Martinus Nijhoff, 1983:D6–05.

49. Stevenson MA, Calderwood SK, Hahn GM. Effect of hyperthermia (45°C) on calcium flux in Chinese hamster ovary HA-1 fibroblasts and its potential role in cytotoxicity and heat resistance. Cancer Res 1987;47:3712–7.

50. Drummond IA, Livingstone D, Steinhardt RA. Heat shock protein synthesis and cytoskeletal rearrangements occur independently of intracellular free calcium increases in Drosophila cells and tissues. Radiat Res 1988;113:402–13.

51. Bagi G, Hidvegi EJ. Protein phosphorylation and kinase activities in tumour cells after hyperthermia. Int J Radiat Biol 1990;58:633–50.

52. Stitt JT. Evidence for the involvement of the organum vasculosum laminae terminalis in the febrile responses of rabbits and rats. J Physiol (Lond) 1985;368:501–11.

53. Hunter WS, Sehic E, Blatteis CM. Fever and the organum vasculosum laminae terminalis: another look. In: Milton AS, ed. Temperature regulation: recent physiological and pharmacological advances. Basel, Switzerland: Birkhuser, 1994:75–9.

54. Boulant JA. Hypothalamic control of thermoregulation: neurophysiological basis. In: Morgane PJ, Panksepp J, eds. Handbook of the hypothalamus. Vol 3. Behavioral studies of the hypothalamus. New York: Dekker, 1980:1–82.

55. Boulant JA, Gonzalez RR. The effect of skin temperature on the hypothalamic control of heat loss and heat production. Brain Res 1977;120:367–72.

56. Hellstrom B, Hammel HT. Some characteristics of temperature regulation in the unanesthetized dog. Am J Physiol 1976;213:547–56.

57. Jacobson FH, Squires RD. Thermoregulatory responses of the cat to preoptic and environmental temperatures. Am J Physiol 1970; 218:1575–82.

58. Smiles KA, Elizondo RS, Barney CC. Sweating responses during changes of hypothalamic temperature in the rhesus monkey. J Appl Physiol 1976;40:653–7.

59. Hammel HT, Hardy JD, Fusco MM. Thermoregulatory responses to hypothalamic cooling in unanesthetized dogs. Am J Physiol 1960; 198:481–6.

60. Banet M, Hensel H. Nonshivering thermogenesis induced by repetitive hypothalamic cooling in the rat. Am J Physiol 1976;230:522–6.

61. Bruck K, Wunnenburg W. "Meshed" control of two effector systems: nonshivering and shivering thermogenesis. In: Hardy JD, Gagge AP, Stolwijk JAJ, eds. Physiological and behavioral temperature regulation. Springfield, Illinois: Thomas, 1970:562–80.

62. Kanosue K, Yanase-Fujiwara M, Hosono T. Hypothalamic network for thermoregulatory vasomotor activity. Am J Physiol 1994;267: R283–8.

63. Adair ER. Skin, preoptic and core temperatures influence behavioral thermoregulation. J Appl Physiol 1977;42:559–64.

64. Satinoff E. Behavioral thermoregulation in response to local cooling of the rat hypothalamus. Am J Physiol 1964;206:1389–94.

65. Boulant JA, Dean JB. Temperature receptors in the central nervous system. Annu Rev Physiol 1986;48:639–54.

66. Dean JB, Boulant JA. In vitro localization of thermosensitive neurons in the rat diencephalon. Am J Physiol 1989a;257:R57–64.

67. Boulant JA, Silva NL. Multisensory hypothalamic neurons may explain interactions among regulatory systems. News in Physiological Sciences 1989;4:245–8.

68. Silva NL, Boulant JA. Effects of testosterone, estradiol, and temperature on neurons in preoptic tissue slices. Am J Physiol 1986;250: R625–32.

69. Silva NL, Boulant JA. Effects of osmotic pressure, glucose, and temperature on neurons in preoptic tissue slices. Am J Physiol 1984;247:R335–45.

70. Guieu JD, Hardy JD. Effects of heating and cooling of the spinal cord on preoptic unit activity. J Appl Physiol 1970;29:675–83.

71. Boulant JA, Bignall KE. Hypothalamic neuronal responses to peripheral and deep-body temperatures. Am J Physiol 1973;225:1371–4.

72. Boulant JA, Hardy JD. The effect of spinal and skin temperatures on the firing rate and thermosensitivity of preoptic neurones. J Physiol (Lond) 1974;240:639–60.

73. Boulant JA, Demieville HN. Responses of thermosensitive preoptic and septal neurons to hippocampal and brain stem stimulation. J Neurophysiol 1977;40:1356–68.

74. Dean JB, Boulant JA. Effects of synaptic blockade on thermosensitive neurons in rat diencephalon in vitro. Am J Physiol 1989;257: R65–73.

75. Kelso SR, Boulant JA. Effect of synaptic blockade on thermosensitive neurons in hypothalamic tissue slices. Am J Physiol 1982;243: R480–90.

76. Curras MC, Kelso SR, Boulant JA. Intracellular analysis of inherent and synaptic activity in hypothalamic thermosensitive neurones in the rat. J Physiol 1991;440:257–71.

77. Boulant JA. Hypothalamic mechanisms in thermoregulation. Fed Proc 1981;40:2843–50.

78. Boulant JA. The effect of firing rate on preoptic neuronal thermosensitivity. J Physiol 1974;240:661–9.

79. Boulant JA. Thermoregulation. In: Mackowiak PA, ed. Fever: basic mechanisms and managements. New York: Raven Press, 1991:1–22.

80. Dinarello CA. Endogenous pyrogens: the role of cytokines in the pathogenesis of fever. In: Mackowiak PA, ed. Fever: basic mechanisms and managements. New York: Raven Press, 1991:23–47.

81. Stitt JT. Prostaglandin E as the neural mediator of the febrile response. Yale J Biol Med 1986;59:137–49.

82. Cannon JG. Is interleukin-1 involved in homeostasis? In: Kluger MJ, Oppenheim JJ, Powanda MC, eds. The physiologic, metabolic, and immunologic actions of interleukin-1. New York: Alan R Liss, 1985:181–9.

83. Clowes GHA, Saravis C, Bigatello L, George BC, Villee C. The hormonal functions of "proteolysis inducing factor" (PIF), the active circulating cleavage fragment of interleukin-1 (IL-1). In: Kluger MJ, Oppenheim JJ, Powanda MC, eds. The physiologic, metabolic, and immunologic

actions of interleukin-1: proceedings of a symposium held in Ann Arbor, Michigan, June 4–6, 1985. New York: Alan R Liss, **1985**: 211–20.

84. Fontana A, Weber E, Dayer JM. Synthesis of interleukin 1/endogenous pyrogen in the brain of endotoxin-treated mice: a step in fever induction? J Immunol **1984**;133:1696–8.

85. Stitt JT. Prostaglandin E$_1$ fever induced in rabbits. J Physiol **1973**;232:163–79.

86. Kluger MJ. Fever and antipyresis. In: Zeisberger E, Schonbaum E, Lomax P, eds. Thermal balance in health and disease: recent basic research and clinical progress. Basel, Switzerland: Birkhauser Verlag, **1994**:343–52.

87. Coceani F, Bishai I, Dinarello CA, Fitzpatrick FA. Prostaglandin E$_2$ and thromboxane B$_2$ in cerebrospinal fluid of afebrile and febrile cat. Am J Physiol **1983**;244:R785–93.

88. Boulant JA, Scott IM. Comparison of prostaglandin E2 and leukocytic pyrogen on hypothalamic neurons in tissue slices. In: Cooper K, Lomax P, Schonbaum E, Veale WL, eds. Homeostasis and thermal stress. Basel, Switzerland: Karger, **1986**:78–80.

89. Hori T, Shibata M, Nakashima T, et al. Effects of interleukin-1 and arachidonate on the preoptic and anterior hypothalamic neurons. Brain Res Bull **1988**;20:75–82.

90. Kasting NW, Veale WL, Cooper KE. Suppression of fever at term of pregnancy. Nature **1978**;271:245–6.

91. Kasting NW, Veale WL, Cooper KE. Endogenous pyrogen release by fetal sheep and pregnant sheep leukocytes. Can J Physiol Pharmacol **1979**;57:1453–6.

92. Cooper KE, Kasting NW, Lederis K, Veale WL. Evidence supporting a role for endogenous vasopressin in natural suppression of fever in the sheep. J Physiol (Lond) **1979**;295:33–45.

93. Kasting NW, Cooper KE, Veale WL. Antipyresis following perfusion of brain sites with vasopressin. Experientia **1979**;35:208–9.

94. Alexander DP, Bashore RA, Britton HG, Forsling ML. Maternal and fetal arginine vasopressin in the chronically catherised sheep. Biol Neonate **1974**;25:242–8.

95. Kasting NW, Veale WL, Cooper KE. Models of endogenous antipyresis. In: Lipton JM, ed. Fever. New York: Raven Press, **1980**:189–96.

96. Pittman QJ, Wilkinson MF. Central arginine vasopressin and endogenous antipyresis. Can J Physiol Pharmacol **1992**;70:786–90.

97. Pittman QJ, Poulin P, Wilkinson MF. Role of neurohypophysial hormones in temperature regulation. Ann NY Acad Sci **1993**;689: 375–81.

98. Kasting NW. Criteria for establishing a physiological role for brain peptides. A case in point: the role of vasopressin in thermoregulation during fever and antipyresis. Brain Res Brain Res Rev **1989**;14: 143–53.

99. Federico P, Malkinson TJ, Cooper KE, Pittman QJ, Veale WL. Vasopressin perfusion within the medial amygdaloid nucleus attenuates prostaglandin fever in the urethane-anaesthetized rat. Brain Res **1992**;587:319–26.

100. Pittman QJ, Naylor A, Poulin P, et al. The role of vasopressin as an antipyretic in the ventral septal area and its possible involvement in convulsive disorders. Brain Res Bull **1988**;20:887–92.

101. Stitt JT, Shimada SG. A comparison of the febrile responses of the Brattleboro and Sprague-Dawley strains of rats to endotoxin and endogenous pyrogens. Can J Physiol Pharmacol **1987**;65:1377–81.

102. Ruwe WD, Veale WL, Cooper KE. Peptide neurohormones: their role in thermoregulation and fever. Can J Biochem Cell Biol **1983**;61: 579–93.

103. Kandasamy SB, William BA. Absence of endotoxin fever but not hyperthermia in Brattleboro rats. Experientia **1983**;39:1343–4.

104. Eagan PC, Kasting NW, Veale WL, Cooper KE. Absence of endotoxin fever but not prostaglandin E$_2$ and its methyl ester in the induction of hyperthermia after their systemic administration in urethane-anesthetized rats. J Pharmacol Exp Ther **1988**;247:671–9.

105. Lipton JM. Disorders of temperature control. In: Rieder P, Kopp N, Pearson J, eds. An introduction to neurotransmission in health and disease. Oxford, England: Oxford University Press, **1990**:119–23.

106. Zeisberger E. The role of septal peptides in thermoregulation and fever. In: Bligh J, Voigt K, eds. Thermoreception and temperature regulation. Berlin: Springer-Verlag, **1990**:273–83.

107. Glyn JR, Lipton JM. Hypothermic and antipyretic effects of centrally administered ACTH (1–24) and α-melanotropin. Peptides **1981**;2:177–87.

108. Glyn-Ballinger JR, Bernardini GL, Lipton JM. α-MSH injected into the septal region reduces fever in rabbits. Peptides **1983**;4:199–203.

109. Lipton JM, Whisenant JD, Gean JT. Hyperthermia produced by peripheral and central injections of chlopramazine in aged rabbits. Brain Res Bull **1979**;4:631–4.

110. Murphy MT, Lipton JM. Peripheral administration of α-MSH reduces fever in older and younger rabbits. Peptides **1982**;13:775–9.

111. Murphy MT, Richards DB, Lipton JM. Antipyretic potency of centrally administered α-melanocyte stimulating hormone. Science **1983**;221:192–3.

112. Deeter LB, Martin LW, Lipton JM. Antipyretic effect of central alpha-MSH summates with that of acetaminophen or ibuprofen. Brain Res Bull **1989**;23:573–5.

113. Shih ST, Khorram O, Lipton JM, McCann SM. Central administration of α-MSH antiserum augments fever in the rabbit. Am J Physiol **1986**;250:R803–6.

114. Bell RC, Lipton JM. Pulsatile release of antipyretic neuropeptide alpha-MSH from septum of rabbit during fever. Am J Physiol **1987**;252:R1152–7.

115. Martin LW, Lipton JM. Acute phase response to endotoxin: rise in plasma alpha-MSH and effects of alpha-MSH injection. Am J Physiol **1990**;259:R768–72.

116. Clark WG, Holdeman M, Lipton JM. Analysis of the antipyretic action of α-melanocyte-stimulating hormone in rabbits. J Physiol (Lond) **1985**;359:459–65.

117. Lipton JM. Modulation of host defense by the neuropeptide α-MSH. Yale J Biol Med **1990**;63:173–82.

118. Feldberg W, Myers RD. A new concept of temperature regulation by amines in the hypothalamus. Nature **1963**;200:1325.

119. Bligh J. Cells, cell-talk and mammalian homeothermy. In: Bligh J, Voigt K, eds. Thermoreception and temperature regulation. Berlin: Springer-Verlag, **1990**:163–73.

120. Morrow LE, McClellan JL, Conn CA, Kluger MJ. Glucocorticoids alter fever and IL-6 responses to psychological stress and to lipopolysaccharide. Am J Physiol **1993**;264:R1010–6.

121. Luedke CE, Cerami A. Interferon-gamma overcomes glucocorticoid suppression of cachectin/tumor necrosis factor biosynthesis by murine macrophages. J Clin Invest **1990**;86:1234–40.

122. Nakano T, Ohara O, Teraoka H, Arita H. Glucocorticoids suppress group II phospholipase A$_2$ production by blocking mRNA synthesis and post-transcriptional expression. J Biol Chem **1990**;265:12745–8.

123. Carey F, Forder R, Edge MD, et al. Lipocortin 1 fragment modifies pyrogenic actions of cytokines in rats. Am J Physiol **1990**;259: R266–9.

124. Bernadini GL, Lipton JM, Clark WG. Intracerebroventricular and septal injections of arginine vasopressin are not antipyretic in the rabbit. Peptides **1983**;4:195–8.

125. Riedel W. Role of thyroid-stimulating hormone (TSH) in endogenous antipyresis and evidence of extrahypothalamic thyroid-stimulating neurons (TSN) in rabbits. Pflugers Arch **1987**;408(suppl):R49.

126. Bahendeka SK, Moor RE, Tomkin GH, Buchanan KD. Gastric inhibitory polypeptide, dietary-induced thermogenesis, and obesity. Can J Physiol Pharmacol **1987**;65:1242–7.

127. Stanley BG, Leibowitz SF. Neuropeptide Y: stimulation of feeding and drinking by injection into the paraventricular nucleus. Life Sci **1984**;35:2635–42.

128. Jansky L, Vybiral S, Moravec J, et al. Neuropeptides and temperature regulation. Journal of Thermal Biology 1986;11:79–83.

129. Schmid H, Pierau Fr-K. Long-term modulation of hypothalamic neurons by neuropeptides. In: Bligh J, Voigt K, eds. Thermoregulation and temperature regulation. Berlin: Springer-Verlag, 1990:53–63.

130. Gale CC, McCreery BR. Mechanism of bombesin hyperthermia. Fed Proc 1979;38:997.

131. Holt SJ, Grimble RF, York DA. Tumor necrosis factor-α and lymphotoxin have opposite effects on sympathetic efferent nerves to brown adipose tissue by direct action in the central nervous system. Brain Res 1989;497:183–6.

132. Ensor JE, Crawford EK, Hasday JD. Elevated temperatures inhibit tumor necrosis factor-α expression by inducing rapid degradation of TNF mRNA. Clin Res 1994;42:135A.

133. Ensor JE, Wiener SM, McCrea KA, Viscardi RM, Crawford EK, Hasday JD. Differential effects of hyperthermia on macrophage interleukin-6 and tumor necrosis factor-α expression. Am J Physiol 1994; 266:C967–74.

134. Fouqueray B, Philippe C, Amrani A, Perez J, Baud L. Heat shock prevents lipopolysaccharide-induced tumor necrosis factor-α synthesis by rat mononuclear phagocytes. Eur J Immunol 1992;22:2983–7.

135. Klostergaard J, Barta M, Tomasovic SP. Hyperthermic modulation of tumor necrosis factor–dependent monocyte/macrophage tumor cytotoxicity in vitro. J Biol Response Mod 1989;8:262–77.

136. Schmidt JA, Abdulla E. Down-regulation of IL-1β biosynthesis by inducers of the heat-shock response. J Immunol 1988;141:2027–34.

137. Snyder YM, Guthrie L, Evans GF, Zuckerman SH. Transcriptional inhibition of endotoxin-induced monokine synthesis following heat shock in murine peritoneal macrophages. J Leukoc Biol 1992;51:181–7.

138. Sivo J, Salkowski CA, Politis AD, Vogel SN. Differential regulation of LPS-induced IL-1β and IL-1 receptor antagonist mRNA by IFNα and IFNγ in murine peritoneal macrophages. Journal of Endotoxin Research 1994;1:30–6.

139. Seckinger P, Lowenthal JW, Williamson K, Dayer JM, MacDonald HR. A urine inhibitor of interleukin-1 activity that blocks ligand binding. J Immunol 1987;139:1546–9.

140. Eisenberg SP, Brewer MT, Verderber E, Heimdal P, Brandhuber BJ, Thompson RC. Interleukin 1 receptor antagonist is a member of the interleukin 1 gene family: evolution of a cytokine control mechanism. Proc Natl Acad Sci USA 1991;88:5232–6.

141. Dripps DJ, Brandhuber BJ, Thompson RC, Eisenberg SP. Interleukin-1 (IL-1) receptor antagonist binds to the 80-kDa IL-1 receptor but does not initiate IL-1 signal transduction. J Biol Chem 1991;266: 10331–6.

142. Dripps DJ, Verderber E, Ng Rk, Thompson RC, Eisenberg SP. Interleukin-1 receptor antagonist binds to the type II interleukin-1 receptor on B cells and neutrophils. J Biol Chem 1991;266:20311–5.

143. Engelmann H, Aderka D, Rubinstein M, Rotman D, Wallach D. A tumor necrosis factor binding protein purified to homogeneity from human urine protects cells from tumor necrosis factor toxicity. J Biol Chem 1989;264:11974–80.

144. Olsson I, Lantz M, Nilsson E, et al. Isolation and characterization of a tumor necrosis factor binding protein from urine. Eur J Haematol 1989;42:270–5.

145. Engleman H, Novick D, Wallach D, Two tumor necrosis factor-binding proteins from human urine. J Biol Chem 1990;265:1531–6.

146. Brockhaus M, Schoenfeld HJ, Schlaeger EJ, Hunziker W, Lesslauer W, Loetscher H. Identification of two types of tumor necrosis factor receptors on human cell lines by monoclonal antibodies. Proc Natl Acad Sci USA 1990;87:3127–31.

147. Porteu F, Nathan C. Shedding of tumor necrosis factor receptors by activated human neutrophils. J Exp Med 1990;172:599–607.