Fever is a complex physiologic response triggered by infectious or aseptic stimuli. Elevations in body temperature occur when concentrations of prostaglandin E₂ (PGE₂) increase within certain areas of the brain. These elevations alter the firing rate of neurons that control thermoregulation in the hypothalamus. Although fever benefits the nonspecific immune response to invading microorganisms, it is also viewed as a source of discomfort and is commonly suppressed with antipyretic medication. Antipyretics such as aspirin have been widely used since the late 19th century, but the mechanisms by which they relieve fever have only been characterized in the last few decades. It is now clear that most antipyretics work by inhibiting the enzyme cyclooxygenase and reducing the levels of PGE₂ within the hypothalamus. Recently, other mechanisms of action for antipyretic drugs have been suggested, including their ability to reduce proinflammatory mediators, enhance anti-inflammatory signals at sites of injury, or boost antipyretic messages within the brain. Although the complex biologic actions of antipyretic agents are better understood, the indications for their clinical use are less clear. They may not be indicated for all febrile conditions because some paradoxically contribute to patient discomfort, interfere with accurately assessing patients receiving antimicrobials, or predispose patients to adverse effects from other medications. The development of more selective fever-relieving agents and their prudent use with attention to possible untoward consequences are important to the future quality of clinical medicine.

—Humanity has but three great enemies: fever, famine, and war, and of these by far the greatest, by far the most terrible, is fever—

This bon mot from Osler cleverly paints the pall of apprehension felt by those who attend febrile patients at the bedside. Practitioners still debate the role or value of fever in disease, and even iatrogenic pyrexia undergoes periodic revival (1). As victor or villain, perhaps no symptom has been viewed so dichotomously. Fever today is generally regarded as a form of patient discomfort. Among acts of caring, pyrexia is treatable, and so it often is treated.

Physicians since antiquity have used various physical means to lower body temperature (2). Applying Peruvian cinchona bark as an antipyretic dates to the early 1600s (3), but by the 18th century overharvesting of cinchona created scarcity (4) and a search for substitutes. In 1763, Reverend Stone reported to the Royal Society of London on the antipyretic effects of “fever bark” from English willow (4). Although his finding appeared novel, it simply confirmed what was known to Hippocrates, Galen, and ancient Egyptians centuries before (5,6). Salicylic acid was first prepared in 1838 from the glucoside salicin, the active component in willow bark (5,7). Another derivative, acetylsalicylic acid (aspirin) was later synthesized in 1853 and made commercially available as an antipyretic in 1899 (2,5). Since then, numerous antipyretics have been introduced into clinical medicine.

The prescription of acetaminophen for fever is more recent. Although precursors such as acetanilid and phenacetine were developed in the second half of the 19th century, the popular use of acetaminophen as an antipyretic and analgesic did not occur until the 1950s (8). The antipyretics in common use today include acetaminophen, aspirin, and other nonsteroidal anti-inflammatory drugs (NSAIDs). The principal action of antipyretics rests in their ability to inhibit the enzyme cyclooxygenase (COX) and interrupt the synthesis of inflammatory prostaglandins (9). Recent studies on the mechanism of antipyretic action of these drugs, however, reveal effects independent of COX inhibition as well.

We review here the mechanisms of commonly used antipyretics, emphasizing their ability to block the febrile response at multiple sites along a physiologic cascade that connects peripheral inflammation with the central nervous system, and conclude with some thoughts on the proper use of antipyretics for patients with fever.
NORMAL THERMOREGULATION

Normal body temperature is circadian and varies from an approximate low of 36.4°C (97.6°F) in the morning to a high of 36.9°C (98.5°F) in the late afternoon (10). At the heart of thermoregulation is an integrated network of neural connections involving the hypothalamus, limbic system, lower brainstem, the reticular formation, spinal cord, and the sympathetic ganglia (11). An area in and near the rostral hypothalamus is also important in orchestrating thermoregulation. This region, the "preoptic area," includes the preoptic nuclei of the anterior hypothalamus (POAH) and the septum.

In simple terms, the POAH maintains mean body temperature around a set point. This thermoneutral set point temperature is modulated by the balanced activities of temperature-sensitive neurons. These neurons integrate afferent messages regarding core body and peripheral (skin) temperatures and evoke various behavioral and physiologic responses controlling heat production or dissipation (11).

Fever describes a regulated rise in body temperature after an increase in the hypothalamic set point (12). Under the influence of the hypothalamus, physiologic and behavioral functions favoring heat production and heat retention are stimulated until arriving at a newly elevated set point temperature (12). Typical early behavioral changes prior to fever include seeking a warmer environment or adding clothing. Physiologic alterations include cutaneous vasoconstriction, shivering, and nonshivering thermogenesis through enhanced release of thyroid hormones, glucocorticoids, and catecholamines (11). Upon reaching the elevated set point of fever, an increase or decrease in core temperature will stimulate thermoregulatory mechanisms similar to those evoked at normal body temperature (5). In other words, normal thermoregulation modulates at this higher set point.

THE PATHOGENESIS OF FEVER

Many of the mediators underlying pyrexia have been described in recent years (Figure 1). The critical "endogenous pyrogens" involved in producing a highly regulated inflammatory response to tissue injury and infection are polypeptide cytokines. Pyrogenic cytokines, such as interleukin-1β (IL-1β), tumor necrosis factor (TNF), and interleukin-6 (IL-6), are those that act directly on the hypothalamus to effect a fever response (13). Exogenous pyrogens, such as microbial surface components, evoke pyrexia most commonly through the stimulation of pyrogenic cytokines. The gram-negative bacterial outer membrane lipopolysaccharide (endotoxin), however, is capable of functioning at the level of the hypothalamus, in much the same way as IL-1β (14).

These signals trigger the release of other mediators, most notably prostaglandin E₂ (PGE₂), in the region of the POAH (12). PGE₂ is believed to be the proximal mediator of the febrile response. Preoptic neurons bearing E-prostanoid receptors alter their intrinsic firing rate in response to PGE₂, evoking an elevation in the thermoregulatory set point. There are four known cellular receptors for PGE₂: EP₁ through EP₄ (15). The particular receptor subtype involved in pyrogenesis is unknown. Although mice lacking the neuronal PGE₂ receptor subtype EP₃ demonstrate an impaired febrile response to both exogenous (endotoxin) and endogenous pyrogens (15), studies in rats appear to implicate the EP₄ receptor (16). The intracellular events triggering pyrexia after PGE₂-EP receptor coupling among species are unclear.

Fever is tightly regulated by the immune response. Inflammatory stimuli triggering the generation of pyrogenic cytokines provoke the release of endogenous antipyretic substances (17). Substances such as arginine vasopressin (AVP), α-melanocyte stimulating hormone, and glucocorticoids act both centrally and peripherally to limit pyrexia (17). The cytokine interleukin-10 (IL-10) has numerous anti-inflammatory properties, including fever suppression (18,19). In addition, a class of lipid compounds known as epoxyeicosanoids generated by certain cytochrome P-450 enzymes play an important role in limiting the fever and inflammation (20) [reviewed in (21)].

Analogous to a biochemical feedback pathway, fever itself appears capable of countering the release of pyrogenic cytokines (22,23). For example, febrile temperatures augment early TNF release in endotoxin-challenged mice, yet limit its prolonged (and perhaps detrimental) expression after either lipopolysaccharide injection or bacterial infection (22,23).

THE ROLE OF PROSTAGLANDIN E₂

PGE₂ is synthesized from arachidonic acid, which is released from cell membrane lipid by phospholipase. Arachidonic acid is metabolized by two isoforms of the COX enzyme, COX-1 and COX-2. COX-1 usually is expressed constitutively and generates prostanoids important to housekeeping functions supporting homeostasis (24). COX-2, on the other hand, is inducible by inflammatory signals such as the pyrogenic cytokines, IL-1β, TNF, and IL-6, and bacterial lipopolysaccharide (24). Genetically engineered mice that lack either the COX-1 or COX-2 gene demonstrate that the inducible isoform is responsible for hypothalamic PGE₂ production during a febrile response (25). As COX-2 is the key provider of PGE₂ during pyrexia, it is not surprising that the selective COX-2 antagonist, rofecoxib, is an effective antipyretic in humans (26).
Many cells, including synoviocytes, macrophages, endothelial cells, and chondrocytes, have the capacity to rapidly up-regulate the expression of the COX-2 during inflammation (24). The most likely cell type in the central nervous system responsible for producing PGE2 is the microvascular endothelial cell, which expresses COX-2 exuberantly after stress (25,27,28).

An effective febrifuge might interrupt pyrexogenesis at any step that connects peripheral inflammation with the central production of PGE2. Stated differently, an antipyretic might blunt peripheral inflammation or depress central pyrogenic signals, or affect both. Inhibiting central production of PGE2 is a well-known mechanism of antipyretic agents, but activated leukocytes and endothelial cells in peripheral areas of inflammation also represent potential drug targets (Table 1).

**The Cyclooxygenase Hypothesis**

The antipyretic drug aspirin was in wide clinical use for more than 70 years (9) before Vane (29) demonstrated in 1971 that it exerted its physiologic action by inhibiting the production of prostaglandins. Further work suggests a current model of how aspirin and similar NSAIDs act as antipyretics.

Aspirin interferes with the biosynthesis of cyclic prostanoids derived from arachidonic acid, such as thromboxane A2 and prostaglandins (30). As a nonselective COX inhibitor, aspirin has been widely studied for its anti-inflammatory, antipyretic, and antithrombotic traits. The major mechanism of action of aspirin and other antipyretics involves lowering PGE2 by directly inhibiting COX enzyme activity (31). Worth noting, how-

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**Figure 1.** Fever generation after infection. Microbial tissue invasion sparks an inflammatory response and activates local vascular endothelial cells and leukocytes. The extravasation of white blood cells into inflamed areas depends on a multistep interaction with endothelial cells regulated by a variety of cytokines, chemokines, and adhesion molecules. Activated leukocytes release the pyrogenic cytokines interleukin-1β (IL-1β), tumor necrosis factor (TNF), and interleukin-6 (IL-6). Hematogenous dissemination (depicted here) allows these endogenous pyrogens to stimulate vascular endothelial cell production of prostaglandin E2 (PGE2) within the central nervous system. Peripheral inflammatory signals may also travel along neural connections (such as the vagus nerve) to trigger central nervous system PGE2 production (96). Neurons within the preoptic area of the anterior hypothalamus (POAH) bearing specific E-prostanoid receptors orchestrate the febrile response after the PGE2 signal. PGE2 alters the firing rate of these neurons, resulting in an elevated thermoregulatory set point. The febrile set point body temperature is reached through the regulated evocation of behavioral and physiologic changes aimed at enhancing heat production and reducing heat dissipation. Fever is believed to augment the peripheral and systemic inflammatory response to infection in part by modulating the expression of inflammatory cytokines and enhancing leukocyte function.
ever, is that sodium salicylate, aspirin’s major metabolite, exhibits similar antipyretic and anti-inflammatory properties as aspirin but shows only weak inhibition of COX-1 and COX-2 in vitro (32,33).

NSAIDs are also capable of reducing PGE2 production by down-regulating the expression of COX enzymes, as opposed to directly inhibiting their enzymatic action. Sodium salicylate and aspirin also inhibit COX-2 transcription induced by lipopolysaccharide and IL-1β (34). The clinical effects of sodium salicylate are likely due in part to its actions on COX gene transcription by disabling the transcriptional activator nuclear factor-κB (NF-κB) (34).

NF-κB is a heterodimeric protein capable of binding DNA in the 5’-promoter regions of many genes involved in the inflammatory response (35). Once bound, NF-κB facilitates the transcription of genes encoding pyrogenic cytokines, chemokines, adhesion molecules, and inflammatory enzymes, including inducible nitric oxide synthase and COX-2 in certain cell types (35,36). NF-κB resides in an inactive state in the cytoplasm, complexed to another protein, IκB (37). Upon activation, the IκB silencer is sequentially phosphorylated, ubiquinated, and degraded, releasing NF-κB to translocate into the nucleus (35).

Salicylates reduce the nuclear translocation of NF-κB through stabilization of cytoplasmic IκB (38) by interfering with its phosphorylation (Figure 2) (39). The ability of antipyretics to disable transcription varies among agents and cell type studied. Salicylate and its progenitor aspirin prevent NF-κB translocation in endothelial cells and leukocytes induced by proinflammatory cytokines or lipopolysaccharide (38–42). NSAIDs like ibuprofen also block the nuclear trafficking of NF-κB in certain tumor cell lines (43) but fail to do so in activated macrophages (38). Indomethacin, another COX inhibitor, does not appear to affect NF-κB (41,42), and therapeutic doses of acetaminophen also fail to suppress it (41,44). The reason for this heterogeneity is unknown.

An NF-κB/IκB mechanism for COX-2 expression may not be the whole story, either, as the COX-2 gene is not solely dependent on activation by the NF-κB cascade (36). In human microvascular endothelial cells, for example, COX-2 activation by IL-1β occurs independently of NF-κB through other transcriptional activators (36).

**NONCYCLOOXYGENASE TARGETS FOR ANTIPYRETICS**

Interestingly, clinically useful actions of antipyretics may also be COX independent (45), and relevant anti-inflammatory effects of aspirin, sodium salicylate, and other NSAIDs are seen only with doses much higher than those required to suppress COX activity (46). Thus, a variety of noncyclooxygenase-dependent functions have been proposed to explain the full effects of salicylates on the pyrogenic cascade (Table 2). For example, salicylates and other antipyretics also suppress tissue inflammation through diminished leukocyte-endothelial cell interactions (39), reduced pyrogenic cytokine production (38), or enhanced expression of anti-inflammatory molecules (45,47). Other mechanisms, such as boosting the activity of endogenous antipyretic messengers, may further contribute (Figure 3) (48). We consider each of these putative actions in turn.

**EFFECTS ON LEUKOCYTES AND ENDOTHELIAL CELLS**

Fever frequently begins with inflammation in peripheral tissues (Figure 1). Infectious and noninfectious diseases...
stimulate regional inflammatory reactions involving activated leukocytes and endothelial cells. Leukocyte adhesion to, and migration through, activated vascular endothelium can be inhibited by aspirin and other NSAIDs (32,39,46,49). Aspirin and sodium salicylate, for example, inhibit leukocyte accumulation at sites of tissue injury (50).

**Reduced Adhesion Molecule Expression**

Ibuprofen, a relatively nonselective COX inhibitor, inhibits neutrophil adherence, swelling, aggregation, and lysosomal enzyme release in high doses (51). Adherence of peripheral blood monocytes, basophils, and mast cells to pyrogen-stimulated human endothelial cells is also reduced by ibuprofen ($I_C_{50} 0.5$ mM) (49). This antipyretic reduces the expression of endothelial cell adhesion molecules (intercellular adhesion molecule-1 [ICAM-1] and vascular cell adhesion molecule-1 [VCAM-1]) upon cytokine stimulation, leading to depressed leukocyte attachment (49). Ibuprofen also suppresses leukocyte migration through cytokine-activated endothelial cell monolayers (52).

Expression of VCAM-1 or ICAM-1 in endothelial cells is also inhibited by sodium salicylate and aspirin, with associated defects in neutrophil adhesion and transmi-
gration through cytokine-stimulated endothelial monolayers (39,53). Additionally, human monocyte expression of ICAM-1 induced by lipopolysaccharide is inhibited by sodium salicylate (54). L-selectin, an adhesion molecule that mediates rolling of leukocytes along vascular endothelium, is rapidly shed from circulating neutrophils in response to treatment with aspirin and other NSAIDs (55).

Although the mechanism underlying the NSAID effect on leukocyte-endothelial cell adhesion is incomplete, the reduction in VCAM-1 and ICAM-1 expression is associated with reduced endothelial transcription, suggesting an effect on gene regulation (39,49). NF-κB can activate the expression of adhesion molecules (39). As noted above, inhibition of NF-κB may be an important mechanism of action for certain NSAIDs and salicylates. Tempering such a conclusion, however, is a human model of systemic endotoxemia that failed to show an effect of a single dose of aspirin on circulating endothelial and leukocyte adhesion molecule concentrations (56). Dose-response effectiveness in humans is unknown.

**Diminished Cytokine Production**

Cytokine production by cells of the immune system also can be inhibited by antipyretics. More than 30 years ago, it was demonstrated that endogenous pyrogen production by leukocytes could be reduced by salicylates (57). The intracellular events underpinning these results are now understood.

Macrophase production of the pyrogenic cytokine TNF is activated by inflammatory stimuli such as exposure to lipopolysaccharide. It has recently been observed that both aspirin and salicylate, at high therapeutic concentrations (1 to 3 mM), inhibit the transcription and

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**Figure 3.** Mechanisms of antipyresis. Antipyretics such as acetaminophen, aspirin, and related nonsteroidal anti-inflammatory drugs (NSAIDs) reduce fever by depressing inflammatory messages at both peripheral sites of tissue inflammation and within central nervous system thermoregulatory sites. Peripherally, aspirin and other NSAIDs suppress production of pyrogenic cytokines such as tumor necrosis factor and interleukin-1β and block endothelial cell/leukocyte interactions through effects on adhesion molecule expression. These agents also promote the creation of anti-inflammatory molecules such as adenosine and aspirin-triggered lipoxins. Centrally, antipyretics lower the thermoregulatory set point primarily by blocking cyclooxygenase production of prostaglandin E₂ (PGE₂). Additional effects may stem from provoking the release of endogenous antipyretic compounds such as arginine vasopressin. Acetaminophen differs from other antipyretic agents by its inability to reduce peripheral inflammation and its lack of effect on endogenous antipyretics.
secretion of TNF by murine macrophages exposed to lipopolysaccharide (38). Similar data were found in activated human endothelial cells exposed to sodium salicylate (39). Not surprisingly, NF-κB mediates enhanced TNF production. As noted, these agents interrupt NF-κB nuclear translocation through stabilization of cytoplasmic IκB (38). In agreement with these data, NF-κB activity in endotoxin-stimulated human monocytes is diminished by ibuprofen, sulindac, aspirin, and sodium salicylate (54).

The antipyresis of NSAIDs also involves the activation of the intracellular protein, heat shock factor-1 (HSF1). HSF1 is an activating polypeptide for the heat shock genes in many cell types that also acts as a repressor of IL-1β gene transcription (54). Millimolar doses of sodium salicylate and sulindac induce HSF1 activity and simultaneously reduce transcription of IL-1β in vitro (54).

Whether these effects on cytokine production have important clinical consequences remains unclear. The influence of antipyretics on circulating levels of pyrogenic cytokines has been studied in human volunteers after lipopolysaccharide injection. With respect to TNF and IL-6, both aspirin and acetaminophen have no effect on circulating levels (58), whereas ibuprofen either does not affect or increases cytokinemias in this model (59–61). Importantly, the intravenous injection of endotoxin provokes a tremendous systemic inflammatory response not characteristic of most fever-producing diseases. Clinical studies of localized inflammation are necessary to further evaluate the effects of antipyretics on peripheral cytokine generation.

Stimulation of Anti-inflammatory Mediators

Another hypothesis explaining the impaired leukocyte adhesion or accumulation seen with aspirin and salicylate during inflammation involves the anti-inflammatory mediator adenosine. Aspirin and sodium salicylate cause leukocytes to produce adenosine at sites of inflammation, and the effect can be reversed by endogenous adenosine deaminase (45,50,53). Adenosine is an autacoid that some investigators believe mediates the immunosuppressive effects of methotrexate and sulfasalazine (62). In general, salicylates promote the breakdown of intracellular adenosine triphosphate (ATP) and extracellular release of adenosine (53). Adenosine acts through four known receptors and inhibits polymorphonuclear leukocyte adherence, superoxide generation, phagocytosis, and secretion (63). The adenosine-mediated effects of salicylates may represent an important anti-inflammatory mechanism for this class of agents.

Another hypothesis regarding aspirin’s ability to inhibit leukocyte function involves alterations in eicosanoid biosynthesis independent of PGE₂ (64). Aspirin inhibits COX-2 through an irreversible acetylation reaction. In so doing, traditional COX-2 activity is shifted to produce 15R-hydroxyeicosatetraenoic acid from arachidonic acid (64). Human neutrophils are able to use this compound to make 15-epi-lipoxin A₄ and 15-epi-lipoxin-B₄ (47,64). These compounds are known as aspirin-triggered lipoxins (ATL) and share physiologic properties with the endogenous enantiomers lipoxin A₄ and lipoxin B₄ (47). ATLs display potent anti-inflammatory effects and interrupt neutrophil chemotaxis, transmigration through endothelial and epithelial cell layers, and diapedesis from postcapillary venules (47). Recently lipoxin A₄ analogs were shown to inhibit adhesion of human neutrophils to endotoxin-activated endothelial cells (65).

EFFECTS ON ENDOGENOUS ANTIPYRETICS

Enhancing the production of the body’s own antipyretic mediators would appear to be a useful method for reducing fever. As noted, hormones such as hypothalamic AVP (5), α-melanocyte stimulating hormone, and glucocorticoids are capable of buffering the magnitude of the febrile response. AVP participates in the antipyretic mechanisms of salicylates and related NSAIDs, but not acetaminophen (48,66,67). The antipyretic effect of sodium salicylate and indomethacin is blocked by administration of an AVP V₁-receptor antagonist (48,66). Interestingly, the degree of fever inhibition by acetaminophen is not influenced by V₁-receptor blockade. In fact, the antipyretic response to indomethacin in rats is accompanied by an increase in hypothalamic AVP, whereas acetaminophen does not alter central AVP concentrations (67).

The epoxycosanoids are a class of endogenous antipyretic compounds that may facilitate the action of fever-suppressing medications. These substances are derived from arachidonic acid not by COX but by cytochrome P-450 mono-oxygenase enzymes. It has been postulated that aspirin enhances the effect of epoxycosanoids through induction of cytochrome P-450 isoforms (20).

Acetaminophen

Acetaminophen is an analgesic that deserves special comment because it is an effective febrifuge but a weak anti-inflammatory drug (68). Its effects differ considerably from salicylates and other NSAIDs. As opposed to aspirin, acetaminophen is a poor inhibitor of platelet function. Believed to be an inhibitor of cyclooxygenase, acetaminophen’s mechanism of action is still poorly understood. Although suprapharmacologic doses of acetaminophen inhibit NF-κB stimulation of inducible nitric oxide synthase (44), it does not possess the same inhibitory effects on NF-κB–mediated gene transcription that salicylates enjoy (38).

Explanation of the antipyretic and analgesic actions of acetaminophen has been based on tissue-specific COX
inhibition not seen with NSAIDs (31). Acetaminophen penetrates the blood-brain barrier, achieving cerebrospinal fluid levels comparable to those in serum (69), and may act preferentially within the central nervous system (31). Central nervous system levels of PGE₂ rise during fever and fall to normal levels upon administration of the drug (70). Acetaminophen reduces the production of prostaglandins in brain preparations more potently than it does from other organs such as spleen (31,71).

In certain cell lines, acetaminophen weakly inhibits COX-1 more than COX-2, but it is a poor inhibitor of either isoenzyme (72,73). The in vitro anti-COX activity of acetaminophen depends on the availability of cofactors such as glutathione and hydroquinone (73). Unlike the majority of other NSAIDs, acetaminophen requires an environment low in peroxides in order to inhibit COX activity (74,75). Neurons may fulfill this requirement, but inflamed peripheral tissues are flooded with leukocytes that generate cellular peroxides (75). Thus, the tissue specificity of acetaminophen may reflect the intracellular balance or availability of cofactors or inhibitors (73).

THE USE OF ANTIPYRETICS

Although the complex biochemistry of antipyretics is increasingly understood, their indications for use are not. Despite the pervasive application of antipyretics by physicians, nurses, pharmacists, and parents, it remains unclear whether reducing the core temperature benefits febrile patients (2). Animal models of infection demonstrate that fever plays an important role in host defense (23,76), and the potential salutary role of pyrexia in disease has been reviewed elsewhere (76,77).

There are certain groups of patients for whom antipyretics are routinely used out of concern that the risks of fever may outweigh its benefit. One such group is children. Febrile seizures occur with a frequency of 2% to 5% in children between 6 and 36 months of age (78). The majority of children with febrile seizures have temperatures above 39.0°C at the time of convolution (78). Prophylaxis against febrile seizures of childhood has been supported by many. A recent controlled trial using ibuprofen to prevent recurrent febrile seizures failed (79), however, as has acetaminophen (80).

Another group of patients felt to be at risk from the deleterious effects of fever includes those with underlying cardiopulmonary disorders (2). The metabolic cost of fever is substantial, particularly during the chill phase of thermogenesis (2). Although antipyretics, by reducing this metabolic burden, could help patients with important cardiopulmonary disease, there are no experiments to support this view (2). In fact, nearly 20 years ago, indomethacin given to patients with serious coronary artery disease decreased coronary blood flow, prompting the authors to warn that indomethacin should be used cautiously for patients with severe anginal symptoms (81). It has also been observed that the repetitive sweating of patients treated intermittently with antipyretics may contribute to unwanted reductions in intravascular volume (82). That has led some to suggest dosing antipyretics on a scheduled basis rather than pro re nata (2,82).

Perhaps the most common rationale for dispensing antipyretics is providing comfort. However, febrile patients feel ill not simply because of an elevated temperature. In fact, an elevated body temperature per se may not be particularly noxious, as evidenced by the popular use of recreational saunas and hot tubs. Much of the discomfort during sickness arises from the symptoms accompanying the inflammatory response. Focal symptoms such as cough, abdominal pain, and back pain can be disconcerting, as can generalized symptoms such as anorexia, arthralgias, headache, nausea, malaise, and myalgias. As a consequence of additional anti-inflammatory and analgesic characteristics, agents such as acetaminophen, aspirin, and other NSAIDs are capable of mollifying many of these other somatic symptoms.

Fever, of course, is a surrogate marker for disease activity in many infectious and inflammatory disorders. Squelching the febrile response removes a clinically important indicator of therapeutic efficacy. A small pediatric study, for example, demonstrated that appropriate changes in antibiotic regimens were delayed for children receiving antipyretics compared with those who were not (83).

Although some antipyretics depress the host immune response to infection, evidence is sparse that these medications adversely affect the outcome of febrile illnesses in humans. Animal models of infection show that antipyretic therapy increases the morbidity and mortality of the host (77). Human studies, although much less controlled, suggest the same (84–88). The notion that antipyretics depress the immune response to bacterial infections dates to the mid-1960s when the activation of latent infection was reported in patients after the use of NSAIDs (89). Twenty years later, the development of fulminant necrotizing fasciitis and a 36% mortality rate were reported among previously healthy persons exposed to therapeutic doses of NSAIDs (84,87). In contrast, 48 hours of intravenous ibuprofen in a large trial of patients with sepsis did not affect the incidence of organ failure or mortality at 30 days (90). Interestingly, ibuprofen treatment drastically reduced mortality among septic patients who were hypothermic (91). This seemingly paradoxical increase in survival (from 10% in the placebo-treated group to 46% in the ibuprofen-treated group) is not understood but perhaps related to the suppression of overwhelming inflammation by the NSAIDs.

Viral infection may also be affected by antipyresis. A randomized trial with acetaminophen prolonged the
time to crusting of lesions in childhood varicella (85). Aspirin increases the rate of virus shedding in patients with rhinovirus-related common colds (88). It is notable that IL-6 appears to modulate the host response and symptom development after rhinovirus infection (92). Rhinovirus stimulation of host IL-6 expression occurs through an NF-κB–mediated pathway (92). If the suppressive effect of aspirin on NF-κB activity is found to occur in humans, this might explain the agent’s ability to augment viral shedding. Studies of parasitic disease also indicate that acetaminophen may lengthen the host response to malaria in children (86).

Finally, similar to many other pharmaceuticals, antipyretics also possess both direct and indirect toxicities. N-acetylimidoquinone, a metabolite of acetaminophen, has intrinsic hepatotoxic effects, particularly when the recommended dose of the parent compound is exceeded or the patient coingests other hepatotoxins such as ethanol. Concomitant use of medications, such as rifampin and phenytoin that induce the cytochrome P-450 enzyme system, may potentiate toxicity through enhanced metabolism of acetaminophen to N-acetylimidoquinone. NSAIDs, particularly those with substantial COX-1 inhibitory effects, are also potentially damaging to the kidneys and gastrointestinal tract (93). A thorough review of the potential adverse effects of these medications is beyond the scope of this discussion.

RECOMMENDATIONS FOR THE USE OF ANTIPYRETICS

If antipyretic effects were truly limited to reducing fever, their use might be appropriate in few circumstances. For example, treating fever in patients with underlying cardiopulmonary disease might be reasonable, as discussed above, assuming these patients cannot tolerate the dilatatory effects of pyrexia (2,82). Patients suffering from noninfectious febrile diseases (such as malignancy or autoimmune phenomena) might also be given antipyretics in an effort to reduce their catabolic rates. Unfortunately, data are not available to assess the efficacy of such practices.

Considering that fever may be an important window to clinically relevant information, one approach to treating acute febrile illnesses is to use alternative, nonantipyretic medications for analgesia and symptom relief. Unfortunately, few substitutes are available apart from oral narcotics such as codeine, hydrocodone, and oxycodone, which are controversial. If antipyretics are used during acute fevers, they should be prescribed on a scheduled basis, as opposed to “as needed,” for reasons noted above. Of course, this approach requires careful attention to the potential adverse effects induced by the antipyretic agents themselves. Examples of scheduled regimens for common antipyretic medications are listed in Table 3.

Deciding on a particular antipyretic also necessitates considering toxicities and comorbid conditions. Predicting temperature-lowering response to a given agent is difficult. Although many “head-to-head” trials of antipyretics have been performed in pediatric groups, few data exist for adults (58). On balance, pediatric studies demonstrate equal efficacy, on a milligram-for-milligram basis, between acetaminophen and aspirin in reducing fever (94). The ability of ibuprofen to decrease fever in children, on the other hand, appears to be 50% to 100% more potent than that of acetaminophen (95). Adult trials are conflicting, although a recent single-dose study with endotoxin-challenged volunteers suggests that acetaminophen is superior to aspirin for endotoxemia (58).

SUMMARY

The antipyretic effects of acetaminophen, aspirin, and other NSAIDs are complex and repress inflammatory signals at many levels. Although COX enzyme inhibition plays a central role in the antipyretic actions of these drugs, other immunomodulatory actions appear to contribute. As our understanding of these medications deepens, indications for their use in treating febrile patients may also change.

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