

Fever—An Update

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Fever is an active yet nonspecific response of the body to infections and other insults that cause immune cells to release cytokines, resulting in a brain prostanoid-mediated rise in body temperature. The causes, types, clinical management, and postoperative consequences of fever are reviewed in this article. Physicians use fever as a clinical sign for diagnoses and prognoses, but “fevers of unknown origin” continue to be problematic. Fevers that arise 1 or 2 days after surgery are usually due to stress and trauma, but later postoperative fevers often have more serious causes and consequences, such as wound infection. Fever is commonly encountered by podiatric physicians and surgeons, and certain procedures with the lower extremity are more likely to eventuate in fever. (J Am Podiatr Med Assoc 100(4): 281-290, 2010)

Fever, characterized as a temporary elevation in internal body temperature to levels approximately 1° to 2° C (2°–4°F) higher than the body’s thermoregulatory set point, is one of the body’s innate immune responses to neutralize a perceived threat inside the body, be it bacterial or viral. Fever has been recognized as a sign of infection since ancient times, and the courses of fever as observed by Hippocrates around 400 BC are generally valid to this day.¹ The purpose of this review is to present a modern view of the causes and types of fever, its clinical management, and the role of antipyretic drugs in combating fever.

Human temperature is regulated in the hypothalamus, specifically, the anterior hypothalamus/preoptic region, and it remains fairly constant at approximately 37°C (98.6°F). It is theorized that the anterior hypothalamus/preoptic region integrates sensory information from thermosensitive neurons, analogous to a household thermostat with a “set point”; however, more recent models incorporate multiple decentralized feedback loops without a unitary set point.² The anterior hypothalamus/preoptic region initiates shivering, vasoconstriction, piloerection, and secretion of thyroid-releasing hormone in response to us sensing a cold environ-

ment. Conversely, vasodilation and sweating are initiated in response to heat.³

Body temperatures can rise above the reference range because of either hyperthermia or fever. Hyperthermia is passive, occurring when a person either gains heat from a hot environment or is unable to lose heat from exercise. Hyperthermic patients will attempt to vasodilate and will move to a cooler environment. Fever on the other hand, occurs when a febrile person’s body actively warms itself in response to microbial or other threats. At the onset of a fever, biochemical signals “reset the thermostat” in the hypothalamic centers to stimulate vasoconstriction, shivering, and warmth-seeking behaviors (eg, adding blankets). Once the body reaches an above-normal temperature, thermoregulation will continue until the fever breaks, when thermoregulatory centers actively return body temperature to the normal set point level via sweating, vasodilation, and behavioral means. Unlike hyperthermia, which is an uncontrolled rise in body temperature,⁴ fever is a deliberate, active thermoregulatory strategy.

Biochemical and Neurologic Features of Fever

When the body encounters infectious microbes and other insults, the immune system first counteracts with innate immune defenses such as the nonspecific “acute-phase response” to infection that includes fever. Infective invaders attract macrophages and other defense cells, which, in turn, release small proteins called cytokines that amplify the immune

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response. Cytokines that can cause fever are referred to as endogenous pyrogens to distinguish them from microbial exogenous pyrogens. Cytokines activate the early nonspecific immune responses, such as fever, lethargy, anorexia, adipisia, behavioral alterations, and the manufacture of hepatic acute-phase proteins. Later, the adaptive immune system, using B and T lymphocytes, challenges the specific infecting entities.

Research in the past three decades has uncovered a large number of cytokines, many of which have redundant actions, that have different actions in different parts of the body and that stimulate or inhibit one another. Cytokines are small protein signals that bind to receptors on many cell types. Although many humoral regulators have pyrogenic activity,⁵ most research has focused on four inflammatory cytokines: tumor necrosis factor and lymphotoxin alpha, interleukin 1 (α and β), interleukin 6, and interferon (α and γ).⁶ All of these cytokines can independently cause fevers when injected into experimental animals or patients with cancer in clinical trials. However, during the course of infection, microbial exogenous pyrogens may induce the cytokines in a cascade fashion. Gram-negative bacterial lipopolysaccharide, for example, induces tumor necrosis factor from macrophages, which, in turn, induces interleukin 1 β , which then induces interleukin 6.⁷ The exact pathway may vary depending on whether the initiator is a local inflammation, a systemic infection, or an infection in the blood-brain barrier.^{8, 9} Many investigators use rodents injected with lipopolysaccharide as a model, wherein a biphasic fever results. Some researchers¹⁰ suggest that the early phase of fever in rats bypasses cytokines and that the immune cells directly synthesize prostaglandin E₂, which then carries the signal to the brain. Others¹¹ hypothesize that lipopolysaccharide activates a complement component, C5a, which causes liver and lung macrophages to elaborate prostaglandin E₂, which, in turn, binds to prostaglandin receptors on sensory vagal nerves, and that the vagus is the afferent path to the brain for early-phase fever. Most investigators concede that the later phase of rodent fever is cytokine mediated and that having several paths to the brain thermoregulatory centers provides the animal with better defense.⁷ Controversy also exists about whether cytokines, which cannot diffuse across the blood-brain barrier, send their signals by being actively transported across, by entering those regions of the brain near the third ventricle that do not have the barrier, or by binding brain endothelial or perivascular cells, which then use a chemical second messenger to signal the

hypothalamus.⁷ Although there may be several routes to the hypothalamus, the common pathway to fever involves release of prostaglandin E₂ in the brain,^{7, 12} where it binds a specific prostaglandin E₂ receptor on preoptic hypothalamic neurons.¹³ Finally, those hypothalamic neurons have an efferent path to the raphe nucleus of the medulla,^{14, 15} which triggers the sympathetic nervous system to vasoconstrict skin blood vessels.

In theory, higher concentrations of pyrogenic cytokines should cause higher fevers, but that dosage effect could not be confirmed by experiments.¹⁶ Unlike hyperthermias, true fevers rarely exceed 41°C (105.8°F),¹⁷ which is crucial because damage to mammals occurs at temperatures higher than 42°C (107.6°F).¹⁸ The magnitude of fever may be limited by natural substances referred to as endogenous antipyretics or endogenous cryogens. Arginine vasopressin,¹⁹ α -melanocyte-stimulating hormone,²⁰ atrial natriuretic peptide,²¹ and corticotropin-releasing hormone are all peptides that suppress fevers caused by lipopolysaccharide in rodents. The immune system has many regulatory mechanisms to prevent overaggressive responses, such as autoimmunity; endogenous antipyretics may provide negative feedback limitations on the fever response. Physicians who prescribe anti-inflammatory corticosteroids should note that glucocorticoids also are endogenous antipyretics.²²

Types of Fever

The most common cause of fever is infection, especially bacterial. Gram-negative bacteria have a complex lipopolysaccharide in their cell walls that is a potent exogenous pyrogen, acting at levels of 2 to 3 ng/kg to induce endogenous pyrogens and fever.⁶ Lipopolysaccharide produces septic shock, with signs of fever (or hypothermia at high doses), chills, hypotension, coagulopathy, and death. Unlike the adaptive immune system, the innate immune system cannot mount a response highly specific to a foreign antigen but instead can use “pattern recognition receptors” that bind to molecules with a common pattern in a given class of microorganisms. The toll-like receptors include one (toll-like receptor 4) that seems to be the receptor for bacterial lipopolysaccharide.²³ When toll-like receptor 4 on peripheral immune cells binds lipopolysaccharide, it recruits intracellular kinases and transcription factors for many inflammatory and immune-responsive genes, including those for cytokines.²⁴ Furthermore, toll-like receptors are also found on endothelial cells in the brain, so bacterial

infections or lipopolysaccharide itself can also directly stimulate fever by an alternate, cytokine-independent path.²⁵ In addition to lipopolysaccharide, gram-positive bacteria, mycobacteria, fungi, and viruses can also provoke fevers. Many other substances can act as pyrogens, including artificial polynucleotides, urate crystals, colchicine, inflammatory bile acids, plant lectins, and antigen-antibody complexes.²⁶

Fevers can also develop in patients who do not have microbial infections. Collagen vascular diseases, autoimmune diseases, and granulomatous diseases are often associated with cytokine-mediated fevers. For example, nearly all patients with adult Still's disease are febrile.²⁷ Rheumatoid arthritis causes tissue injury and the release of cytokines responsible for inflammation and joint destruction.²⁸ Recently, patients have been receiving monoclonal antibodies that inactivate cytokines as therapy for Crohn's disease, rheumatoid arthritis, and psoriasis. Infliximab and etanercept are anti-tumor necrosis factor antibodies approved by the Food and Drug Administration for treating rheumatoid arthritis.²⁹ Dinarello and Porat⁶ caution that these patients are at risk for opportunistic infections and that it is uncertain whether fever as a clinical sign of infection is partially masked by this therapy.

Less commonly, central fevers or neurogenic hyperthermias can arise from traumatic, surgical, or hemorrhagic harm to the thermoregulatory regions of the brain.³⁰ Fevers also result from psychogenic,^{31, 32} toxic,³³ neoplastic,³⁴⁻³⁶ and factitious causes.

Fever of Unknown Origin

Fever always has a cause, but if that cause cannot be easily diagnosed, it is said to be of unknown origin until a definitive diagnosis can be made. One standard definition of fever of unknown origin is illness longer than 3 weeks, fever higher than 38.3°C (100.9°F) on several occasions, and unsuccessful attempts at diagnosis after 3 days of testing in the hospital.^{37, 38} When physicians eventually determine fever of unknown origin causes, the most common are infection, neoplasia, noninfectious inflammatory diseases, and miscellaneous causes.³⁹ Fever of unknown origin is usually caused by common diseases with unusual presentations, although more than 200 individual causes of fever of unknown origin have been tabulated.⁴⁰ Nonspecific early treatment of patients with fever of unknown origin is rarely curative and may obscure the final diagnosis, yet many physicians use empiric antibiotic drug therapy preemptively to avoid more costly

and prolonged diagnostic tests. Most fevers resolve after 4 to 5 weeks without further consequences.⁴¹

A common cause of fever of unknown origin is drug fever, affecting as many as 3% to 5% of hospitalized patients.⁴² Drug fever is likely if a patient has no infection or disease and if a 72-hour suspension of all medication administration causes the fever to abate. Drugs cause fevers by hypersensitivity reactions, injection-related effects, cytokine release, alteration of thermoregulation, or idiosyncratic causes.⁴² The most likely candidates are sympathomimetics and monoamine oxidase inhibitors, dopamine and acetylcholine blockers, serotonergic agonists, uncouplers of oxidative phosphorylation, inhalation anesthetics,⁴³ and antibiotics, especially sulfonamides. Clinical signs and symptoms of drug-induced fever include a temperature of 39° to 41° C (102.2°–105.8° F), no myalgia, relative bradycardia (pulse-temperature dissociation), and the "patient appears inappropriately well for the degree of fever present."⁴⁴ (p125) The treatment for drug fever is immediate discontinuation of any suspect medications or, if necessary, switching to a nonsensitizing alternative. Several drug fevers are actually hyperthermias because body temperatures are not diminished by antipyretics and can rise to fatal levels. Two clinically similar but not identical examples are neuroleptic malignant syndrome, a rare adverse effect of antipsychotic drugs that lowers dopamine levels, and serotonin syndrome, a rare consequence of taking antidepressants that elevates serotonin levels.⁴⁵ Cases of serotonin syndrome with fatal outcomes have been reported for recreational use of MDMA (3,4-methylenedioxymethamphetamine, or "Ecstasy") and similar compounds, with hyperthermias of 42°C (107.6°F) on admission.⁴⁶ The high temperatures and muscle rigidity of neuroleptic malignant syndrome are similar to those of malignant hyperthermia, but malignant hyperthermia is acute, whereas neuroleptic malignant syndrome occurs after drug exposure of days to weeks, and neuroleptic malignant syndrome has no genetic predisposition.⁴⁷ Physicians who treat patients in locations where antipsychotic or antidepressant drugs are often used, such as nursing homes, hospitals, and psychiatric facilities, should have a high index of suspicion for neuroleptic malignant syndrome or serotonin syndrome when body temperature is elevated.⁴⁸

Diagnosis and Clinical Management of Fever

Local signs and symptoms can often help diagnose infectious and inflammatory causes of fever (eg,

appendicitis or gout). In cases in which clinical signs and symptoms are absent, such as mononucleosis and typhoid, fever itself may be the only clue. It is, therefore, imperative to chart fever patterns and fluctuations throughout the day.³⁸ Some diseases have characteristic patterns such as intermittent (hectic), sustained, remittent, or double quotidian fevers. Fever associated with leishmania, for example, has two peaks per day. Although Musher et al⁴⁹ and others have questioned the diagnostic value of reading fever patterns, Woodward⁵⁰ noted that diseases with unusual fever patterns, such as Rocky Mountain spotted fever, can be preliminarily diagnosed while awaiting slower and more costly laboratory tests.

Regarding thermometry, clinicians should ideally know the calibrations and limitations of the instrument and its sources of error.⁵¹ There is considerable debate about modern tools that are convenient but that may be inaccurate in the clinical setting.⁵² Clinicians should also be aware that body temperature varies by site, time of day, and method of measurement. Furthermore, the commonly accepted benchmark of normalcy, 37°C (98.6°F), was based on Wunderlich's 19th century study; Mackowiak et al,⁵³ using modern thermometry, recommended a slight alteration to 36.8°C (98.2°F) and fever thresholds of 37.2°C (99.0°F) in the early morning and 37.8°C (100.0°F) in the evening.

Differential diagnosis of patients with fevers can be aided with algorithms. Diagnostic clues should include the characteristics and patterns of fever, medical and social history, laboratory and imaging information, underlying diseases (such as human immunodeficiency virus or pneumonia), and patient characteristics/risk factors (elderly, critically ill, or immunosuppressed).⁵⁴ Cunha⁵⁵ categorized fevers seen in hospitals into two categories: diseases causing fever peaks lesser than or greater than 39°C (102°F). Body temperatures higher than 41°C (106°F) rule out infectious causes.

Childhood fever is the most common reason for a nonroutine visit to the pediatrician's office.⁵⁶ One survey found that many parents have "fever phobia," which is exacerbated by inconsistent educational messages from pediatricians.^{57, 58} Two issues are important: the risk of febrile convulsions and antipyresis for patient comfort during routine infections. Children aged 9 months to 5 years have a 3% to 4% incidence of febrile convulsions, causing acute parental anxiety.⁵⁹ Modern clinical management recognizes that most febrile seizures are benign and do not require immediate or prophylactic use of anticonvulsants.⁶⁰ However, many physicians still

recommend antipyretic treatment of fevers in children younger than 3 years as prophylaxis against febrile seizures despite the lack of definitive evidence that temperature reduction per se will stop a seizure or prevent a rapid recurrence.⁶¹ Although it is generally believed that fever itself causes convulsions, there is no conclusive evidence of this in the literature.^{62, 63} It may be that convulsions are triggered by other concomitants of infection besides temperature elevation. Prophylactic use of antipyretics is of questionable value for routine febrile illnesses.^{64, 65}

Elderly people develop fevers upon infection, but as many as 30% of them are afebrile, especially if they are frail, and in others, the fever magnitude is blunted.⁶⁶ However, experimental and clinical evidence is equivocal about whether fever diminishes with age.³⁰ If fever is one of the defenses against infection, then its absence may lead to greater morbidity and mortality in afebrile infected patients. Furthermore, its absence as a sign may mean that the doctor or patient may not recognize the infection early enough. Certain disorders with fevers are more common in elderly patients such as tuberculosis, colon cancer, polymyalgia rheumatica, and others.⁶⁷

Antipyretic agents may reduce the rise in temperature during a fever, but they do not affect those who are afebrile or hyperthermic. Three common drugs prescribed for antipyresis are aspirin (acetylsalicylic acid), acetaminophen, and nonsteroidal anti-inflammatory drugs. Acetylsalicylic acid and its congeners act by inhibiting the cyclooxygenase enzyme in the arachidonic acid pathway to prostaglandin formation.⁶⁸ Schwartz et al⁶⁹ used the cyclooxygenase 2 inhibitor rofecoxib to demonstrate that the inducible isoform of cyclooxygenase (cyclooxygenase 2) is responsible for fever. The cyclooxygenase 2 isoform is normally quiescent but can be induced by inflammatory signals, such as lipopolysaccharide, interleukin 1, or interleukin 6, whereas the cyclooxygenase 1 isoform is constitutively active to perform housekeeping functions such as gastric protection and renal function. Acetylsalicylic acid and many of the nonsteroidal anti-inflammatory drugs nonspecifically inhibit the cyclooxygenase 1 and cyclooxygenase 2 isoforms, resulting in gastric, renal, and clotting adverse effects, which are avoided by the specific cyclooxygenase 2 inhibitors, such as rofecoxib, valdecoxib, and celecoxib. However, their cardiac and renal adverse effects have led to the scrutiny of all three drugs, and rofecoxib has been withdrawn from the market by the Food and Drug Administra-

tion.⁷⁰ The exact mechanism of action of acetaminophen is still unclear; the acetaminophen-sensitive isoform of cyclooxygenase (cyclooxygenase 3) found in some animals apparently has no role in humans.⁷¹ Recent research into antipyretics has been targeting the prostaglandin E₂-synthesizing enzyme downstream of cyclooxygenase.⁷² Nonetheless, the analgesic and antipyretic properties have not been separated for any of these drugs. Thus, it is sometimes difficult to ascertain which property a physician is prescribing for.

According to surveys, many health-care professionals consider fever itself to be harmful.⁷³ In a retrospective study, Isaacs et al⁷⁴ found that antipyretic orders in a hospital were often written without a documented rationale. A national survey of nurses revealed that 77% initiated treatment specifically to reduce fevers, which was consistent with nursing texts but not necessarily the research literature.⁷⁵ Styrt and Sugarman⁷⁶ suggested that antipyresis should be ordered much less frequently and with greater justification. Although antipyresis by pharmacologic agents or physical cooling is common for intensive care unit patients with fevers, there is little effect on outcomes,⁷⁷ and the common practice of physically cooling critically ill febrile patients with underlying cardiovascular disease might trigger a harmful cold pressor vasospasm.⁷⁸ However, antipyresis does seem to benefit severely ill septic patients⁷⁹ or those with brain injury.⁸⁰

The risks versus benefits of antipyretic treatment are a topic of debate. Zoologists argue that fever has a long evolutionary history as an infection-fighting mechanism, so fever should not be abrogated by antipyretics.⁸¹ This argument is bolstered by abundant in vitro evidence that the immune system is enhanced at the temperatures of moderate fevers,^{82, 83} although fevers higher than 41°C (105.8°F) can hinder immune responses.⁸⁴ On the other hand, practicing clinicians argue that antipyretic drugs alleviate the pain and discomfort that accompany fever and that more than 100 years of antipyretic drug use has proved relatively benign.⁸⁵ Fever brought on by an infection is associated with other symptoms of the acute-phase response such as irritability, poor appetite, malaise, and pain. Because the common antipyretics are also analgesics, physicians often recommend them to relieve these symptoms. This rationale is especially compelling for sick children. Because of the risk of Reye's syndrome with acetylsalicylic acid, children are usually treated with ibuprofen or acetaminophen,⁸⁶ despite surveys revealing that many parents are unaware of the latter's hepatotoxicity.⁸⁷

Several studies^{88, 89} question acetaminophen's efficacy on the outcome of common childhood infections. An editorial in *The Lancet* argued that because there was no strong evidence that antipyresis affects childhood illness, non-acetylsalicylic acid antipyretics should be given to sick children "to relieve the child's discomfort and thereby anxiety in the parents."⁹⁰ In 2007, Powell^{91(p1086)} recommended no antipyretic therapy for fevers under 39°C (102.2°F), although it may provide "symptomatic" relief for higher fevers and may reduce the metabolic demands of fever in high-risk children with cardiovascular, diabetic, or neurologic diseases.

In frail elderly patients, antipyretic therapy is occasionally recommended to relieve mental delirium and to obtund the high metabolic demands put on the cardiovascular and respiratory systems by higher temperatures.⁶⁷ However, physicians must be careful about pharmacokinetics and the gastrointestinal and other adverse effects of antipyretic drugs in aged patients.⁷³

Plaisance and Mackowiak⁷³ concluded that antipyretics carry a low risk of toxic effects, so they can be used for symptomatic relief and analgesia in febrile patients, for reduction of the metabolic demands of fever in chronically debilitated patients, and for alleviation of mental confusion in febrile elderly patients. They recommended that prescribing physicians should be aware of the toxic effects of each antipyretic, and they noted that antipyresis could prolong some infections.

Surgery and Fever

Perioperative fevers are not uncommon in patients who undergo the stress and trauma of surgery and who may be exposed to various infectious and inflammatory insults. Preoperative fever is a reason to cancel elective surgery. During the operation itself, general anesthesia and, to a lesser extent, neuraxial anesthesia hinder thermoregulatory centers in the brain, and the concomitant use of paralyzing drugs inhibits shivering thermogenesis.⁵¹ In fact, most patients become hypothermic during surgery, and Kurz et al⁹² found that patients who were artificially warmed to near 37°C (98.6°F) during surgery developed fewer infections and had shorter wound-healing times than the hypothermic (35°C [95.0°F]) control group. Postoperative fevers are a particular problem with the recent frequency of outpatient surgeries because the fever may develop outside the view of medical professionals. Postoperative fever that develops within 24 hours of surgery most likely is caused by interleukin 6

released by stress and tissue damage.⁹³ With a few rare exceptions, most early postoperative fevers are not due to infections, and Frank et al⁹³ recommended that fever alone not be used as the basis for ordering costly diagnostic tests to locate infections. Table 1 lists some of the common causes of fever that occur in the days following surgical procedures. In general, fever developing within 2 to 3 days postoperatively is likely caused by urinary tract infections or respiratory difficulties. Contrary to earlier beliefs, surgeons do not find a relationship between early postoperative fever and atelectasis.⁹⁴ Fevers that develop after 72 hours are likely due to wound infections, bladder catheter infections, or leaky surgical anastomoses.⁹⁷ Fever caused by deep venous thrombosis can occur as late as 5 to 7 days postoperatively, but fever is a poor predictor of deep venous thrombosis.⁹⁸ The trauma of surgery can trigger acute gout attacks, always with fever, within 8 days after surgery.⁹⁹ In the intensive care unit, fevers often have multiple causes, including sinusitis caused by irritation from nasogastric tubes, infection of vascular and urinary catheters, and ventilator-associated pneumonia.¹⁰⁰ The latest consensus from the Critical Care Medicine and Infectious Disease groups recommends careful assessment of new fevers in patients in the intensive care unit rather than automatic orders for radiologic and laboratory tests.¹⁰¹ Because 40% of postoperative fevers resolve spontaneously,¹⁰² there is little need for antipyretics and physical cooling, and the latter increases the metabolic rate, activates the autonomic nervous system, and provokes thermal discomfort.¹⁰³ However, surgeons may treat some patients with high fever who cannot tolerate the hypermetabolic demands.

Although not a true fever, malignant hyperthermia is a rare condition that may arise when some surgical patients are anesthetized with inhalation anesthetics and depolarizing muscle relaxants,

especially halothane and succinylcholine.¹⁰⁴ Fulminant incidents of malignant hyperthermia were often fatal in the 1960s, but deaths are now rare in developed countries because of better awareness, earlier diagnoses, and better therapy.^{105, 106} Nonetheless, the incidence of malignant hyperthermia in the United States has increased in recent years.¹⁰⁷ Human genetic analyses and biochemical research with a porcine animal model have found that susceptibility to malignant hyperthermia is most often due to autosomal dominant mutations in a sarcoplasmic reticular muscle protein that releases calcium ions into the cytoplasm.¹⁰⁸ High intracellular calcium levels and adenosine triphosphate depletion account for the clinical signs of malignant hyperthermia: hypermetabolism, hypercarbia and acidosis, rigidity, tachycardia, high fever, desaturation of blood in the operating field, and elevated serum creatine phosphokinase levels.¹⁰⁹ In fulminant cases, temperature can rise at a rate of 1° to 2° C (2°–4°F) every 5 min and can reach 46°C (115°F).⁴⁷

Malignant hyperthermia can be prevented by avoiding trigger agents such as halogenated inhalation anesthetics, including halothane, enflurane, sevoflurane, desflurane, isoflurane, chloroform, and trichloroethylene, and the depolarizing muscle relaxant succinylcholine. Medications considered safe are barbiturates, intravenous anesthetics, narcotics (opioids), tranquilizers, nondepolarizing muscle relaxants, and local anesthetics. In 1989, Rosenberg and Seitman⁴⁷ noted that there had been no recorded deaths from malignant hyperthermia when the anesthesia team was aware of the problem, and, thus, they recommended that preoperative management of susceptible patients include a careful patient and family history and reassurances to the patient. Acute malignant hyperthermia can be treated by protocols that require discontinuing all triggering agents and then counteracting the hyperthermia, hypercarbia, hyperkalemia, etc.¹¹⁰ A labeled malignant hyperthermia cart in the surgical area should facilitate further treatment, including hyperventilation with 100% oxygen, administration of dantrolene, bicarbonate for acidosis, external and internal cooling, and monitoring and treating blood pressure, blood gases, urine output, hyperkalemia, dysrhythmias, and blood enzyme levels.¹¹¹ Dantrolene is a muscle relaxant that acts to reduce calcium release from sarcoplasmic reticulum,^{112, 113} and it has been approved by the Food and Drug Administration since 1979 for the treatment of malignant hyperthermia.

Table 1. Time Courses for Postoperative Fevers^a

Time After Surgery	Causes of Fever
Day 1	Systemic inflammatory response syndrome (SIRS)
Days 2–3	Respiratory problems
Days 3–5	Urinary tract infection (bladder catheter infection)
Days 4–7	Wound infection, deep venous thrombosis, acute gout
Days 5–8	Drug fever

^aThis table is based on Fischer,⁹⁷ Dayton,⁹⁵ and Bal-
lestas.⁹⁶

Fever and Podiatric Medicine

Fever in podiatric medical practice is most likely to be encountered in patients with postoperative or ulcerative infections of the lower extremities.¹¹⁴ Infectious fevers may also result from osteomyelitis, cellulitis, infected wounds, trauma, and other diseases. Several of the collagen vascular diseases or autoimmune diseases with lower-extremity manifestations, such as rheumatoid arthritis and erythema nodosum, can cause fevers. Inflammatory conditions of peripheral joints result in fevers; Duff et al¹¹⁵ attributed the fever of gout to the release of interleukin 1. Patients under podiatric medical care are also susceptible to fevers of unknown origin, including drug fevers. Lists of causes of fevers of unknown origin⁴⁰ include many of the infections and disorders encountered by podiatric physicians. Pharmacologic agents, such as sulfonamides and trimethoprim-sulfamethoxazole, commonly prescribed by podiatric physicians¹¹⁶ are among the agents likely to cause drug fevers.⁴² Furthermore, podiatric physicians frequently prescribe drugs that have antipyretic action,¹¹⁷ although they are intended for analgesia and anti-inflammation.¹¹⁸

A retrospective study¹¹⁹ of 300 medical records of patients who underwent foot surgery revealed an approximately 24-hour period of hypothermia after surgery followed by a febrile period. Sepsis is a possible, although rare, outcome of foot surgery.¹²⁰ Boegel and Miller cautioned that “[t]he use of antipyretic agents [postoperatively] is discouraged until the cause of the fever has been determined or at least until a major pathologic condition has been ruled out.”^{121(p215)}

Malignant hyperthermia has been reported by podiatric physicians in surgical procedures where general anesthesia had been used¹²²⁻¹²⁵; however, the paucity of recent reported cases perhaps reflects better awareness and prevention and less use of general anesthesia. Surgeons should have a high index of suspicion when treating patients with foot deformities or congenital myopathies, such as clubfoot or the rare central core disease, which have been linked to malignant hyperthermia susceptibility.^{126, 127} Furthermore, there have been reports of hyperthermic episodes associated with the use of tourniquets in foot operations in children.^{128, 129} Podiatric surgeons are encouraged to report malignant hyperthermia episodes to the North American MH Registry.

Fever is a symptom that is often encountered by the podiatric physician. Although a common sign associated with infection, fever can be secondary to

a myriad of other causes. The podiatric physician should, therefore, be cautious and meticulous in the recognition of the types of fever, especially fevers of unknown origin that occur without other clinical signs.

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References

1. ATKINS E: Fever: new perspectives on an old phenomenon. *N Engl J Med* **308**: 958, 1983.
2. ROMANOVSKY A: Thermoregulation: some concepts have changed: functional architecture of the thermoregulatory system. *Am J Physiol Regul Integr Comp Physiol* **292**: R37, 2007.
3. COOPER KE: *Fever and Antipyresis*, Cambridge University Press, Cambridge, 1995.
4. SHARMA HS: Methods to produce hyperthermia-induced brain dysfunction. *Prog Brain Res* **162**: 173, 2007.
5. IVANOV AI, PATEL S, KULCHITSKY VA, ET AL: Platelet-activating factor: a previously unrecognized mediator of fever. *J Physiol* **553**: 221, 2003.
6. DINARELLO C, PORAT R: “Fever and Hypothermia,” in *Harrison’s Principles of Internal Medicine*, 17th Ed, ed by AS Fauci, p 117, McGraw Hill, New York, 2008.
7. ROTH J, RUMMEL C, BARTH SW, ET AL: Molecular aspects of fever. *Neurol Clin* **24**: 421, 2006.
8. BLATTEIS CM, SEHIC E: Fever: how may circulating pyrogens signal the brain? *News Physiol Sci* **12**: 1, 1997.
9. KOZAK W, KLUGER MJ, SOSZYNSKI D, ET AL: “IL-6 and IL-1b in Fever: Studies Using Cytokine-Deficient (Knockout) Mice,” in *Molecular Mechanisms in Fever*, Vol 856, ed by MJ Kluger, p 33, New York Academy of Sciences, New York, 1998.
10. OOTSUKA Y, BLESSING WW, STEINER AA, ET AL: Fever response to intravenous prostaglandin E2 is mediated by the brain but does not require afferent vagal signaling. *Am J Physiol Regul Integr Comp Physiol* **294**: R1294, 2008.
11. BLATTEIS C: The onset of fever: new insights into its mechanism. *Prog Brain Res* **162**: 3, 2007.
12. MILTON AS, WENDLANDT S: Effects on body temperature of prostaglandins of the A, E, and F series on injection into the third ventricle of unanaesthetized cats and rabbits. *J Physiol* **218**: 325, 1971.
13. USHKUBI F, SEGI E, SUGIMOTO Y, ET AL: Impaired febrile response in mice lacking the prostaglandin E receptor subtype EP₃. *Nature* **395**: 281, 1998.
14. NAKAMURA K, MATSUMURA K, KANEKO T, ET AL: The rostral raphe pallidus nucleus mediates pyrogenic transmission from the preoptic area. *J Neurosci* **22**: 4600, 2002.
15. MORRISON SF, NAKAMURA K, MADDEN CJ: Central control

- of thermogenesis in mammals. *Exp Physiol* **93**: 773, 2008.
16. KLUGER MJ: Fever: role of pyrogens and cryogens. *Physiol Rev* **71**: 93, 1991.
 17. DuBois E: Why are fever temperatures over 106 degrees F rare? *Am J Med Sci* **217**: 361, 1949.
 18. BOUCHAMA A, KNOCHEL JP: Heat stroke. *N Engl J Med* **346**: 1978, 2002.
 19. COOPER K, NAYLOR AM, VEALE WL: Evidence supporting a role for endogenous vasopressin in fever suppression in the rat. *J Physiol* **387**: 163, 1987.
 20. SINHA P, SCHIOTH HB, TATRO JB: Activation of central melanocortin-4 receptor suppresses lipopolysaccharide-induced fever in rats. *Am J Physiol Regul Integr Comp Physiol* **284**: R1595, 2003.
 21. MIYOSHI M, KITAGAWA Y, IMOTO T, ET AL: Effect of natriuretic peptide receptor antagonist on lipopolysaccharide-induced fever in rats: is natriuretic peptide an endogenous antipyretic? *J Pharmacol Exp Ther* **318**: 1163, 2006.
 22. MORROW LE, MCCLELLAN JL, CONN CA, ET AL: Glucocorticoids alter fever and IL-6 responses to psychological stress and to LPS. *Am J Physiol* **264**: R1010, 1993.
 23. MEDZHITOV R, JANEWAY C: Innate immunity. *N Engl J Med* **343**: 338, 2000.
 24. SABROE I, PARKER LC, DOWER SK, ET AL: The role of TLR activation in inflammation. *J Pathol* **214**: 126, 2008.
 25. DINARELLO CA: Infection, fever, and exogenous and endogenous pyrogens: some concepts have changed. *J Endotoxin Res* **10**: 201, 2004.
 26. DINARELLO CA, WOLFF SM: "Exogenous Pyrogens," in *Pyretics and Antipyretics*, ed by AS Milton, p 73, Springer-Verlag, Berlin, 1982.
 27. SWARTZ MN, SIMON HB: "Pathophysiology of Fever and Fever of Undetermined Origin," in *Scientific American Medicine*, Vol 7, p 1, Freeman, San Francisco, 1992.
 28. AREND WP, DAYER JM: Cytokines and cytokine inhibitors or antagonists in rheumatoid arthritis. *Arthritis Rheum* **33**: 305, 1990.
 29. ELLIOTT MJ, MAINI RN, FELDMANN M, ET AL: Randomised double-blind comparison of chimeric monoclonal antibody to tumour necrosis factor α (cA2) versus placebo in rheumatoid arthritis. *Lancet* **344**: 1105, 1994.
 30. MOLTZ H: Fever: causes and consequences. *Neurosci Biobehav Rev* **17**: 237, 1993.
 31. HASAN MK, WHITE AC: Psychogenic fever: entity or nonentity? *Postgrad Med* **66**: 152, 1979.
 32. OKA T, OKA K, HORI T: Mechanisms and mediators of psychological stress-induced rise in core temperature. *Psychosom Med* **63**: 476, 2001.
 33. GORDON C, ROWSEY P: Poisons and fever. *Clin Exp Pharmacol Physiol* **25**: 145, 1998.
 34. ZELL JA, CHANG JC: Neoplastic fever: a neglected paraneoplastic syndrome. *Support Care Cancer* **13**: 870, 2005.
 35. DINARELLO C, BUNN P: Fever. *Semin Oncol* **24**: 288, 1997.
 36. CHANG JC: Neoplastic fever: a proposal for diagnosis. *Arch Intern Med* **149**: 1728, 1989.
 37. PETERSDORF RG: Fever of unknown origin: an old friend revisited. *Ann Intern Med* **152**: 21, 1992.
 38. CUNHA B: Fever of unknown origin: clinical overview of classic and current concepts. *Infect Dis Clin North Am* **21**: 867, 2007.
 39. KNOCKAERT DC, VANDERSCHUEREN S, BLOCKMANS D: Fever of unknown origin in adults: 40 years on. *J Intern Med* **253**: 263, 2003.
 40. ARNOW PM, FLAHERTY JP: Fever of unknown origin. *Lancet* **350**: 575, 1997.
 41. DURACK DT: "Fever of Unknown Origin," in *Fever: Basic Mechanisms and Management*, 2nd Ed, ed by PA Mackowiak, p 237, Lippincott-Raven, Philadelphia, 1997.
 42. HANSON MA: Drug fever: remember to consider it in diagnosis. *Postgrad Med* **89**: 167, 1991.
 43. EYER F, ZILKER T: Bench-to-bedside review: mechanisms and management of hyperthermia due to toxicity. *Crit Care* **11**: 236, 2007.
 44. CUNHA BA: Drug fever: the importance of recognition. *Postgrad Med* **80**: 123, 1986.
 45. NISIJIMA K, SHIODA K, IWAMURA T: Neuroleptic malignant syndrome and serotonin syndrome. *Prog Brain Res* **162**: 81, 2007.
 46. MUELLER P, KOREY W: Death by "ecstasy": the serotonin syndrome? *Ann Emerg Med* **32**: 377, 1998.
 47. ROSENBERG H, SEITMAN D: "Pharmacogenetics," in *Clinical Anesthesia*, ed by PG Barash, BF Cullen, RK Stoelting, p 459, JB Lippincott, Philadelphia, 1989.
 48. DYKSTRA TJ, MENOLASINO MJ: Neuroleptic malignant syndrome: case report and review. *J Am Osteopath Assoc* **97**: 355, 1997.
 49. MUSER DM, FAIRSTEIN V, YOUNG EJ, ET AL: Fever patterns: their lack of clinical significance. *Arch Intern Med* **139**: 1225, 1979.
 50. WOODWARD TE: "The Fever Pattern as a Diagnostic Aid," in *Fever: Basic Mechanisms and Management*, 2nd Ed, ed by PA Mackowiak, p 215, Lippincott-Raven, Philadelphia, 1997.
 51. SESSLER D: Temperature monitoring and perioperative thermoregulation. *Anesthesiology* **109**: 318, 2008.
 52. MCCARTHY PW, HEUSCH AI: The vagaries of ear temperature assessment. *J Med Eng Technol* **30**: 242, 2006.
 53. MACKOWIAK PA, WASSERMAN SS, LEVIN 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* **268**: 1578, 1992.
 54. HENKER R, CARLSON KK: Fever: applying research to bedside practice. *AACN Adv Crit Care* **18**: 76, 2007.
 55. CUNHA BA: The clinical significance of fever patterns. *Infect Dis Clin North Am* **10**: 33, 1996.
 56. TUNNESSEN WW: *Signs and Symptoms in Pediatrics*, Lippincott Williams & Wilkins, Philadelphia, 1999.
 57. SCHMITT B: Fever phobia: misconceptions of parents about fevers. *Am J Dis Child* **134**: 176, 1980.
 58. CROCETTI M, MOGHBELI N, SERWINT J: Fever phobia revisited: have parental misconceptions about fever changed in 20 years? *Pediatrics* **107**: 1241, 2001.
 59. HASLAM RH: "Febrile Seizures," in *Nelson Textbook of*

- Pediatrics*, 18th Ed, ed by RM Kliegman, RE Behrman, HB Jenson, et al, p 2457, Saunders, Philadelphia, 2007.
60. KNUDSEN FU: Febrile seizures: treatment and prognosis. *Epilepsia* **41**: 2, 2000.
61. BAUMANN RJ: Technical report: treatment of the child with simple febrile seizures. *Pediatrics* **103**: e86, 1999.
62. APPLGATE MS, LO W: Febrile seizures: current concepts concerning prognosis and clinical management. *J Fam Pract* **29**: 422, 1989.
63. KLUGER MJ: Fever revisited. *Pediatrics* **90**: 846, 1992.
64. UHARI M, RANTALA H, VAINIONPAA L, ET AL: Effect of acetaminophen and of low intermittent doses of diazepam on prevention of recurrences of febrile seizures. *J Pediatr* **126**: 991, 1995.
65. FETVEIT A: Assessment of febrile seizures in children. *Eur J Pediatr* **167**: 17, 2008.
66. NORMAN DC, WONG MB, YOSHIKAWA TT: Fever of unknown origin in older persons. *Infect Dis Clin North Am* **21**: 937, 2007.
67. JONES SR: "Fever in the Elderly," in *Fever: Basic Mechanisms and Management*, 1st Ed, ed by PA Mackowiak, p 233, Raven Press, New York, 1991.
68. VANE J: Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. *Nat New Biol* **231**: 232, 1971.
69. SCHWARTZ JI, CHAN CC, MUKHOPADHYAY S, ET AL: Cyclooxygenase-2 inhibition by rofecoxib reverses naturally occurring fever in humans. *Clin Pharmacol Ther* **65**: 653, 1999.
70. SOLOMON DH, SCHNEEWEISS S, GLYNN RJ, ET AL: Relationship between selective cyclooxygenase-2 inhibitors and acute myocardial infarction in older adults. *Circulation* **109**: 2068, 2004.
71. HINZ B, CHEREMINA O, BRUNE K: Acetaminophen (paracetamol) is a selective cyclooxygenase-2 inhibitor in man. *FASEB J* **22**: 383, 2007.
72. ROMANOVSKY AA, ALMEIDA MC, ARONOFF DM, ET AL: Fever and hypothermia in systemic inflammation: recent discoveries and revisions. *Front Biosci* **10**: 2193, 2005.
73. PLAISANCE KI, MACKOWIAK PA: Antipyretic therapy: physiologic rationale, diagnostic implications, and clinical consequences. *Arch Med* **160**: 449, 2000.
74. ISAACS SN, AXELROD PI, LORBER B: Antipyretic orders in a university hospital. *Am J Med* **88**: 31, 1990.
75. THOMAS V, RIEGEL B, ANDREA J, ET AL: National survey of pediatric fever management practices among emergency department nurses. *J Emerg Nurs* **20**: 505, 1994.
76. STYRT B, SUGARMAN B: Antipyresis and fever. *Arch Intern Med* **150**: 1589, 1990.
77. GOZZOLI V, SCHOTTKER P, SUTER PM, ET AL: Is it worth treating fever in intensive care unit patients? *Arch Intern Med* **161**: 121, 2001.
78. MACKOWIAK P: The febrile patient: diagnostic, prognostic and therapeutic considerations. *Front Biosci* **9**: 2297, 2004.
79. FERGUSON A: Evaluation and treatment of fever in intensive care unit patients. *Crit Care Nurs Q* **30**: 347, 2007.
80. AXELROD YK, DIRINGER MN: Temperature management in acute neurologic disorders. *Neurol Clin* **26**: 585, 2008.
81. KLUGER MJ: "The Adaptive Value of Fever," in *Fever: Basic Mechanisms and Management*, 1st Ed, ed by PA Mackowiak, p 105, Raven Press, New York, 1991.
82. ROBERTS NJ: Impact of temperature elevation on immunological defenses. *Rev Infect Dis* **13**: 462, 1991.
83. OSTBERG JR, REPASKY EA: Emerging evidence indicates that physiologically relevant thermal stress regulates dendritic cell function. *Cancer Immunol Immunother* **55**: 292, 2006.
84. HASDAY JD, GARRISON A: Antipyretic therapy in patients with sepsis. *Clin Infect Dis* **31**: S234, 2000.
85. MACKOWIAK PA, PLAISANCE KI: "Benefits and Risks of Antipyretic Therapy," in *Molecular Mechanisms of Fever*, Vol 856, ed by MJ Kluger, p 214, New York Academy of Sciences, New York, 1998.
86. WALSH A, EDWARDS H: Management of childhood fever by parents: literature review. *J Adv Nurs* **54**: 217, 2006.
87. LINDER N, SIROTA L, SNAPIR A, ET AL: Parental knowledge of the treatment of fever in children. *Israeli Med Assoc J* **1**: 158, 1999.
88. DORAN TF, DE ANGELIS C, BAUMGARDNER RA, ET AL: Acetaminophen: more harm than good for chickenpox? *J Pediatr* **114**: 1045, 1989.
89. KRAMER MS, NAIMARK LE, ROBERTS-BRAUER R, ET AL: Risks and benefits of paracetamol antipyresis in young children with fever of presumed viral origin. *Lancet* **337**: 591, 1991.
90. CASTEELS-VAN DAELE M: Management of childhood fever. *Lancet* **338**: 1049, 1991.
91. POWELL KR: "Fever," in *Nelson Textbook of Pediatrics*, 18th Ed, ed by RM Kliegman, RE Behrman, HB Jenson, BM Stanton, p 1084, Saunders, Philadelphia, 2007.
92. KURZ A, SESSLER DI, LENHARDT R: Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. *N Engl J Med* **334**: 1209, 1996.
93. FRANK SM, KLUGER MJ, KUNKEL SL: Elevated thermodynamic setpoint in postoperative patients. *Anesthesiology* **93**: 1426, 2000.
94. ENGOREN M: Lack of association between atelectasis and fever. *Chest* **107**: 81, 1995.
95. DAYTON MT: "Surgical Complications," in *Sabiston Textbook of Surgery*, 17th Ed, ed by CM Townsend, p 297, Elsevier-Saunders, Philadelphia, 2005.
96. BALLESTAS HC: Postoperative fever: to what is the body really responding? *AORN J* **86**: 983, 2007.
97. FISCHER JE, FEGELMAN E, JOHANNIGMAN J: "Surgical Complications," in *Principles of Surgery*, 7th Ed, ed by S Schwartz, p 447, McGraw-Hill, New York, 1999.
98. DIAMOND PT, MACCIOCHI SN: Predictive power of clinical symptoms in patients with presumptive deep venous thrombosis. *Am J Physical Med Rehabil* **76**: 49, 1997.
99. KANG KH, LEE EY, LEE YJ, ET AL: Clinical features and risk factors of postsurgical gout. *Ann Rheum Dis* **67**: 1271, 2008.

100. MARIK PE: Fever in the ICU. *Chest* **117**: 855, 2000.
101. O'GRADY NP, BARIE PS, BARTLETT JG, ET AL: Guidelines for evaluation of new fever in critically ill adult patients: 2008 update from the American College of Critical Care Medicine and the Infectious Diseases Society of America. *Crit Care Med* **36**: 1330, 2008.
102. KENNEDY C, LEFOR AT: "Routine and Specialized Postoperative Care," in *Perioperative Care, Anesthesia, Medicine and Surgery*, ed by DJ Stone, p 758, Mosby, St Louis, 1998.
103. LENHARDT R, NEGISHI C, SESSLER DI, ET AL: The effects of physical treatment on induced fever in humans. *Am J Med* **106**: 550, 1999.
104. LARACH MG: *Making Anesthesia Safer: Unraveling the Malignant Hyperthermia Puzzle*, Federation of American Societies of Experimental Biology, Bethesda, MD, 2001.
105. DENBOROUGH M: Malignant hyperthermia. *Lancet* **352**: 1131, 1998.
106. LARACH MG, BRANDOM BW, ALLEN GC, ET AL: Cardiac arrests and deaths associated with malignant hyperthermia in North America from 1987 to 2006: a report from the North American malignant hyperthermia registry of the malignant hyperthermia association of the United States. *Anesthesiology* **108**: 603, 2008.
107. ROSERO EB, ADESANYA AO, TIMARAN CH, ET AL: Trends and outcomes of malignant hyperthermia in the United States, 2000 to 2005. *Anesthesiology* **110**: 89, 2009.
108. MACLENNAN DH, PHILLIPS MS: Malignant hyperthermia. *Science* **256**: 789, 1992.
109. LOKE J, MACLENNAN DH: Malignant hyperthermia and central core disease: disorders of Ca^{2+} release channels. *Am J Med* **104**: 470, 1998.
110. ROSENBERG H, DAVIS M, JAMES D, ET AL: Malignant hyperthermia. *Orphanet J Rare Dis* **2**: 21, 2007.
111. DONNELLY AJ: Malignant hyperthermia. *AORN J* **59**: 394, 1994.
112. HARRISON GG: Control of the malignant hyperpyrexia syndrome in MHS swine by dantrolene sodium. *Br J Anaesthesia* **47**: 62, 1975.
113. KRAUSE T, GERBERSHAGEN MU, FIEGE M, ET AL: Dantrolene: a review of its pharmacology, therapeutic use and new developments. *Anaesthesia* **59**: 364, 2004.
114. JOSEPH WS: "Infections," in *Principles and Practice of Podiatric Medicine*, ed by LA Levy, VJ Hetherington, p 277, Churchill-Livingstone, New York, 1990.
115. DUFF GW, ATKINS E, MALAWISTA SE: The fever of gout: urate crystals activate endogenous pyrogen production from human and rabbit mononuclear phagocytes. *Trans Assoc Am Physicians* **96**: 234, 1983.
116. DENNO GJ, ed: *Podiatric Therapeutic Digest*, 3rd Ed, Odontos Publishing, Eastlake, OH, 1999.
117. DONOGHUE S: Fighting for every dollar. *Podiatry Manage* **28**: 97, 2009.
118. SULLI MM, ETZEL JV: Using of non-steroidal anti-inflammatory drugs. *Podiatry Manage* **21**: 109, 2000.
119. MILLER SJ: Temperature regulation and postoperative fever: a preliminary study. *JAPA* **74**: 373, 1984.
120. STRENCE KB, MANGAN DB, IDUSUYI OB: Postoperative toxic shock syndrome after excision of a ganglion cyst from the ankle. *J Foot Ankle Surg* **45**: 275, 2006.
121. BOEGEL WA, MILLER SJ: "Perioperative Considerations for Foot and Ankle Surgery," in *Comprehensive Textbook of Foot Surgery*, 2nd Ed, ed by ED McGlamry, AS Banks, MD Downey, p 181, Williams & Wilkins, Baltimore, 1992.
122. GRONEN WW, RODA PL: Malignant hyperthermia: a case report. *JAPA* **66**: 31, 1976.
123. GOHIL B, FORMAN WM: Malignant hyperthermia: description and case report. *J Foot Surg* **21**: 7, 1982.
124. HABER J, HAMMER DJ, BUTLER B: Malignant hyperthermia: a review and case report. *JAPA* **73**: 422, 1983.
125. LOWE MK: Malignant hyperthermia, a surgeon's nightmare. *J Foot Surg* **24**: 139, 1985.
126. ZANETTE G, ROBB N, ZADRA N, ET AL: Undetected central core disease myopathy in an infant presenting for clubfoot surgery. *Pediatr Anesth* **17**: 380, 2007.
127. SHUAIB A, PAASUKE RT, BROWNELL KW: Central core disease: clinical features in 13 patients. *Medicine* **66**: 389, 1987.
128. BLOCH EC, GINSBERG B, BINNER RA, ET AL: Limb tourniquets and central temperature in anesthetized children. *Pediatr Anesth* **74**: 486, 1992.
129. MOTEGI Y, SHIRAI M, ARAI M, ET AL: Malignant hyperthermia during epidural anesthesia. *J Clin Anesthesia* **8**: 157, 1996.

ADDITIONAL REFERENCES

- IBELGAUF H: COPE: Cytokines & Cells Online Pathfinder Encyclopedia Web site. Available at: <http://www.copewithcytokines.de/>. Accessed May 28, 2010.
- Malignant Hyperthermia Association of the United States Web site. Available at: <http://www.mhaus.org>. Accessed May 28, 2010.
- NINDS febrile seizures information page. National Institute of Neurological Disorders and Stroke Web site. Available at: http://www.ninds.nih.gov/disorders/febrile_seizures/febrile_seizures.htm. Accessed May 28, 2010.