

## Review Article

*Medical Progress***HEAT STROKE**

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**H**EAT stroke is a life-threatening illness characterized by an elevated core body temperature that rises above 40°C and central nervous system dysfunction that results in delirium, convulsions, or coma.<sup>1</sup> Despite adequate lowering of the body temperature and aggressive treatment, heat stroke is often fatal, and those who do survive may sustain permanent neurologic damage.<sup>1,2</sup> Data from the Centers for Disease Control and Prevention show that from 1979 to 1997, 7000 deaths in the United States were attributable to excessive heat.<sup>3</sup> The incidence of such deaths may increase with global warming and the predicted worldwide increase in the frequency and intensity of heat waves.<sup>4-8</sup>

Research performed during the past decade has shown that heat stroke results from thermoregulatory failure coupled with an exaggerated acute-phase response and possibly with altered expression of heat-shock proteins.<sup>9-23</sup> The ensuing multiorgan injury results from a complex interplay among the cytotoxic effect of the heat and the inflammatory and coagulation responses of the host.<sup>9-21</sup> In this article, we summarize the pathogenesis of heat stroke as it is currently understood and explore the potential therapeutic and preventive strategies. Key terms used in this discussion are defined in Table 1.

**DEFINITION AND INCIDENCE**

Heat stroke is defined clinically as a core body temperature that rises above 40°C and that is accompanied by hot, dry skin and central nervous system abnormalities such as delirium, convulsions, or coma. Heat stroke results from exposure to a high environmental temperature (in which case it is called classic,

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**TABLE 1.** GLOSSARY OF TERMS.

CONDITION	DEFINITION
Heat wave	Three or more consecutive days during which the air temperature is >32.2°C
Heat stress	Perceived discomfort and physiological strain associated with exposure to a hot environment, especially during physical work
Heat stroke	Severe illness characterized by a core temperature >40°C and central nervous system abnormalities such as delirium, convulsions, or coma resulting from exposure to environmental heat (classic heat stroke) or strenuous physical exercise (exertional heat stroke)
Heat exhaustion	Mild-to-moderate illness due to water or salt depletion that results from exposure to high environmental heat or strenuous physical exercise; signs and symptoms include intense thirst, weakness, discomfort, anxiety, dizziness, fainting, and headache; core temperature may be normal, below normal, or slightly elevated (>37°C but <40°C)
Hyperthermia	A rise in body temperature above the hypothalamic set point when heat-dissipating mechanisms are impaired (by drugs or disease) or overwhelmed by external (environmental or induced) or internal (metabolic) heat
Multiorgan-dysfunction syndrome	Continuum of changes that occur in more than one organ system after an insult such as trauma, sepsis, or heat stroke <sup>24</sup>

or nonexertional, heat stroke) or from strenuous exercise (in which case it is called exertional heat stroke).<sup>1</sup> On the basis of our understanding of the pathophysiology of heat stroke, we propose an alternative definition of this condition: it is a form of hyperthermia associated with a systemic inflammatory response leading to a syndrome of multiorgan dysfunction in which encephalopathy predominates.

Data on the incidence of heat stroke are imprecise because this illness is underdiagnosed and because the definition of heat-related death varies.<sup>25,26</sup> In an epidemiologic study during heat waves in urban areas in the United States, the incidence of heat stroke varied from 17.6 to 26.5 cases per 100,000 population.<sup>26</sup> Most people affected by classic heat stroke are very young or elderly, poor, and socially isolated and do not have access to air conditioning.<sup>25,27</sup> In Saudi Arabia, the incidence varies seasonally, from 22 to 250 cases per 100,000 population.<sup>28</sup> The crude mortality rate

associated with heat stroke in Saudi Arabia is estimated at 50 percent.<sup>28</sup>

The incidence of heat exhaustion in Saudi Arabia, in contrast, ranges from 450 to more than 1800 cases per 100,000 population. Why a mild illness develops in response to heat (as in heat exhaustion) in some people, whereas in others the condition progresses to heat stroke, is unknown. Genetic factors may determine the susceptibility to heat stroke; candidate susceptibility genes include those that encode cytokines, coagulation proteins, and heat-shock proteins involved in the adaptation to heat stress.<sup>13-23</sup>

### **PATHOGENESIS**

To understand the pathogenesis of heat stroke, the systemic and cellular responses to heat stress must be appreciated. These responses include thermoregulation (with acclimatization), an acute-phase response, and a response that involves the production of heat-shock proteins.

#### **Thermoregulation**

Body heat is gained from the environment and is produced by metabolism. This overall heat load must be dissipated to maintain a body temperature of 37°C, a process called thermoregulation.<sup>1</sup> A rise in the temperature of the blood by less than 1°C activates peripheral and hypothalamic heat receptors that signal the hypothalamic thermoregulatory center,<sup>29</sup> and the efferent response from this center increases the delivery of heated blood to the surface of the body. Active sympathetic cutaneous vasodilation then increases blood flow in the skin by up to 8 liters per minute.<sup>30</sup> An increase in the blood temperature also initiates thermal sweating.<sup>31,32</sup> If the air surrounding the surface of the body is not saturated with water, sweat will vaporize and cool the body surface. The evaporation of 1.7 ml of sweat will consume 1 kcal of heat energy.<sup>32</sup> At maximal efficiency in a dry environment, sweating can dissipate about 600 kcal per hour.<sup>31-33</sup> The thermal gradient established by the evaporation of sweat is critical for the transfer of heat from the body to the environment. An elevated blood temperature also causes tachycardia, increases cardiac output, and increases minute ventilation.<sup>1,30-33</sup> As blood is shunted from the central circulation to the muscles and skin to facilitate heat dissipation, visceral perfusion is reduced, particularly in the intestines and kidneys.<sup>30</sup> Losses of salt and water by sweating, which may amount to 2 liters or more per hour, must be balanced by generous salt supplementation to facilitate thermoregulation.<sup>33,34</sup> Dehydration and salt depletion impair thermoregulation.<sup>34</sup>

#### **Acclimatization**

Successive increments in the level of work performed in a hot environment result in adaptations that

eventually allow a person to work safely at levels of heat that were previously intolerable or life-threatening.<sup>1</sup> The process of acclimatization to heat takes several weeks and involves enhancement of cardiovascular performance, activation of the renin-angiotensin-aldosterone axis, salt conservation by the sweat glands and kidneys, an increase in the capacity to secrete sweat, expansion of plasma volume, an increase in the glomerular filtration rate, and an increase in the ability to resist exertional rhabdomyolysis.<sup>35</sup>

#### **Acute-Phase Response**

The acute-phase response to heat stress is a coordinated reaction that involves endothelial cells, leukocytes, and epithelial cells and that protects against tissue injury and promotes repair.<sup>36</sup> Interleukin-1 was the first known mediator of the systemic inflammation induced by strenuous exercise.<sup>37</sup> A variety of cytokines are now known to be produced in response to endogenous or environmental heat (Table 2).<sup>22,38-43,46-51</sup> Cytokines mediate fever, leukocytosis, increased synthesis of acute-phase proteins, muscle catabolism, stimulation of the hypothalamic-pituitary-adrenal axis, and activation of leukocytes and endothelial cells.<sup>22,51-53</sup> The interleukin-6 produced during heat stress modulates local and systemic acute inflammatory responses by controlling the levels of inflammatory cytokines<sup>22,51,54</sup>; interleukin-6 also stimulates hepatic production of antiinflammatory acute-phase proteins, which inhibit the production of reactive oxygen species and the release of proteolytic enzymes from activated leukocytes.<sup>36,51,54</sup> Other acute-phase proteins stimulate endothelial-cell adhesion, proliferation, and angiogenesis, thus contributing to repair and healing.<sup>36</sup> The increased expression of the gene encoding interleukin-6 in human muscle cells, but not in blood monocytes, during the acute-phase response to exercise suggests that the onset of inflammation is local.<sup>22,41,42</sup> The systemic progression of the inflammatory response is secondary and involves other cells, such as monocytes.<sup>41</sup> A similar sequence of events has been shown to occur in sepsis.<sup>55</sup>

#### **Heat-Shock Response**

Nearly all cells respond to sudden heating by producing heat-shock proteins or stress proteins.<sup>56,57</sup> Expression of heat-shock proteins is controlled primarily at the level of gene transcription. During heat stress, one or more heat-shock transcription factors bind to the heat-shock element, resulting in an increased rate of transcription of heat-shock proteins.<sup>56,57</sup> Increased levels of heat-shock proteins in a cell induce a transient state of tolerance to a second, otherwise lethal, stage of heat stress, allowing the cell to survive.<sup>23,56,57</sup> Blocking the synthesis of heat-shock proteins either at the gene-transcription level or by specific antibodies

**TABLE 2.** EFFECT OF HEAT STRESS AND HEAT STROKE ON CIRCULATING CYTOKINES, CYTOKINE RECEPTORS, GROWTH FACTORS, AND CHEMOKINES.\*

CYTOKINE OR FACTOR	HEAT STRESS			HEAT STROKE		REFERENCE
	EXERCISE-INDUCED	ENVIRONMENTAL	THERAPEUTIC†	CLASSIC	EXERTIONAL	
Tumor necrosis factor $\alpha$	Increased or unchanged	Unchanged	Increased or unchanged	Increased or unchanged	Increased	Bouchama et al., <sup>11</sup> Espersen et al., <sup>38</sup> Robins et al., <sup>39</sup> Camus et al., <sup>40</sup> Ostrowski et al., <sup>41</sup> Moldoveanu et al., <sup>42</sup> Suzuki et al., <sup>43</sup> Chang <sup>44</sup>
Interleukin-1 $\beta$	Increased or unchanged	NA	Increased	Increased or unchanged	Increased	Cannon and Kluger, <sup>37</sup> Robins et al., <sup>39</sup> Ostrowski et al., <sup>41</sup> Moldoveanu et al., <sup>42</sup> Chang, <sup>44</sup> Bouchama et al. <sup>45</sup>
Interleukin-2	Decreased or unchanged	NA	Unchanged	NA	NA	Espersen et al., <sup>38</sup> Robins et al. <sup>39</sup>
Interleukin-6	Increased	Increased	Increased	Increased	Increased	Robins et al., <sup>39</sup> Moldoveanu et al., <sup>42</sup> Suzuki et al., <sup>43</sup> Chang, <sup>44</sup> Bouchama et al., <sup>45</sup> Hammami et al. <sup>46</sup>
Interleukin-8	Increased	NA	Increased	NA	NA	Pedersen and Hoffman-Goetz, <sup>22</sup> Robins et al., <sup>39</sup> Suzuki et al. <sup>43</sup>
Interleukin-10	Increased	Increased	Increased	Increased	NA	Pedersen and Hoffman-Goetz, <sup>22</sup> Robins et al., <sup>39</sup> Suzuki et al., <sup>43</sup> Bouchama et al. <sup>47</sup>
Interleukin-12	Increased or unchanged	NA	Unchanged	NA	NA	Pedersen and Hoffman-Goetz, <sup>22</sup> Robins et al., <sup>39</sup> Suzuki et al., <sup>43</sup> Akimoto et al. <sup>48</sup>
Interleukin-1-receptor antagonist	Increased	NA	NA	NA	NA	Pedersen and Hoffman-Goetz, <sup>22</sup> Ostrowski et al., <sup>41</sup> Suzuki et al. <sup>43</sup>
Soluble interleukin-2 receptor	Increased	NA	NA	Increased	NA	Pedersen and Hoffman-Goetz, <sup>22</sup> Suzuki et al., <sup>43</sup> Hammami et al. <sup>46</sup>
Soluble interleukin-6 receptor	NA	Increased	NA	Decreased	NA	Hammami et al. <sup>49</sup>
Soluble tumor necrosis factor receptors (p55 and p75)	Increased	Increased or unchanged	Increased	Increased	NA	Pedersen and Hoffman-Goetz, <sup>22</sup> Hammami et al. <sup>49</sup>
Interferon- $\gamma$	Increased or unchanged	NA	Unchanged	Increased	NA	Pedersen and Hoffman-Goetz, <sup>22</sup> Robins et al., <sup>39</sup> Suzuki et al., <sup>43</sup> Bouchama et al. <sup>45</sup>
Interferon- $\alpha$	Increased or unchanged	NA	Unchanged	NA	NA	Suzuki et al., <sup>43</sup> Viti et al. <sup>50</sup>
Granulocyte colony-stimulating factor	Increased	NA	Increased	NA	NA	Pedersen and Hoffman-Goetz, <sup>22</sup> Robins et al., <sup>39</sup> Suzuki et al. <sup>43</sup>
Macrophage-inhibitor proteins	Increased	NA	Unchanged	NA	NA	Pedersen and Hoffman-Goetz, <sup>22</sup> Robins et al. <sup>39</sup>

\*Data are from studies in human subjects. NA denotes data not available.

†Whole-body hyperthermia may be induced in cancer therapy.

renders the cells extremely sensitive to a minor degree of heat stress.<sup>16,58</sup> In vivo, cellular tolerance protects laboratory animals against hyperthermia, arterial hypotension, and cerebral ischemia.<sup>15,16</sup> The protection conferred against heat-stroke injury correlates with the level of heat-shock protein 72, which accumulates in the brain after the priming heat-shock treatment.<sup>15,16</sup> The mechanism by which heat-shock proteins protect cells may relate to their function as molecular chaperones that bind to partially folded or misfolded proteins, thus preventing their irreversible denaturation.<sup>56</sup> Another possible mechanism involves heat-shock proteins that act as central regulators of

the baroreceptor-reflex response during severe heat stress, abating hypotension and bradycardia and conferring cardiovascular protection.<sup>16</sup>

#### Progression from Heat Stress to Heat Stroke

Thermoregulatory failure, exaggeration of the acute-phase response, and alteration in the expression of heat-shock proteins may contribute to the progression from heat stress to heat stroke.

#### Thermoregulatory Failure

The normal cardiovascular adaptation to severe heat stress is an increase in cardiac output by up to 20 liters

per minute and a shift of heated blood from the core circulation to the peripheral circulation.<sup>30</sup> An inability to increase cardiac output because of salt and water depletion, cardiovascular disease, or a medication that interferes with cardiac function can impair heat tolerance and result in increased susceptibility to heat stroke.<sup>1</sup>

#### **Exaggeration of the Acute-Phase Response**

It is possible that the gastrointestinal tract fuels the inflammatory response.<sup>12,40,59-63</sup> During strenuous exercise or hyperthermia, blood shifts from the mesenteric circulation to the working muscles and the skin, leading to ischemia of the gut and intestinal hyperpermeability.<sup>12,30,59-63</sup> There is abundant evidence of hyperpermeability during heat stress in animal models but much less evidence of this phenomenon in humans.<sup>9,10,12,59-63</sup> In rats, heat stress leads to increased metabolic demand and reduced splanchnic blood flow, which in turn induce intestinal and hepatocellular hypoxia; the hypoxia results in the generation of highly reactive oxygen and nitrogen species that accelerate mucosal injury.<sup>12,59</sup>

Intestinal mucosal permeability to iodine-125-labeled endotoxin increases in heat-stressed rats that have a core temperature of 45°C.<sup>60</sup> In heat-stressed primates, endotoxin from the gut enters the circulation at a core temperature of 40°C, and its concentration increases as the core temperature rises.<sup>9,10</sup> Endotoxemia may then cause hemodynamic instability and death. Administration of antiendotoxin antibodies before heat stress occurs attenuates hemodynamic instability and improves outcome, suggesting that endotoxin is involved in the progression from heat stress to heat stroke.<sup>10</sup> In humans, high concentrations of endotoxin, inflammatory cytokines, and acute-phase proteins are found in the blood after strenuous exercise.<sup>22,40,61,62</sup> Increased intestinal permeability occurs in athletes exercising at 80 percent or more of maximal oxygen consumption.<sup>61</sup>

In summary, in the model of heat stroke based on experiments in animals and observations in humans (Fig. 1), local and systemic insults associated with heat stress, such as splanchnic hypoperfusion, alter the immunologic and barrier functions of the intestines.<sup>12,59-63</sup> This alteration allows leakage of endotoxins, increased production of inflammatory cytokines that induce endothelial-cell activation, and release of endothelial vasoactive factors such as nitric oxide and endothelins.<sup>9,10,12,63,64</sup> Both pyrogenic cytokines and endothelium-derived factors can interfere with normal thermoregulation by raising the set point at which sweating is activated and by altering vascular tone, particularly in the splanchnic circulation, thereby precipitating hypotension, hyperthermia, and heat stroke.<sup>9,10,12,63</sup>

#### **Alteration of Heat-Shock Response**

Increased levels of heat-shock proteins protect cells from damage by heat, ischemia, hypoxia, endotoxin, and inflammatory cytokines.<sup>23,56,57</sup> In persons who are subjected to heat stress, examination of muscle tissue, blood monocytes, and serum reveals that such a heat-shock response occurs *in vivo*.<sup>17,65-67</sup> Attenuation of the heat-shock response during heat stroke suggests that this adaptative response is protective.<sup>17,23</sup> Conditions associated with a low level of expression of heat-shock proteins — for instance, aging, lack of acclimatization to heat, and certain genetic polymorphisms — may favor the progression from heat stress to heat stroke.<sup>17,23,68</sup>

### **PATHOPHYSIOLOGY**

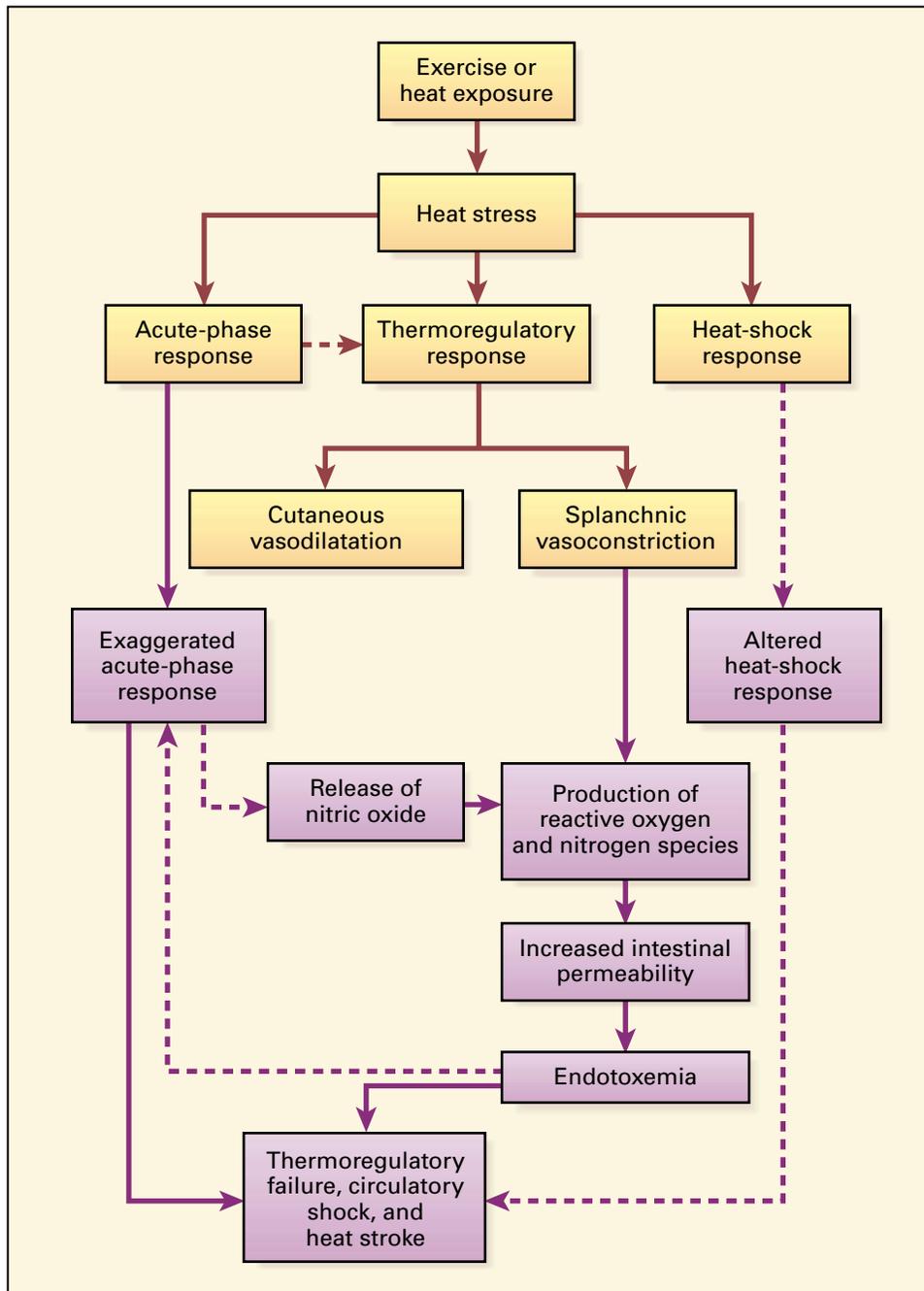
Heat stroke and its progression to multiorgan-dysfunction syndrome are due to a complex interplay among the acute physiological alterations associated with hyperthermia (e.g., circulatory failure, hypoxia, and increased metabolic demand), the direct cytotoxicity of heat, and the inflammatory and coagulation responses of the host.<sup>11-15,18-21,44,45,69-72</sup> This constellation of events leads to alterations in blood flow in the microcirculation and results in injury to the vascular endothelium and tissues (Fig. 2).<sup>18,19,73-76</sup>

#### **Heat**

Studies in cell lines and animal models suggest that heat directly induces tissue injury.<sup>69,70</sup> The severity of the injury depends on the critical thermal maximum, a term that attempts to quantify the level and duration of heating that will initiate tissue injury.<sup>69-71</sup> A critical thermal maximum beyond which near-lethal or lethal injury occurs has been determined in various mammalian species.<sup>71</sup> Observations in selected groups, including marathon runners, normal volunteers, and patients with cancer who are treated with whole-body hyperthermia, suggest that the critical thermal maximum in humans is a body temperature of 41.6°C to 42°C for 45 minutes to 8 hours.<sup>71</sup> At extreme temperatures (49°C to 50°C), all cellular structures are destroyed and cellular necrosis occurs in less than five minutes.<sup>69</sup> At lower temperatures, cell death is largely due to apoptosis.<sup>70</sup> Although the pathways of heat-induced apoptosis have not been identified, the induction of heat-shock proteins is protective.<sup>57</sup>

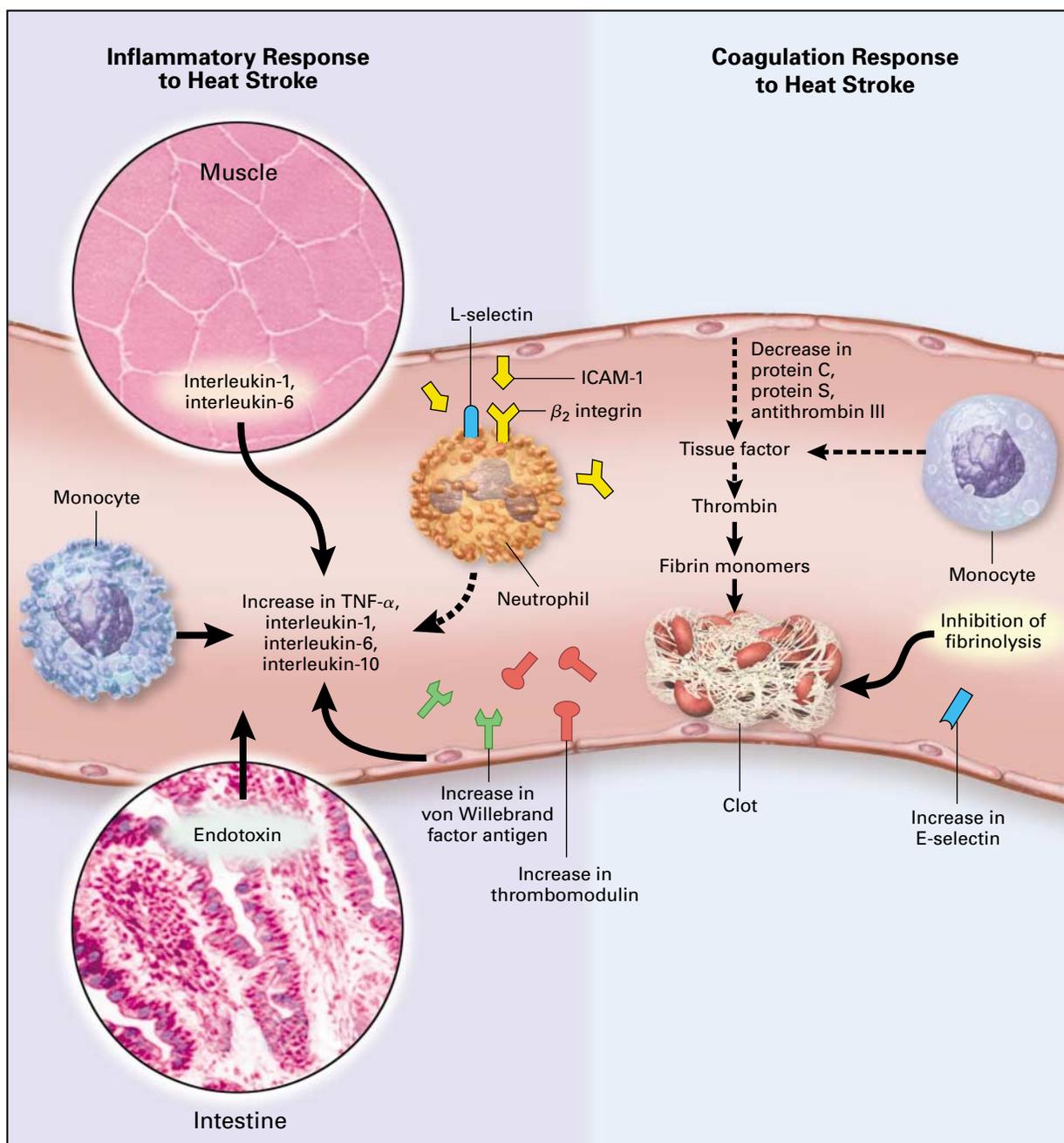
#### **Cytokines**

The plasma levels of inflammatory cytokines (tumor necrosis factor  $\alpha$  [TNF- $\alpha$ ], interleukin- $1\beta$ , and interferon- $\gamma$ ) and antiinflammatory cytokines (interleukin-6, soluble TNF receptors p55 and p75, and interleukin-10) are elevated in persons with heat stroke; cooling of the body to a normal temperature does not result in the suppression of these factors.<sup>11,44,45,47,49</sup> The



**Figure 1.** The Sequence of Events in the Progression of Heat Stress to Heat Stroke.

Heat stress induces thermoregulatory, acute-phase, and heat-shock responses. Thermoregulatory failure, exaggeration of the acute-phase response, and alteration in the expression of heat-shock proteins, individually or collectively, may contribute to the development of heat stroke. Active cutaneous vasodilatation and splanchnic vasoconstriction permit the shift of heated blood from the central organs to the periphery, from which heat is then dissipated to the environment. This change may also lead to splanchnic hypoperfusion and ischemia, resulting in increased production of reactive oxygen and nitrogen species, which may in turn induce intestinal mucosal injury and hyperpermeability. Endotoxins may then leak into the circulation and enhance the acute-phase response, leading to increased production of pyrogenic cytokines and nitric oxide. Both cytokines and nitric oxide can interfere with thermoregulation and precipitate hyperthermia, hypotension, and heat stroke. The solid arrows indicate pathways for which there is clinical or experimental evidence, and the broken arrows indicate putative pathways.



**Figure 2.** Possible Pathophysiological Mechanisms of Heat Stroke.

Hyperthermia due to passive heat exposure or to exercise may facilitate the leakage of endotoxin from the intestine to the systemic circulation as well as the movement of interleukin-1 or interleukin-6 proteins from the muscles to the systemic circulation. The result is excessive activation of leukocytes and endothelial cells, manifested by the release of proinflammatory and antiinflammatory cytokines (e.g., tumor necrosis factor  $\alpha$  [TNF- $\alpha$ ], interleukin-1, interleukin-6, and interleukin-10), up-regulation of cell-surface adhesion molecules, and shedding of soluble cell-surface adhesion molecules (e.g., E-selectin, L-selectin, and intercellular adhesion molecule 1 [ICAM-1]) as well as activation of coagulation (with decreased levels of proteins C and S and antithrombin III) and inhibition of fibrinolysis. The inflammatory and coagulation responses to heat stroke, together with direct cytotoxic effects of heat, result in injury to the vascular endothelium and microthrombosis. The solid arrows indicate pathways for which there is clinical or experimental evidence, and the broken arrows indicate putative pathways.

levels of interleukin-6 and TNF receptors correlate with severity of heat stroke.<sup>45,49</sup>

An imbalance between inflammatory and anti-inflammatory cytokines may result in either inflammation-associated injury or refractory immunosuppression. Although dynamic studies of the cytokine response in patients with heat stroke have not yet been performed, both of these mechanisms may be important. In patients with heat stroke, the incidence of infection is high.<sup>2</sup> Studies in rats and rabbits have shown that heat stroke induces systemic and local (central nervous system) production of TNF- $\alpha$  and interleukin-1.<sup>13,72</sup> The increase in the levels of these inflammatory cytokines is associated with high intracranial pressure, decreased cerebral blood flow, and severe neuronal injury. Interleukin-1-receptor antagonists or corticosteroids given to animals before heat stroke attenuate neurologic injury, prevent arterial hypotension, and improve survival.<sup>13,14</sup> Although such studies support the possibility that cytokines have a pathogenic role, studies of neutralizing antibodies or genetically modified mice are needed to determine both the pattern and the role of these factors in heat stroke.

#### Coagulation Disorders and Endothelial-Cell Injury

Endothelial-cell injury and diffuse microvascular thrombosis are prominent features of heat stroke. Therefore, disseminated intravascular coagulation and alterations in the vascular endothelium may be important pathologic mechanisms in heat stroke.<sup>18-21,73-76</sup>

Studies involving the use of molecular markers of coagulation and fibrinolysis have delineated the early steps of coagulation abnormalities.<sup>20,21</sup> The onset of heat stroke coincides with the activation of coagulation, as assessed by the appearance of thrombin-antithrombin III complexes and soluble fibrin monomers and below-normal levels of protein C, protein S, and antithrombin III. Fibrinolysis is also highly activated, as shown by increased levels of plasmin- $\alpha_2$ -antiplasmin complexes and D-dimers and decreased levels of plasminogen. Normalization of the core temperature inhibits fibrinolysis but not the activation of coagulation, which continues; this pattern resembles that seen in sepsis.<sup>20</sup>

The endothelium controls vascular tone and permeability, regulates leukocyte movement, and maintains a balance between procoagulant and anticoagulant substances. Hyperthermia *in vitro* promotes a prothrombotic state, enhances vascular permeability, and increases the cell-surface expression of adhesion molecules and the shedding of their soluble form.<sup>77,78</sup> Circulating levels of von Willebrand factor antigen, thrombomodulin, endothelin, metabolites of nitric oxide, soluble E-selectin, and intercellular adhesion molecule 1 are elevated in patients with heat

stroke.<sup>18,19,53,64,79</sup> Modulation of the expression of  $\beta_2$ -integrins, characterized by up-regulation of CD11b and down-regulation of CD11a on the surface of circulating lymphocytes, has been reported in patients with heat stroke, suggesting that there is an active endothelial cell-leukocyte interaction *in vivo*.<sup>53</sup>

#### CLINICAL AND METABOLIC MANIFESTATIONS

Two findings — hyperthermia and central nervous system dysfunction — must be present for a diagnosis of heat stroke (Table 3).<sup>1,86</sup> The core temperature may range from 40°C to 47°C.<sup>1</sup> Brain dysfunction is usually severe but may be subtle, manifesting only as inappropriate behavior or impaired judgment; more often, however, patients have delirium or frank coma.<sup>1,86</sup> Seizures may occur, especially during cooling.<sup>1</sup> All patients have tachycardia and hyperventilation. In either classic or exertional heat stroke, the arterial carbon dioxide tension is often less than 20 mm Hg.<sup>1</sup> Twenty-five percent of patients have hypotension.<sup>86</sup>

Patients with nonexertional heat stroke usually have respiratory alkalosis.<sup>1</sup> In contrast, those with exertional heat stroke nearly always have both respiratory alkalosis and lactic acidosis.<sup>1</sup> Hypophosphatemia and hypokalemia are common at the time of admission. Hypoglycemia is rare. Hypercalcemia and hyperproteinemia, reflecting hemoconcentration, may also occur. In patients with exertional heat stroke, rhabdomyolysis, hyperphosphatemia, hypocalcemia, and hyperkalemia may be important events after complete cooling.

The most serious complications of heat stroke are those falling within the category of multiorgan-dysfunction syndrome. They include encephalopathy, rhabdomyolysis, acute renal failure, acute respiratory distress syndrome, myocardial injury, hepatocellular injury, intestinal ischemia or infarction, pancreatic injury, and hemorrhagic complications, especially disseminated intravascular coagulation, with pronounced thrombocytopenia.<sup>1,21</sup>

#### TREATMENT

Immediate cooling and support of organ-system function are the two main therapeutic objectives in patients with heat stroke (Table 3).<sup>1,2,80-87</sup>

##### Cooling

Effective heat dissipation depends on the rapid transfer of heat from the core to the skin and from the skin to the external environment.<sup>80-82</sup> In persons with hyperthermia, transfer of heat from the core to the skin is facilitated by active cutaneous vasodilatation.<sup>30,81,82</sup> Therapeutic cooling techniques are therefore aimed at accelerating the transfer of heat from the skin to the environment without compromising

TABLE 3. MANAGEMENT OF HEAT STROKE.\*

CONDITION	INTERVENTION	GOAL
<b>Out of hospital</b>		
Heat stress (due to heat wave, summer heat, or strenuous exercise), with changes in mental status (anxiety, delirium, seizures, or coma)	Measure the patient's core temperature (with a rectal probe)	Diagnose heat stroke†
	If the core temperature is >40°C, move the patient to a cooler place, remove his or her clothing, and initiate external cooling‡: cold packs on the neck, axillae, and groin; continuous fanning (or opening of the ambulance windows); and spraying of the skin with water at 25°C to 30°C	Lower the core temperature to <39.4°C, promote cooling by conduction, and promote cooling by evaporation
	Position an unconscious patient on his or her side and clear the airway	Minimize the risk of aspiration
	Administer oxygen at 4 liters/min Give isotonic crystalloid (normal saline) Rapidly transfer the patient to an emergency department	Increase arterial oxygen saturation to >90% Provide volume expansion
<b>In hospital</b>		
Cooling period	Confirm diagnosis with thermometer calibrated to measure high temperatures (40°C to 47°C)	
Hyperthermia	Monitor the rectal and skin temperatures; continue cooling	Keep rectal temperature <39.4°C§ and skin temperature 30°C–33°C
Seizures	Give benzodiazepines	Control seizures
Respiratory failure	Consider elective intubation (for impaired gag and cough reflexes or deterioration of respiratory function)	Protect airway and augment oxygenation (arterial oxygen saturation >90%)
Hypotension¶	Administer fluids for volume expansion, consider vasopressors, and consider monitoring central venous pressure	Increase mean arterial pressure to >60 mm Hg and restore organ perfusion and tissue oxygenation
Rhabdomyolysis	Expand volume with normal saline and administer intravenous furosemide, mannitol, and sodium bicarbonate	Prevent myoglobin-induced renal injury: promote renal blood flow, diuresis, and alkalization of urine
	Monitor serum potassium and calcium levels and treat hyperkalemia	Prevent life-threatening cardiac arrhythmia
After cooling	Supportive therapy	Recovery of organ function
Multiorgan dysfunction		

\*Data are from Knochel and Reed,<sup>1</sup> Graham et al.,<sup>80</sup> Wyndham et al.,<sup>81</sup> Weiner and Khogali,<sup>82</sup> Al-Aska et al.,<sup>83</sup> White et al.,<sup>84,85</sup> and Bouchama et al.<sup>86</sup>

†Heat stroke should be suspected in any patient with changes in mental status during heat stress, even if his or her core temperature is <40°C.

‡There is no evidence that one cooling technique is superior to another. Noninvasive techniques that are easy to apply, well tolerated, and not likely to cause cutaneous vasoconstriction are preferred.

§There is no evidence to support a specific temperature end point at which cooling should be halted. However, a rectal temperature of 39.4°C has been used in large series and has proved to be safe.<sup>86</sup>

¶Hypotension usually responds to volume expansion and cooling. Vasodilatory shock and primary myocardial dysfunction may underlie sustained hypotension that is refractory to volume expansion. Therapy should be individualized and guided by the patient's clinical response.

the flow of blood to the skin.<sup>80-85</sup> This is accomplished by increasing the temperature gradient between the skin and the environment (for cooling by conduction) or by increasing the gradient of water-vapor pressure between the skin and the environment (for cooling by evaporation), as well as by increasing the velocity of air adjacent to the skin (for cooling by convection). In practice, cold water or ice is applied to the skin, which is also fanned (Table 4). Most such methods lower the skin temperature to below 30°C, triggering cutaneous vasoconstriction and shivering. To overcome this response, the patient may be vigorously massaged, sprayed with tepid water (40°C), or exposed to hot moving air (45°C), either at the same time as cooling methods are applied or in an alternating fashion.<sup>80-83</sup> There have been no controlled studies com-

paring the effects of these various cooling techniques on cooling times and outcome in patients with heat stroke.

No pharmacologic agents that accelerate cooling are helpful in the treatment of heat stroke. Although the use of dantrolene sodium has been considered, this agent was found ineffective in a double-blind, randomized study.<sup>86</sup> The role of antipyretic agents in heat stroke has not been evaluated, despite findings that pyrogenic cytokines are implicated in heat stress.

Recovery of central nervous system function during cooling is a favorable prognostic sign and should be expected in the majority of patients who receive prompt and aggressive treatment. Residual brain damage occurs in about 20 percent of the patients and is associated with high mortality.<sup>1,2</sup>

TABLE 4. METHODS OF COOLING.

**Techniques based on conductive cooling**

## External\*

- Cold-water immersion
- Application of cold packs or ice slush over part of the body or the whole body
- Use of cooling blankets

## Internal†

- Iced gastric lavage
- Iced peritoneal lavage

**Techniques based on evaporative or convective cooling**

- Fanning the undressed patient at room temperature (20°C to 22°C)
- Wetting of the body surface during continuous fanning‡
- Use of a body-cooling unit§

\*Because external cooling results in cutaneous vasoconstriction, vigorous massaging of the skin is recommended.<sup>81,82</sup>

†Internal cooling, which has been investigated in animals, is infrequently used in humans.<sup>84,85</sup> Gastric or peritoneal lavage with ice water may cause water intoxication.

‡The skin is covered with a fine gauze sheet that has been soaked in water at 20°C while the patient is fanned. The fanning is reduced or stopped if the skin temperature drops to <30°C.<sup>83</sup>

§A body-cooling unit is a special bed that sprays atomized water at 15°C and warm air at 45°C over the whole body surface to keep the temperature of the wet skin between 32°C and 33°C.<sup>82</sup>

**Prevention**

Heat stroke is a preventable illness, and thorough knowledge of the disorder can help to reduce mortality and morbidity.<sup>1,3</sup> Although classic heat stroke is predominant in very young or elderly persons and in those who have no access to air conditioning,<sup>1-3,25-27</sup> it is also relatively common among persons with chronic mental disorders or cardiopulmonary disease and those receiving medications that interfere with salt and water balance, such as diuretics, anticholinergic agents, and tranquilizers that impair sweating.<sup>1-3,25-27</sup> Exertional heat stroke may be seen in manual laborers, military personnel, football players, long-distance runners, and those who ingest an overdose of cocaine or amphetamines.<sup>1</sup> To prevent both types of heat stroke, people can acclimatize themselves to heat, schedule outdoor activities during cooler times of the day, reduce their level of physical activity, drink additional water, consume salty foods, and increase the amount of time they spend in air-conditioned environments.<sup>1,3</sup> Automobiles should be locked, and children should never be left unattended in an automobile during hot weather.

Despite accumulated knowledge and experience, deaths during heat waves are still common<sup>88-90</sup> and have been associated largely with social isolation in vulnerable populations, lack of air conditioning, and increases in heat during large gatherings for cultural or religious purposes.<sup>25-28,88-90</sup> A plan to improve weather forecasting, alert those at risk, provide readily acces-

sible air-conditioned shelters, and reduce energy costs during extreme weather so that air conditioning is affordable may decrease morbidity and mortality during heat waves.<sup>88-90</sup> In football players, modification of practice schedules and avoidance of dehydration and salt depletion have been found to be effective means of preventing heat stroke.<sup>91</sup>

**Emerging Concepts**

After the onset of heat stroke, normalizing the body temperature may not prevent inflammation, coagulation, and progression to multiorgan dysfunction.<sup>2,11,18,20,45,49,53</sup> For this reason, new approaches to modulation of the inflammatory response are being studied in animals. Immunomodulators such as interleukin-1-receptor antagonists, antibodies to endotoxin, and corticosteroids improve survival in animals but have not yet been studied in humans.<sup>10,13,14</sup> It is uncertain whether anticytokine and anti-endotoxin strategies will be more successful in heat stroke than they have been in sepsis. New therapeutic interventions aimed at limiting the activity of nuclear factor- $\kappa$ B, a critical transcription factor in the regulation of acute inflammation, may prove more successful: in a model of inflammation-associated injury (mice with sepsis), inhibition of nuclear factor- $\kappa$ B activity has been found to improve survival, but it also appears to promote apoptosis of hepatocytes.<sup>92,93</sup>

Coagulation and fibrinolysis are frequently activated during heat stroke and may lead to disseminated intravascular coagulation.<sup>20,21</sup> Replacement therapy with recombinant activated protein C, which attenuates both the coagulation and the inflammation, reduces mortality in patients with severe sepsis and may be useful in those with heat stroke as well.<sup>20,94</sup> Elucidation of the molecular mechanisms that trigger the activation of coagulation may lead to more specific therapy, such as tissue-factor pathway inhibitors.

More important are potential therapeutic applications based on knowledge of the stress-response proteins.<sup>15,16</sup> A logical goal for the next generation of immunomodulators is selective pharmacologic induction of the expression of heat-shock proteins. Salicylate and nonsteroidal antiinflammatory drugs activate heat-shock transcription factors and induce the transcription and translation of heat-shock proteins in mammalian cells.<sup>57</sup> This response enhances tolerance of heat and cellular protection against heat stress. Although excessive expression of the heat-shock proteins blocks essential cellular processes, partial up-regulation of these proteins may prove beneficial, particularly as a preventive measure during a heat wave. Further studies are required to define the degree to which inflammatory and stress responses can be modulated in humans without interfering with essential immunologic mechanisms.

## CONCLUSIONS

The threat of heat stroke is increasing. Global warming is already causing heat waves in temperate climates.<sup>4-8</sup> The recognition that thermoregulatory failure and impaired regulation of inflammatory and stress responses facilitate the progression from heat stress to heat stroke and contribute to the severity of tissue injury should make research in this direction a priority. Greater knowledge of the cellular and molecular responses to heat stress will help point to novel preventive measures and a new paradigm of immunomodulation. In this way, the multiorgan injury caused by heat stroke might be minimized in many patients.

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## REFERENCES

1. Knochel JP, Reed G. Disorders of heat regulation. In: Narins RG, ed. Maxwell & Kleeman's clinical disorders of fluid and electrolyte metabolism. 5th ed. New York: McGraw-Hill, 1994:1549-90.
2. Dematte JE, O'Mara K, Buescher J, et al. Near-fatal heat stroke during the 1995 heat wave in Chicago. *Ann Intern Med* 1998;129:173-81.
3. Heat-related illnesses, deaths, and risk factors — Cincinnati and Dayton, Ohio, 1999, and United States, 1979–1997. *MMWR Morb Mortal Wkly Rep* 2000;49:470-3.
4. Easterling DR, Meehl GA, Parmesan C, Changnon SA, Karl TR, Mearns LO. Climate extremes: observations, modeling, and impacts. *Science* 2000;298:2068-74.
5. Rooney C, McMichael AJ, Kovats RS, Coleman MP. Excess mortality in England and Wales, and in Greater London, during the 1995 heatwave. *J Epidemiol Community Health* 1998;52:482-6.
6. Sartor F, Snacken R, Demuth C, Walckiers D. Temperature, ambient ozone levels, and mortality during summer 1994, in Belgium. *Environ Res* 1995;70:105-13.
7. Katsouyanni K, Trichopoulos D, Zavitsanos X, Touloumi G. The 1987 Athens heatwave. *Lancet* 1988;2:573.
8. Nakai S, Itoh T, Morimoto T. Deaths from heat stroke in Japan: 1968-1994. *Int J Biometeorol* 1999;43:124-7.
9. Gathiram P, Wells MT, Raidoo D, Brock-Utne JG, Gaffin SL. Portal and systemic plasma lipopolysaccharide concentrations in heat-stressed primates. *Circ Shock* 1988;25:223-30.
10. Gathiram P, Wells MT, Brock-Utne JG, Gaffin SL. Antilipopolysaccharide improves survival in primates subjected to heat stroke. *Circ Shock* 1987;23:157-64.
11. Bouchama A, Parhar RS, el-Yazigi A, Sheth K, al-Sedairy S. Endotoxemia and release of tumor necrosis factor and interleukin 1 alpha in acute heatstroke. *J Appl Physiol* 1991;70:2640-4.
12. Hall DM, Buettner GR, Oberley LW, Xu L, Matthes RD, Gisolfi CV. Mechanisms of circulatory and intestinal barrier dysfunction during whole body hyperthermia. *Am J Physiol Heart Circ Physiol* 2001;280:H509-H521.
13. Lin MT, Liu HH, Yang YL. Involvement of interleukin-1 receptor mechanisms in development of arterial hypotension in rat heatstroke. *Am J Physiol* 1997;273:H2072-H2077.
14. Liu CC, Chien CH, Lin MT. Glucocorticoids reduce interleukin-1 concentration and result in neuroprotective effects in rat heatstroke. *J Physiol* 2000;27:333-43.
15. Yang YL, Lin MT. Heat shock protein expression protects against cerebral ischemia and monoamine overload in rat heatstroke. *Am J Physiol* 1999;276:H1961-H1967.
16. Li PL, Chao YM, Chan SH, Chan JY. Potentiation of baroreceptor reflex response by heat shock protein 70 in nucleus tractus solitarius confers cardiovascular protection during heatstroke. *Circulation* 2001;103:2114-19.
17. Wang ZZ, Wang CL, Wu TC, Pan HN, Wang SK, Jiang JD. Autoantibody response to heat shock protein 70 in patients with heatstroke. *Am J Med* 2001;111:654-7.
18. Bouchama A, Hammami MM, Haq A, Jackson J, al-Sedairy S. Evidence for endothelial cell activation/injury in heatstroke. *Crit Care Med* 1996;24:1173-8.
19. Shieh SD, Shiang JC, Lin YF, Shiao WY, Wang JY. Circulating angiotensin-converting enzyme, von Willebrand factor antigen and thrombomodulin in exertional heat stroke. *Clin Sci (Lond)* 1995;89:261-5.
20. Bouchama A, Bridey F, Hammami MM, et al. Activation of coagulation and fibrinolysis in heatstroke. *Thromb Haemost* 1996;76:909-15.
21. al Mashhadani SA, Gader AG, al Harthi SS, Kangav D, Shaheen FA, Bogus F. The coagulopathy of heatstroke: alterations in coagulation and fibrinolysis in heatstroke patients during the pilgrimage (Haj) to Makkah. *Blood Coagul Fibrinolysis* 1994;5:731-6.
22. Pedersen BK, Hoffman-Goetz L. Exercise and the immune system: regulation, integration, and adaptation. *Physiol Rev* 2000;80:1055-81.
23. Moseley PL. Heat shock proteins and heat adaptation of the whole organism. *J Appl Physiol* 1997;83:1413-7.
24. Beal AL, Cerra FB. Multiple organ failure syndrome in the 1990s: systemic inflammatory response and organ dysfunction. *JAMA* 1994;271:226-33.
25. Semenza JC, Rubin CH, Falter KH, et al. Heat-related deaths during the July 1995 heat wave in Chicago. *N Engl J Med* 1996;335:84-90.
26. Jones TS, Liang AP, Kilbourne EM, et al. Morbidity and mortality associated with the July 1980 heat wave in St. Louis and Kansas City, Mo. *JAMA* 1982;247:3327-31.
27. Kilbourne EM, Choi K, Jones TS, Thacker SB. Risk factors for heatstroke: a case-control study. *JAMA* 1982;247:3332-6.
28. Ghaznawi HI, Ibrahim MA. Heat stroke and heat exhaustion in pilgrims performing the Haj (annual pilgrimage) in Saudi Arabia. *Ann Saudi Med* 1987;7:323-6.
29. Mackowiak PA, ed. Fever: basic mechanisms and management. 2nd ed. Philadelphia: Lippincott-Raven, 1997:35-40.
30. Rowell LB. Cardiovascular aspects of human thermoregulation. *Circ Res* 1983;52:367-79.
31. Buono MJ, Sjöholm NT. Effect of physical training on peripheral sweat production. *J Appl Physiol* 1988;65:811-4.
32. Nelson N, Eichna LW, Horvath SM, Shelley WB, Hatch TF. Thermal exchanges of man at high temperatures. *Am J Physiol* 1947;151:626-52.
33. Adams WC, Fox RH, Fry AJ, MacDonald IC. Thermoregulation during marathon running in cool, moderate, and hot environments. *J Appl Physiol* 1975;38:1030-7.
34. Deschamps A, Levy RD, Cosio MG, Marliss EB, Magder S. Effect of saline infusion on body temperature and endurance during heavy exercise. *J Appl Physiol* 1989;66:2799-804.
35. Knochel JP. Catastrophic medical events with exhaustive exercise: "white collar rhabdomyolysis." *Kidney Int* 1990;38:709-19.
36. Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. *N Engl J Med* 1999;340:448-54. [Erratum, *N Engl J Med* 1999;340:1376.]
37. Cannon JG, Kluger MJ. Endogenous pyrogen activity in human plasma after exercise. *Science* 1983;220:617-9.
38. Espersen GT, Elbaek A, Ernst E, et al. Effect of physical exercise on cytokines and lymphocyte subpopulations in human peripheral blood. *APMIS* 1990;98:395-400.
39. Robins HI, Kutz M, Wiedemann GJ, et al. Cytokine induction in humans by 41.8 degrees C whole body hyperthermia. *Cancer Lett* 1995;97:195-201.
40. Camus G, Nys M, Poortmans JR, et al. Endotoxaemia, production of tumour necrosis factor alpha and polymorphonuclear neutrophil activation following strenuous exercise in humans. *Eur J Appl Physiol Occup Physiol* 1998;79:62-8.
41. Ostrowski K, Rohde T, Zacho M, Asp S, Pedersen BK. Evidence that interleukin-6 is produced in human skeletal muscle during prolonged running. *J Physiol* 1998;508:949-53.
42. Moldoveanu AI, Shephard RJ, Shek PN. Exercise elevates plasma levels but not gene expression of IL-1beta, IL-6 and TNF-alpha in blood mononuclear cells. *J Appl Physiol* 2000;89:1499-504.
43. Suzuki K, Yamada M, Kurakake S, et al. Circulating cytokines and hormones with immunosuppressive but neutrophil-priming potentials rise after endurance exercise in humans. *Eur J Appl Physiol* 2000;81:281-7.
44. Chang DM. The role of cytokines in heatstroke. *Immunol Invest* 1993;22:553-61.
45. Bouchama A, al-Sedairy S, Siddiqui S, Shail E, Rezeig M. Elevated pyrogenic cytokines in heatstroke. *Chest* 1993;104:1498-502.
46. Hammami MM, Bouchama A, Shail E, al-Sedairy S. Elevated serum level of soluble interleukin-2 receptor in heatstroke. *Intensive Care Med* 1998;24:988.
47. Bouchama A, Hammami MM, Al Shail E, De Vol E. Differential ef-

- fects of in vitro and in vivo hyperthermia on the production of interleukin-10. *Intensive Care Med* 2000;26:1646-51.
48. Akimoto T, Akama T, Tatsuno M, Saito M, Kono I. Effect of brief maximal exercise on circulating levels of interleukin-12. *Eur J Appl Physiol* 2000;81:510-2.
49. Hammami MM, Bouchama A, Al-Sedairy S, Shail E, AlOhalay Y, Mohamed GE. Concentrations of soluble tumor necrosis factor and interleukin-6 receptors in heatstroke and heatstress. *Crit Care Med* 1997;25:1314-9.
50. Viti A, Muscettola M, Paulesu L, Bocci V, Almi A. Effect of exercise on plasma interferon levels. *J Appl Physiol* 1985;59:426-8.
51. Cannon JG. Inflammatory cytokines in nonpathological states. *News Physiol Sci* 2000;15:298-303.
52. Hietala J, Nurmi T, Uhari M, Pakarinen A, Kouvalainen K. Acute phase proteins, humoral and cell mediated immunity in environmentally-induced hyperthermia in man. *Eur J Appl Physiol Occup Physiol* 1982;49:271-6.
53. Hammami MM, Bouchama A, Shail E, Aboul-Enein HY, Al-Sedairy S. Lymphocyte subsets and adhesion molecules expression in heatstroke and heat stress. *J Appl Physiol* 1998;84:1615-21.
54. Xing Z, Gaudie J, Cox G, et al. IL-6 is an antiinflammatory cytokine required for controlling local or systemic acute inflammatory responses. *J Clin Invest* 1998;101:311-20.
55. Kurahashi K, Kajikawa O, Sawa T, et al. Pathogenesis of septic shock in *Pseudomonas aeruginosa* pneumonia. *J Clin Invest* 1999;104:743-50.
56. Welch WJ. Mammalian stress response: cell physiology, structure/function of stress proteins, and implications for medicine and disease. *Physiol Rev* 1992;72:1063-81.
57. Polla BS, Bachelet M, Elia G, Santoro MG. Stress proteins in inflammation. *Ann N Y Acad Sci* 1998;851:75-85.
58. Riabowol KT, Mizzen LA, Welch WJ. Heat shock is lethal to fibroblasts microinjected with antibodies against hsp70. *Science* 1988;242:433-6.
59. Hall DM, Baumgardner KR, Oberley TD, Gisolfi CV. Splanchnic tissues undergo hypoxic stress during whole body hyperthermia. *Am J Physiol* 1999;276:G1195-G1203.
60. Shapiro Y, Alkan M, Epstein Y, Newman F, Magazanik A. Increase in rat intestinal permeability to endotoxin during hyperthermia. *Eur J Appl Physiol Occup Physiol* 1986;55:410-2.
61. Pals KL, Chang RT, Ryan AJ, Gisolfi CV. Effect of running intensity on intestinal permeability. *J Appl Physiol* 1997;82:571-6.
62. Bosenberg AT, Brock-Utne JG, Gaffin SL, Wells MT, Blake GT. Strenuous exercise causes systemic endotoxemia. *J Appl Physiol* 1988;65:106-8.
63. Sakurada S, Hales JR. A role for gastrointestinal endotoxins in enhancement of heat tolerance by physical fitness. *J Appl Physiol* 1998;84:207-14.
64. Bouchama A, Hammami MM. Endothelin-1 in heatstroke. *J Appl Physiol* 1995;79:1391.
65. Ryan AJ, Gisolfi CV, Moseley PL. Synthesis of 70K stress protein by human leukocytes: effect of exercise in the heat. *J Appl Physiol* 1991;70:466-71.
66. Febbraio MA, Koukoulas I. HSP72 gene expression progressively increases in human skeletal muscle during prolonged, exhaustive exercise. *J Appl Physiol* 2000;89:1055-60.
67. Fehrenbach E, Niess AM, Scholtz E, Passek F, Dickhuth HH, Northoff H. Transcriptional and translational regulation of heat shock proteins in leukocytes of endurance runners. *J Appl Physiol* 2000;89:704-10.
68. Milner CM, Campbell RD. Polymorphic analysis of the three MHC-linked HSP70 genes. *Immunogenetics* 1992;36:357-62.
69. Buckley IK. A light and electron microscopic study of thermally injured cultured cells. *Lab Invest* 1972;26:201-9.
70. Sakaguchi Y, Stephens LC, Makino M, et al. Apoptosis in tumors and normal tissues induced by whole body hyperthermia in rats. *Cancer Res* 1995;55:5459-64.
71. Bynum GD, Pandolf KB, Schuette WH, et al. Induced hyperthermia in sedated humans and the concept of critical thermal maximum. *Am J Physiol* 1978;235:R228-R236.
72. Lin MT, Kao TY, Su CF, Hsu SS. Interleukin-1 beta production during the onset of heat stroke in rabbits. *Neurosci Lett* 1994;174:17-20.
73. Malamud N, Haymaker W, Custer RP. Heat stroke: a clinico-pathologic study of 125 fatal cases. *Mil Surg* 1946;99:397-449.
74. Sohal RS, Sun SC, Colcolough HL, Burch GE. Heatstroke: an electron microscopic study of endothelial cell damage and disseminated intravascular coagulation. *Arch Intern Med* 1968;122:43-7.
75. Chao TC, Sinniah R, Pakiam JE. Acute heat stroke deaths. *Pathology* 1981;13:145-56.
76. el-Kassimi FA, Al-Mashhadani S, Abdullah AK, Akhtar J. Adult respiratory distress syndrome and disseminated intravascular coagulation complicating heat stroke. *Chest* 1986;90:571-4.
77. Ang C, Dawes J. The effects of hyperthermia on human endothelial monolayers: modulation of thrombotic potential and permeability. *Blood Coagul Fibrinolysis* 1994;5:193-9.
78. Lefor AT, Foster CE III, Sartor W, Engbrecht B, Fabian DF, Silverman D. Hyperthermia increases intercellular adhesion molecule-1 expression and lymphocyte adhesion to endothelial cells. *Surgery* 1994;116:214-21.
79. Alzeer AH, Al-Arifi A, Warsy AS, Ansari Z, Zhang H, Vincent JL. Nitric oxide production is enhanced in patients with heat stroke. *Intensive Care Med* 1999;25:58-62.
80. Graham BS, Lichtenstein MJ, Hinson JM, Theil GB. Nonexertional heatstroke: physiologic management and cooling in 14 patients. *Arch Intern Med* 1986;146:87-90.
81. Wyndham CH, Strydom NB, Cooke HM, et al. Methods of cooling subjects with hyperpyrexia. *J Appl Physiol* 1959;14:771-6.
82. Weiner JS, Khogali M. A physiological body-cooling unit for treatment of heat stroke. *Lancet* 1980;1:507-9.
83. Al-Aska AK, Abu-Aisha H, Yaqub B, Al-Harhi SS, Sallam A. Simplified cooling bed for heatstroke. *Lancet* 1987;1:381.
84. White JD, Riccobene E, Nucci R, Johnson C, Butterfield AB, Kamath R. Evaporation versus iced gastric lavage treatment of heatstroke: comparative efficacy in a canine model. *Crit Care Med* 1987;15:748-50.
85. White JD, Kamath R, Nucci R, Johnson C, Shepherd S. Evaporation versus iced peritoneal lavage treatment of heatstroke: comparative efficacy in a canine model. *Am J Emerg Med* 1993;11:1-3.
86. Bouchama A, Cafège A, Devol EB, Labdi O, el-Assil K, Seraj M. Ineffectiveness of dantrolene sodium in the treatment of heatstroke. *Crit Care Med* 1991;19:176-80.
87. Knochel JP. Pigment nephropathy. In: Greenberg A, Cheung AK, eds. *Primer on kidney diseases*. 2nd ed. San Diego, Calif.: Academic Press, 1998:273-6.
88. Changnon SA, Easterling DR. Disaster management: U.S. policies pertaining to weather and climate extremes. *Science* 2000;289:2053-5.
89. Kalkstein LS. Saving lives during extreme weather in summer. *BMJ* 2000;321:650-1.
90. Kellerman AL, Todd KH. Killing heat. *N Engl J Med* 1996;335:126-7.
91. Knochel JP. Dog days and siriasis: how to kill a football player. *JAMA* 1975;233:513-5.
92. Tak PP, Firestein GS. NF- $\kappa$ B: a key role in inflammatory diseases. *J Clin Invest* 2001;107:7-11.
93. Bohrer H, Qiu F, Zimmerman T, et al. Role of NF- $\kappa$ B in the mortality of sepsis. *J Clin Invest* 1997;100:972-85.
94. Bernard GR, Vincent J-L, Laterre P-F, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001;344:699-709.