Chapter 5

PATHOPHYSIOLOGY OF HEATSTROKE

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INTRODUCTION

If the pathophysiology of heat stress and heatstroke were well understood, then this entire chapter could be written in only three or four pages. The length of this chapter indicates that although many facts are known, the relative importance of their roles is poorly understood. If there is a hierarchy of homeostatic mechanisms, then which is more important: the need to control elevated body temperature by sweating, or the need to maintain plasma volume by not sweating? Heat alters the physiology of all the systems in the body. Here are presented the facts, and our interpretations of them, based on current knowledge (Figure 5-1). Certainly, most observers agree that work in the heat is an enormous regulatory challenge. The existence of heat illness within a given population at risk suggests four simple observations or assumptions:

1. Excess physiological strain results in homeostatic failure.
2. There is a natural variation between individuals in the response to heat and exercise.
3. Hemodynamic failure (ie, syncope, hypotension, and heat exhaustion) may not prevent severe hyperthermia.
4. Because hyperthermia is not painful and may even be euphoric, volitional behavior, expressed as continued performance of exercise, is often maintained even as the risk of heat injury increases (ie, an individual sees others collapse but rejects the notion of personal risk).

More complete clinical and theoretical descriptions of heat illnesses are contained in other chapters in this textbook and in Chapter 8 of *Wilderness Medicine: Management of Wilderness and Environmental Emergencies*.[1]

Four thousand years ago, denial of water to the enemy through siege was a well-recognized form of warfare. However, siege in those days was considered the least desirable and most expensive method of the routes of attacking a walled city (going over, through, or under the wall; by ruse; or any combination).[2] The defending forces safely within the walls could minimize their exposure to the sun and heat, thus reducing their requirements for water, which was stored in large cisterns, in addition to any obtained from springs or wells. As a result, a siege could last for months or even years, and severely damage the attacker's economy. Eventually, however, a combination of dehydration, starvation, and disease could sufficiently weaken defenses for a successful attack, or could lower morale enough for surrender. Modern sieges similarly last for months and often fail because the defender usually has sufficient water in storage (eg, Jerusalem, 1947) or a "back door" for supplies (eg, Iraq, Desert Shield, 1990/91).

Modern warfare is usually characterized by high-intensity battles with rapid troop movements, and may occur in tropical countries with high heat loads. Therefore, soldiers lose a great amount of water through sweating, which must be made up by extensive diversion of logistical resources. Because each soldier requires a minimum of 4.5 gal/day (~ 16 L/d) during summer combat, for a 10,000-man division, at least 160 tons of water or more per day would be required, which must be carefully distributed and dispensed. The consequences of insufficient water can be avoided even in a desert, but soldiers must be instructed where and how to look for underground supplies (Exhibit 5-1).

Heatstroke, a potentially lethal illness, is important even among the lower animals, where it is sometimes used (seemingly deliberately) in interspecies conflict. If hornets attack the hives of Japanese honey bees, scores of bees closely crowd around the invading hornet, forming a "ball of bees" several layers thick.[3] The bees rapidly vibrate their thoracic muscles, heating themselves and the hornet to approximately 116°F (46.7°C). But while the bees are relatively heat-tolerant and survive, the invading hornet collapses and dies of "heatstroke." There is a circuitous military lesson here: try to raise the core temperature of the enemy as much as possible, and by any means possible, such as by forcing them to be on the move, or to wear encapsulation gear, or to prevent their consumption of water.

The following historical narrative is a classic description of the devastating impact of the failure of logistics to provide water to a military unit, this one deployed in Texas. This excerpt is from the official report to the Medical Director, Department of Texas, September 1877, titled "A Cavalry Detachment Three and a Half Days Without Water," by Captain J. H. T. King, Assistant Surgeon, US Army Post Surgeon, Fort Concho, Texas[4]:

> The next day found them still marching onwards, and the mid-day tropical heat causing great suffering. The desire for water now became uncontrollable. The most loathsome fluid would now have been accepted to moisten their swollen tongues and supply their inward craving. The salivary and mucous secretions had long been absent, their mouths and throats were so parched that they could

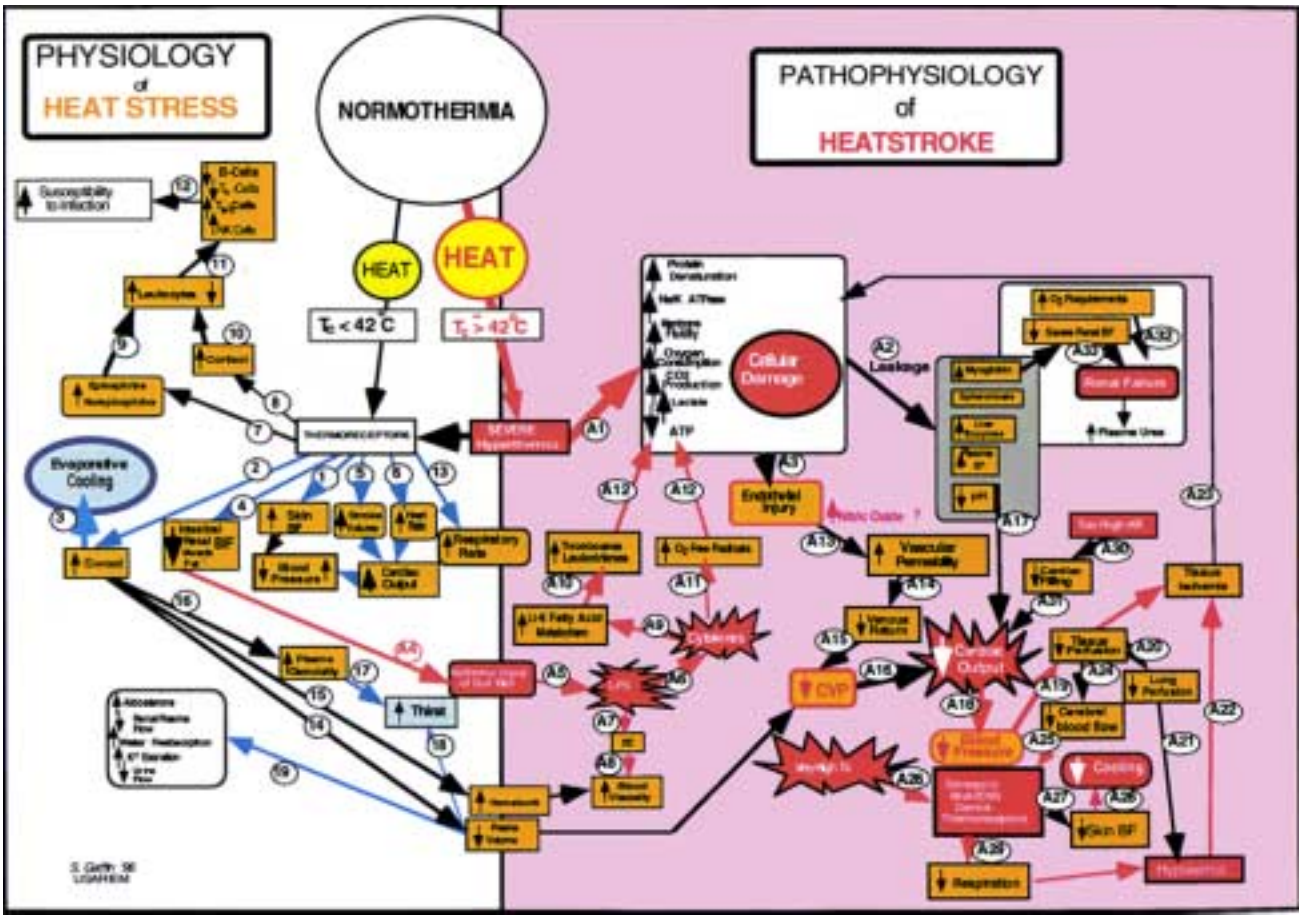

Fig. 5-1. A model of the physiology and pathophysiology of heat stress and heatstroke. To clarify physiological mechanisms, core temperature (T_c) has been divided into two regions: normal thermoregulation (left, 1–19) and impaired homeostasis (right, A1–A33).

Normal Thermoregulation. Under a moderate heat load, as skin or T_c or both rise, thermoreceptors (1) increase skin blood flow (skin BF) and (2) cause the secretion of sweat to (3) result in evaporative cooling. To prevent a drop in blood pressure (4), blood flow to the splanchnic regions and to muscle are reduced and (5) stroke volume and then (6) heart rate are increased. Then (7) catecholamines are secreted, followed by corticotropin releasing factor (CRF), which leads to the secretion of adrenocorticotropic hormone (ACTH), followed by (8) cortisol. Catecholamines (9) cause a leukocytosis, while cortisol (10) causes a leukopenia, leading to (11) changes in the amounts of leukocyte subsets. If the heat stress is prolonged and severe, the immunosuppression could (12) lead to subsequent increased susceptibility to infections. As temperature rises (13), the respiratory rate increases. As a result of sweating, (14) plasma volume decreases and (15) hematocrit and (16) plasma osmolality rise, leading to (17,18) the sensation of thirst and release of antidiuretic hormone (ADH). Reduced plasma volume (14), together with reduced renal blood flow, lead to (19) rises in water-sparing hormones and reduced kidney function.

Impaired Homeostasis. In the event or prior or concurrent exercise, these events occur at lower T_c and earlier. As T_c continues to rise above approximately 40°C to 42°C (104°F–107.6°F), direct hyperthermic damage (A1) to cells commences with increases in membrane fluidity and permeability, increases in metabolic rate, including the activity of the Na^+-K^+ adenosine triphosphatase (ATPase) pump, increases in a variety of metabolites and decreases in cellular adenosine triphosphate (ATP) content. At the same time, the reduction in intestinal blood flow (4) becomes more severe, leading to (A4) ischemic injury of the gut wall. This in turn leads to rises in (A5) circulating toxic lipopolysaccharides (LPS) and (A6) cytokines. By activating a blood factor (A7), LPS causes (A8) disseminated intravascular coagulation (DIC) and its consequent rise in blood viscosity. Thermal injury of endothelia (A3), together with elevated cytokines, leads to (A9) enhanced metabolism of omega-6 fatty acids, including (A10) the production of thromboxanes and leukotrienes, (A11) oxygen free radicals and (A12) further cellular injury, probably production of toxic nitric oxide, and (A13) increased vascular permeability. This leads to the loss of fluids into the tissues and thus (A14) reduced venous return and (A15) consequent reduced central venous pressure (CVP). Through Starling's Law of the Heart (A16), cardiac output begins to fall. This is exacerbated (A17) by electrolyte changes in the blood. Eventually, (A18) blood pressure falls, leading (A19) to reduced tissue perfusion. In lung (A20), reduced perfusion leads to (A21) systemic hypoxemia and, eventually, (A22) ischemia of various tissues and organs and its consequent (A23) contribution to further cellular damage. (A24) Reduced blood flow to the brain (A25), as well as (A26) probable direct thermal denaturation, leads to damage of centrally mediated homeostatic mechanisms, (A27) reduced skin blood flow and (A28) drop in cooling rate, and (A29) a fall in respiration.

In a separate pathway, cardiac output is also depressed as a result of a (A30) too-rapid pulse, causing (A31) incomplete cardiac filling. Electrolyte derangements are made more severe by (A32) an increased metabolic rate and (A33) reductions of renal blood flow.

Adapted with permission from Hubbard RW, Gaffin SL, Squire DL. Heat-related illnesses. In: Auerbach PS, ed. *Wilderness Medicine: Management of Wilderness and Environmental Emergencies*. St. Louis, Mo: Mosby; 1995: 203.

EXHIBIT 5-1

FINDING WATER IN THE DESERT

At the end of the 1973 Yom Kippur War, a large group of Egyptian soldiers was found dead without battle wounds in Sinai near El Arish, undoubtedly heat casualties. Yet adequate amounts of drinkable water were very near, *just a foot and a half below the sand.* If these soldiers had been instructed in desert survival, they probably would have survived.

When rain falls slowly, it enters the soil and gradually percolates downward until it hits solid bedrock, where it accumulates. At this point, as water continues to flow downward, its upper surface within the soil gradually rises, saturates the soil, and becomes the "water table." A hole dug deeply enough into the soil will eventually reach the water table. If the hole is dug deeper than the water table, water will slowly percolate out of the soil (over several minutes to several hours) and fill the hole to the level of the water table. If the underlying bedrock is sloped, then the water may continue slowly moving downward, eventually connecting to a stream; or it may lead to a depression in the soil and create a saturated region or swamp; or the water may remain buried for hundreds and even thousands of years.

The question is, How do you find it? To find underground water in the desert, the soldier should search for the presence of markers such as vegetation growing where there is no visible water. Presumably, the plants' roots have found subsurface water. If the plant is small, then the water would not be expected to be too far down. The soldier should dig at least 5 or 6 feet until wet sand is reached, and then dig a little deeper. Gradually, the hole will fill with water. The amount of water available could be very little or very great.

Appropriate places in the desert to search for plant life indicating the presence of water would be along wadis (dry river beds), or in spots under cliffs where *surfaces have been ground smooth* from rocks in mudslides or from flash floods from the occasional rainstorms. Grinding rocks sometimes wear away deep holes in stone beneath cliffs, which become filled with a mixture of rocks and water, and then are covered with a thick layer of mud. The water remains to be found and used.

Source: Y. Gutterman, PhD; Professor, Blaustein Institute for Desert Research, Ben-Gurion University of the Negev, Sede Boker, Israel. Personal communication, 1980.

not swallow the Government hard bread; after being masticated it accumulated between the teeth and in the palate, whence it had to be extracted with the fingers; the same occurred with mesquite beans and whatever else they attempted to eat. The sensibility of the lingual and buccal mucous membranes was so much impaired that they could not perceive when anything was in their mouths. … [B]rown sugar would not dissolve in their mouths, and it was impossible for them to swallow it. Vertigo and dimness of vision affected all; they had difficulty in speaking, voices weak and strange sounding, and they were troubled with deafness, appearing stupid to each other, questions having to be repeated several times before they could be understood; they were also very feeble and had a tottering gait. Many were delirious. What little sleep they were able to get was disturbed with ever recurring dreams of banquets, feasts, and similar scenes in which they were enjoying every kind of dainty food and delicious drink. At this stage they would in all likelihood have perished had they not resorted to the use of horse blood. As the horses gave out they cut them open and drank their blood. The horses had been so long deprived of every kind of fluid that their blood was thick and coagulated instantly on exposure; nevertheless, at the time it appeared more delicious than anything they had ever tasted; in fact every one was so eager to obtain it that discipline alone prevented them from struggling for more than the stinted share allowable to each. The heart and other viscera were grasped and sucked as if to secure even the semblance of moisture. At first they could not swallow the clotted blood, but had to hold it in their mouths, moving it to and fro between the teeth until it became somewhat broken up, after which they were enabled to force it down their parched throats. This horse blood quickly developed diarrhea, passing though the bowels almost as soon as taken; their own urine, which was very scanty and deep colored, they drank thankfully, first sweetening it with sugar. The inclination to urinate was absent and micturition performed with difficulty. A few drank the horses' urine, although at times it was caught in cups and given to the animals themselves. They became oppressed with dyspnea and a feeling of suffocation as though the sides of the trachea were adhering, to relieve which they closed the lips and breathed through the nose, prolonging the intervals between each inspiration as much as possible, gazing on each other, their lips thus closed were

observed to be covered with a whitish, dry froth and had a ghostly, pale, lifeless appearance as though they would never be opened again. Their fingers and the palms of their hands looked shrivelled and pale; some who had removed their boots suffered from swollen feet and legs.[4(pp194–195)]

PATHOPHYSIOLOGY OF HEATSTROKE

Hyperthermia and dehydration are two different illnesses, but which interact and may cause heatstroke. A given hyperthermic core temperature (T_c) leads to one level of altered cardiovascular functions (cardiac output, stroke volume, blood pressure, systemic vascular resistance) and dehydration, another. However, when a subject is rendered both hyperthermic and dehydrated, the alterations in cardiovascular variables may become even greater than their sum.[5] Soldiers in a hot environment, even at rest, are usually moderately dehydrated (except immediately after a meal) unless they are forced to drink by command. Therefore, in summer, heatstroke is accompanied by some degree of dehydration. For details of the mechanisms of heat production and dissipation see Chapter 2, Human Adaptation to Hot Environments, and Chapter 3, Physical Exercise in Hot Climates: Physiology, Performance, and Biomedical Issues.

Effect of Hyperthermia on Cells

Ion Pathways in the Plasma Membrane

Ions do not readily cross lipid bilayers despite their large concentration gradients across plasma membranes. In general, they require specialized channels or carriers to do so (Figure 5-2). Membrane channels are proteins that contain hydrophilic pores that penetrate the lipid bilayer, permitting the diffusion of specific ions down their electrochemical gradients to enter or leave cells.[6] Cotransporters are different types of pathways, which move the ions across the cell membranes *up* their electrochemical gradients by coupling the translocation of at least two ions (eg, K^+ and Cl^-), using the energy stored in preformed chemical gradients such as those of H^+ or Na^+ (rather than the concentration gradients of the transported ions).[6]

The Na-K-2Cl Cotransporter. This important family is present in most cell types, especially in excitable cells and red blood cells (RBCs), and mediates the coupled, electrically neutral movement of Na^+, K^+, and Cl^-, and water. The driving force is solely the chemical gradients of the three ions. Under normal conditions, on the one hand the force mediates an inward movement of Na^+, K^+, and Cl^-, and, on the other hand, interacts with K^+ channels and the Na^+/K^+ adenosine triphosphatase (ATPase) pump for the secretion of salt.[7]

The K-Cl Cotransporter. This pathway is present in many cell types but is not normally active. However, heat and osmotic swelling activate this cotransporter and lead to a *net efflux of K^+, Cl^-, and water,* with a consequent decrease in cell volume. Furthermore, it may be involved in the heat-induced exacerbation of sickle-cell disease. In that disease, there is a genetic defect in the hemoglobin (Hb) ß-chain, leading to polymerization of the hemoglobin and causing characteristic sickling of the cells. The rate and extent of polymerization greatly increase with small decreases in RBC volume. Patients with sickle-cell anemia have very active K-Cl cotransport mechanisms in their RBCs. As a result, during heat stress the K-Cl cotransporter is activated, resulting in smaller volumes in those RBCs, increased polymerization of hemoglobin, and, consequently, enhanced pathology.[8,9]

The Na^+/H^+ Exchanger. This is an electrically neutral transporter that exchanges *extra*cellular Na^+ with *intra*cellular H^+ (ie, Na^+ *enters* and H^+ *leaves*). In many cell types it regulates (*a*) both intracellular pH (pH_i) and plasma H^+, (*b*) the concentration of intracellular sodium ($[Na^+]_i$), and (*c*) cell volume. The exchanger is normally "silent" and is activated by intracellular acidosis, returning pH_i to resting levels, and only indirectly regulates $[Na^+]_i$. It is powerfully stimulated by cell shrinkage (which occurs during the hypovolemia associated with heat stress) and regulates cell volume together with the Na^+-K^+-$2Cl^-$ cotransporter.

The Na^+/Ca^{2+} Exchanger. Normally, the Na^+/Ca^{2+} exchanger in the "forward" mode transports Ca^{2+} out of cells coupled to Na^+ influx with a usual stoichiometry of 3 Na^+ to 1 Ca^{2+}.[10] However, in some cell types, particularly in excitable cells, elevated $[Na^+]_i$ may cause the exchanger to operate in the "reverse" mode and transport Na^+ out of the cell, coupled with the entry of Ca^{2+}.[10] The Na^+/Ca^{2+} exchanger normally operates at only a very small fraction of its maximum capacity and is capable of great activity, fast enough so that *during an action potential in muscle, the transient local elevation of $[Na^+]_i$ triggers the Na^+/Ca^{2+} exchanger, speeding Ca^{2+} influx* and causing the subsequent regenerative release of Ca^{2+} from the sarcoplasmic reticulum.

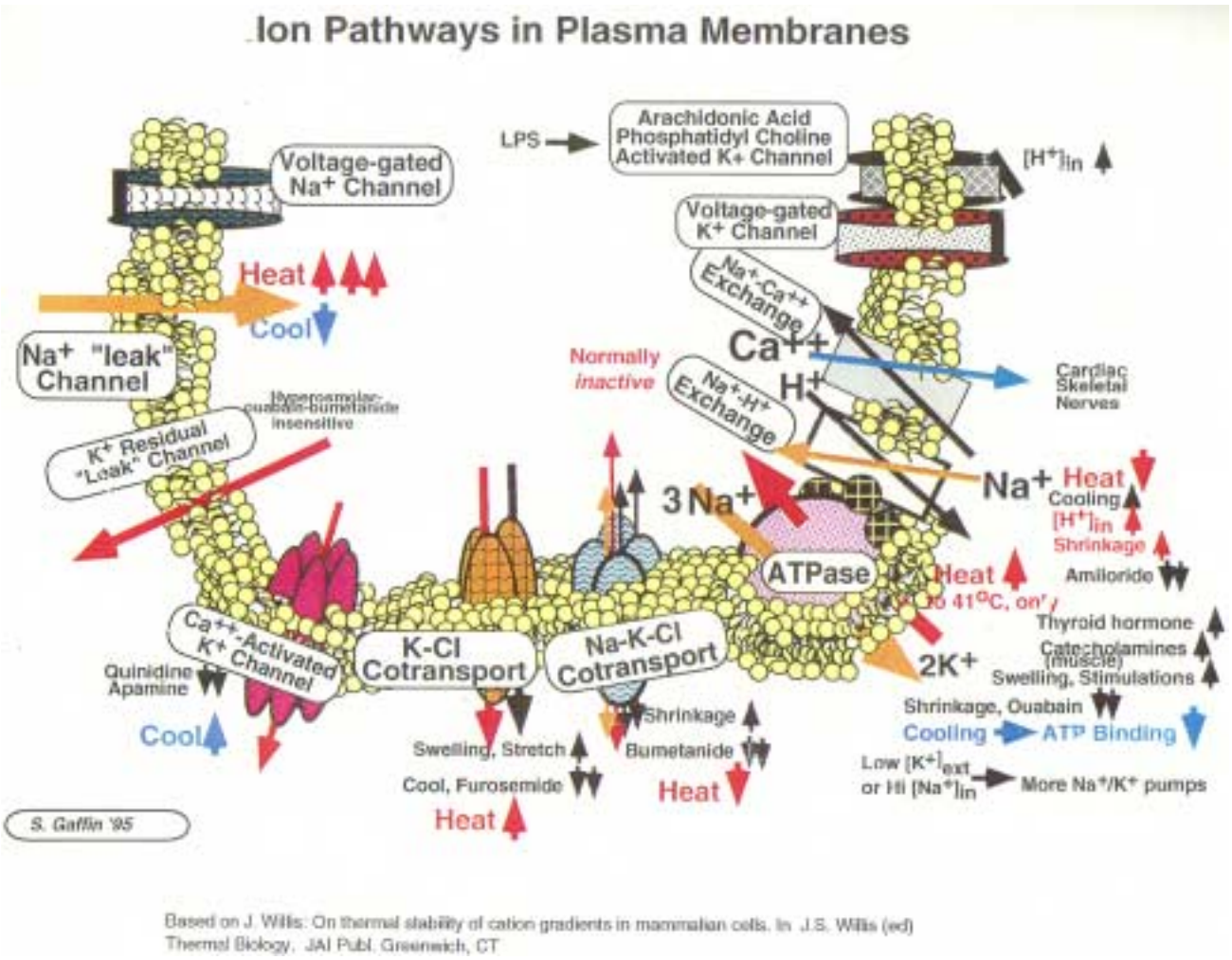

Fig. 5-2. Membrane pumps and ion pathways. Cell membranes contain a variety of specialized proteins that mediate ion transport across the plasma membrane and intracellular ion concentrations. These proteins may form channels through which ions travel passively, according to their electrochemical gradients, and may have gates "opened" or "closed" by elevated or reduced transmembrane potential, or the presence of specific intracellular ions, metabolites, or extracellular hormones (voltage-gated Na^+ channel, Na^+ leak channel, K^+ residual "leak" channel, Ca^{2+} voltage– or arachidonic acid–activated K^+ channel). Other substances may be transported across cell membranes by a "pump" mechanism (Na^+K^+ATPase) requiring a chemical energy source (adenosine triphosphate), by using the energy of preformed gradients (Na^+–H^+ exchanger, Na^+–Ca^{2+} exchanger, or by carrying along other ions (Na–K–Cl cotransporters). Temperature changes alter the transport rate of each process, which, in turn, can alter intracellular (in) and extracellular (ext) ion concentrations.
Source: Willis JS. Thermal compensation of passive membrane transport of cations: A lesson from nonhibernators. In: Geiser F, Hulbert AJ, Nicol SC, eds. *Adaptations to the Cold: 10th International Hibernation Symposium*. Armidale, New South Wales, Australia: University of New England Press; 1996: 253.

Other Pathways. Other pathways present in most cells include the Na^+/K^+ ATPase pump, Ca^{2+} ATPase pump, and Ca^{2+} channels, as well as the passive diffusion channels for Na^+, K^+, and Cl^- (see Figure 5-2).[11] Heat alters the rate and function of some of those pathways, leading to changes in intracellular concentrations of Na^+, K^+, Ca^{2+}, and Cl^-, all of which may alter cellular metabolism, tissue function, and reflexes, and lead to dyshomeostasis and heat illness. Specifically, both $[Na^+]_i$ and the concentration of intracellular calcium ($[Ca^{2+}]_i$) increase with heating.[12,13]

Cell Shape

Heat stress causes changes in the structure of subcellular organelles in many cell types including

detachment of cortical microfilaments from the plasma membrane,[14] collapse of the cytoskeleton, swelling of the mitochondria and the endoplasmic reticulum,[15] and disaggregation of polyribosomes[16,17] and nucleoli.[17] Furthermore, heat causes the plasma membrane to undergo gross deformations, forming bulges known as blebs.[18] Blebs result from heat-induced increases in membrane fluidity,[19,20] altered membrane function,[21] increased permeability[22] with solute leakage,[23–27] and alterations in the linkage of the cytoskeleton to the plasma membrane.[28] Such changes are not necessarily lethal and, up to a point, bleb formation may be adaptive, leading to increased survival of the cell.[29–31] The more severely the cells are heated in vitro, the greater the extent of blebbing and greater is the proportion of cells killed.[30,32] For additional information, see the review by Hales, Hubbard, and Gaffin in the *Handbook of Physiology*.[33]

RBCs also undergo rearrangements in the cytoskeleton with heat and, rather than forming blebs, they form spheroids at elevated temperatures. These enlarged, spherically shaped cells are much less efficient at gas exchange than normal RBCs and probably contribute to reduced partial pressure of oxygen (Po_2) in the tissues at elevated temperatures. Spheroid formation has been found in athletes during long-distance running and may contribute to their physical collapse during exercise.[34]

Increased membrane permeability is indicated by rises in circulating enzymes. Creatine kinase is the first enzyme detected at a T_c as low as 39.5°C in monkeys,[35] and 42.5°C in rats, followed by lactate dehydrogenase.[36]

Apoptosis

Suicide of certain individual cells in the body (apoptosis) is genetically programmed and necessary during embryogenesis, development, metamorphosis, normal cell turnover, and tissue repair. In this process, cells are broken into small vesicles containing characteristic highly condensed chromatin surrounded by intact cell membranes (apoptotic bodies), which become phagocytosed by macrophages or neighboring cells. Apoptosis differs from necrosis in that the latter involves early swelling, destruction of the plasma membrane, and spewing of cell contents into the extracellular milieu. Furthermore, necrosis may provoke an inflammatory response and lead to damage or death of neighboring cells.[37]

Whereas apoptosis had been considered to be a normal, genetically programmed event, high temperatures also cause apoptosis in experimental animals and cultured cells. Hyperthermia to 41.5°C to 42.0°C for a few minutes to an hour or two caused some cells in a variety of mammalian cell types to undergo apoptosis during the next several hours.[38,39] The greatest level of whole-body hyperthermia-induced apoptosis occurs in the thymus, spleen, and lymph nodes, and in the small intestinal mucosa. Resistance to inappropriate apoptosis can be experimentally induced in cultured cells by stresses that induce heat shock proteins (see discussion below).[40] In polymorphonuclear leukocytes, the presence of interleukin-6 delays normal apoptosis following inflammation, and in that case, may lead to tissue injury through excess local production of active oxygen species from the too-old polymorphonuclear leukocytes.[41–43] Long-distance running or marching with a heavy load in the summer can lead to a T_c of 41.5°C to 42.0°C. In principle, this rise in temperature may lead to inappropriate apoptosis in some cells and render a soldier at risk during the following day. Table 5-1 displays the rise in core (rectal, T_{re}) temperatures of eight acclimatized Israeli soldiers, each carrying a 35-kg pack, after they marched 8 hours on an "ordinary" summer day; short rest periods were taken during the march. The core temperatures of all soldiers rose, the lowest by 0.9 Centigrade degrees and the highest by 5.0 Centigrade degrees.

In response to a rising local temperature, the least stable proteins within the body denature and their functional activities fall. However, because of the presence of diverse alternative metabolic pathways within individual cells, the cells are able to survive for minutes to hours or longer, or until temperature rises so much that even those pathways are compro-

TABLE 5-1

ISRAELI SOLDIERS' CORE TEMPERATURE RISE DURING AN 8-HOUR MARCH*

Soldier No.	T_{re} Before March	T_{re} at End of March
1	37.6	39.9
2	37.3	40.6
3	37.4	38.3
4	37.4	42.1
5	37.8	41.5
6	37.4	42.4
7	37.6	42.2
8	37.3	41.5

*Carrying a 35-kg pack
T_{re}: Rectal temperature
Reprinted with permission from Gilat T, Shibolet S, Sohar E. The mechanism of heatstroke. *J Trop Med Hyg.* 1963;66:208.

mised. Membrane pumps may increase their activities with temperature, but eventually they peak and then decline, leading to alterations in the concentrations of intracellular electrolytes (see Figure 5-2). There is probably also a time–temperature relationship at which the pump deteriorates at lower temperatures, if held there for sufficient time. In addition, the increasing fluidity of the membrane with temperature further alters membrane permeability and function.

Rises in temperature increase rates of chemical reactions including adenosine 5'-triphosphate (ATP) hydrolysis, thereby requiring greater O_2 and nutrient delivery to each cell, and faster transport of CO_2 and waste products to the lungs, liver, and kidneys. Consequently, a soldier's respiratory rate rises with temperature but eventually peaks and then declines, resulting in reduced arterial O_2 concentration, rising CO_2 concentration, and falling pH.[44] (The rise in respiratory rate leads to deleterious alterations in blood chemistry and an increase in O_2 demand by the muscles of respiration, which in extreme situations, can lead to respiratory failure. Consequently, respiratory failure is often a component of the pathophysiology of severe heatstroke.) Such conditions lead to increased lactate production by anaerobic pathways and acidosis. Furthermore, if the temperature is sufficiently elevated, then additional lactate may be produced even in the presence of normal O_2 delivery.[44] Overall, in response to hyperthermia and elevated rates of ATP hydrolysis, there occur relative and absolute reductions in O_2 and nutrient delivery, acidosis, and a drop in intracellular ATP concentration.

Calcium

Because so many metabolic pathways are activated by transient high $[Ca^{2+}]_i$, including the opening of Ca^{2+}-activated K^+ channels for K^+ efflux, Ca^{2+} regulation is critical for cell survival. Because of its double charge, Ca^{2+} cannot "leak" through a normal plasma membrane by diffusion but requires a variety of Ca^{2+} channels, exchangers, and pumps. Because its electrochemical gradient permits inward diffusion, influx of Ca^{2+} is mediated by both the reverse mode of the Na^+/Ca^{2+} exchanger and by calcium channels. Ionic calcium efflux, however, is strongly impeded by both unfavorable concentration gradient and charge. Ca^{2+} has two mechanisms for exiting from the cell[10]:

1. a rapid, high-capacity but low-affinity Na^+/Ca^{2+} exchanger, mentioned above, and
2. a slower but high-affinity membrane Ca^{2+} ATPase pump, which is ATP-dependent.

Heating a variety of cell types causes an elevation of $[Ca^{2+}]_i$ from a "resting" level of approximately 100 to 300 nmol, to 700 to 1,000 nmol by the entry of Ca^{2+} from external solution and from the release of Ca^{2+} from the intracellular calcium stores.[13] This rise appears to be greater in cells obtained from black individuals than in those from white individuals, but the biochemical and physiological implications are unclear.[45] Heat acclimation of certain cell lines blunts this heat-induced rise in $[Ca^{2+}]_i$.[46]

Sodium

Because of the well-known pH-dependence of chemical reactions, the maintenance of intracellular pH within very narrow limits is an important cellular requirement. During cellular acidosis a major pathway for proton removal is the Na^+/H^+ exchanger (Na^+ enters, H^+ leaves), which is "quiet" at normal pH but is activated by acidification and by cell shrinkage.[11,47] Heat activates the exchanger indirectly through both pathways. The temperatures observed in heat illnesses alter metabolism and acidify cells by 0.1 to 0.4 pH units, and sweating caused by hyperthermia leads to hyperosmolality, causing cells to shrink. Both the acidosis and shrinkage pathways activate the Na^+/H^+ exchanger, leading to a rise in $[Na^+]_i$ as protons are removed. The activity of the Na^+/H^+ exchanger may also be seasonally adjusted (presumably it is more active in summer), as part of a more general acclimatization response, because the Na^+/H^+ exchanger is only minimally active in bears during hibernation.[11] The increase in $[Na^+]_i$ in severe hyperthermia is not a transient event but probably is sustained for several minutes to hours after return to normothermia, until it is eventually returned to normal values by other pathways such as the Na^+/K^+ ATPase pump.

Heating cells to 42°C to 43°C causes a rise in $[Na^+]_i$, which may activate the Na^+/Ca^{2+} exchanger, thus indirectly altering $[Ca^{2+}]_i$. This rise in $[Na^+]_i$ persists for minutes to hours after a cell returns to 37°C, and thus alters cell physiology for a prolonged period of time. This temperature seems to be a "critical" temperature in heatstroke pathophysiology because significant deaths in passive heatstroke (ie, in a resting or anesthetized experimental animal) also commence at rectal temperatures of 42°C to 43°C. However, the temperature leading to injury and death depends on a variety of factors and is lower during exercise and varies with health status, hydration, and recent illness. A highly motivated soldier may not admit any illness, and this is a particularly serious risk factor.

Possibly, elevated $[Na^+]_i$ is a "trigger," which through elevated $[Ca^{2+}]_i$, activates cell metabolic pathways and consequent pathophysiological actions, leading to irreversibility and heatstroke death. A rise in $[Na^+]_i$ in excitable cells, according to the Nernst relationship, leads to a reduced magnitude of action potential. In the brain, this would reduce the amount of neurotransmitter released, which in turn, would alter synaptic-dependent events such as cognition, initiation of reflexes, possibly causing inappropriate changes in skin blood flow (BF_{sk}) and sweat secretion, and lead to an overall rise in T_c and death. High temperatures due to infection would also be expected to show rises in $[Na^+]_i$ with similar alterations in brain function.

This rise in $[Na^+]_i$ due to hyperthermia may have important biochemical, metabolic, and physiological effects:

1. Because of the 3:1 stoichiometry of Na^+:Ca^{2+} in the Na^+/Ca^{2+} exchanger, its energetics and direction depend on the cube of the Na^+ concentration gradient. Therefore, a small change in $[Na^+]_i$ would greatly alter the driving force of Ca^{2+} movements via the Na^+/Ca^{2+} exchanger. With a typical $[Na^+]_i$ of 6 mmol and a resting membrane potential (Em) of –70 mV, the driving force is in the direction of net Ca^{2+} efflux, as is normally required by the cell. However, if $[Na^+]_i$ should rise to 15 mmol, then the exchanger would catalyze net *Ca^{2+}influx* in resting cells, obviously leading to major metabolic changes, including the lowering of $[K^+]_i$ through the opening of Ca^{2+}-activated K^+ channels.[48]
2. A rise in $[Na^+]_i$ in nerve and muscle cells would reduce the magnitude of action potentials, according to the Nernst relationship, and in the brain would reduce the amount of neurotransmitter released in synapses. Alterations in synaptic activity could affect reflexes and sensoria and could account for the dyshomeostasis in much of the pathophysiology described here, as well as explain the altered mental activity of heatstroke.

This pathway may be involved in a positive feedback loop, in which high T_c (through acidosis) increases $[Na^+]_i$, which elevates the Na^+-K^+ ATPase activity, and results in still greater production of heat. In addition, dehydration would lead to cell shrinkage, in turn activating the Na^+-H^+ exchange, leading to a positive feedback loop of more rapid entry of Na^+, raised $[Na^+]_i$, consequent speed-up of the Na^+/K^+ ATPase pump, and even more elevated heat production.

Potassium

Experimentally, heating causes a *net loss* of potassium ions from cultured cells in vitro and causes a *rise* in plasma K^+ in vivo.[26,49,50] Up to a T_c of approximately 41°C, $[K^+]_i$ and $[Na^+]_i$ remain approximately constant despite their increased influxes and effluxes through diffusion and the Na^+/K^+ ATPase pump.[51] However, the 3:2 stoichiometry of the Na^+/K^+ ATPase pump should lead to a net rise in $[K^+]_i$. Because this does not occur, excess K^+ must be transferred out of the cell by other pathways, which may include the K^+-Cl^- cotransporter, Na^+-K^+-$2Cl^-$ cotransporter, diffusion through Ca^{2+}-activated K^+ channels, or arachidonic acid (AA)–activated K^+ channels. Because the K^+-Cl^- cotransporter is activated by warming, this is probably the main pathway by which K^+ leaves cells during hyperthermia.

The decline in $[K^+]_i$ indicates the ultimate inability of the Na^+/K^+ ATPase pump and Na^+-K^+-$2Cl^-$ cotransporter to balance the increased K^+ efflux through the K-Cl cotransporter. Because a good deal of wasted heat is liberated during the hydrolysis of ATP by the Na^+/K^+ ATPase pump, the benefits of rapid cooling in cases of mammalian heatstroke are due, in part, to the slowing of this pump.

Hyperthermia as well as physical exercise leads to a progressive rise in plasma K^+ concentration, reaching almost twice the normal value in some studies.[52] Such elevated plasma values during heat and exercise suggest that in tissues, concentrations may reach as high as 16 mEq/L, enough to substantially depolarize cell membranes, alter nerve and muscle function, and increase metabolic activity.[53] This rise in ionic potassium concentration outside the cell ($[K^+]_o$) might contribute to any pathophysiology induced by elevated $[Na^+]_i$ causing heat illnesses.

During low-intensity exercise, for each contraction of skeletal muscle, 7 to 11 nmol/g of Na^+ and K^+ enter and leave the cell, with a net gain of Na^+ and loss of K^+ before the Na^+/K^+ ATPase pumps are activated.[54] During near-tetanic and tetanic contractions, these changes in ion concentrations may overwhelm the pumps' capacity, even when operating at maximum rates. As a result, during exercise at normal or only moderately elevated T_c, plasma $[K^+]$ rises.[52,55] Because heat alone causes hyperkalemia, the additional K^+ due to exercise in the heat may place an insurmountable burden on a soldier, ren-

dering him susceptible to muscle weakness, fatigue, and exertional heatstroke. Elevating $[K^+]_i$ to 7 mmol causes profound weakness in humans by reducing the propagation velocities of action potentials and reducing the amplitude of the action potentials (because the membrane potentials depolarize from a less negative voltage), which reduces the amount of Ca^{2+} released into the cytoplasm of a muscle fiber.[54,56] This weakness is a protective negative feedback process, as it inhibits further muscular activity. On the other hand, certain pharmaceutical agents can reverse these effects. Treating K^+-depressed muscle with insulin, $ß_2$ blockers, and calcitonin gene-related peptide activates the Na^+/K^+ ATPase pumps within minutes, reducing $[Na^+]_i$; effects hyperpolarization; and restores muscle strength. In the future, these treatments may be found to be therapeutic for muscle weakness, fatigue, and heatstroke.

Elevations in K^+ concentrations may not be all bad. Elevated extracellular $[K^+]$ would affect nerve endings, thereby altering their sensitivities, and may be involved in a neural feedback mechanism that modulates the firing rate of motor neurons during exercise, especially exercise in the heat. This feedback mechanism could initiate protective cardiovascular reflexes such as postexercise hyperemia and rapid heart rate.[57] After exercise has ceased, reuptake of K^+ into the exercising muscles may take minutes of increased blood flow, but restoration of overall water and electrolyte balances with the various body compartments could take much longer.[54]

Energy Depletion Model

During heat stress and elevated T_c, the Na^+/K^+ ATPase pumps operate at increasing rates, hence hydrolyzing ATP more rapidly and liberating waste heat into the body faster. If the body cannot dissipate all this heat though radiation, conduction, convection, and evaporation of sweat, then, according to the laws of thermodynamics, T_c must rise, leading to still greater rates of the Na^+/K^+ ATPase pumps—an ominous positive feedback loop. The total amount of energy available to a cell is limited. Therefore, at a certain elevated temperature, ATP utilized by the activated Na^+/K^+ ATPase pump is no longer available for normal cellular processes and the cell becomes energy depleted. Experimental support for this concept is the presence of swollen cells (implying a slowing of ion pumps, which affect water transport) and the rapid development of rigor mortis (caused by depletion of ATP) at the end stage of heatstroke pathophysiology.[58] Furthermore, this concept also explains the occurrence of heatstroke deaths at lower T_c in persons exercising in the heat.[59]

Because plasma $[K^+]$ eventually rises during heat stress, and the main store of K^+ is in cells, then $[K^+]_i$ must fall. This fall would be mediated by such means as the K-Cl cotransporter and Ca^{2+}-activated K^+ channels. Overall, the rise in activity of the various ion pumps provides more waste heat, which, near the limit of sweat secretion, increases T_c still more.

Pathological Manifestations of Heatstroke in Mammals

In contrast to threshold hyperthermia mortality temperature of 42°C to 43°C for animals at rest, in exercised, heat-stressed rats, mortality occurs at a lower temperature: 40.4°C.[60] What may account for this critical temperature? Between 37°C and 40.4°C and higher, two fundamental cellular functions are altered: (1) the rate of transmembrane ion flux is increased, and (2) the rate of protein synthesis is inhibited.

As T_c rises toward and above 42°C, most of the homeostatic systems within the body are near crucial limits for proper functioning. Severe hyperthermia acts on thermoreceptors to maximize their inputs to the hypothalamus to increase stroke volume and heart rate; BF_{sk} has reached its maximum; sweating has caused plasma osmolality to rise well above the thirst threshold, and the victim experiences severe thirst (unless there has been adequate ingestion of fluids by command). Plasma volume is greatly reduced, leading to high hematocrit values and greatly increased blood viscosity, which in turn, require the heart to use more energy to maintain the same cardiac output. As plasma volume continues to fall and osmolality to rise, the secretion of sweat falls, leading to reduced rates of evaporation and cooling and even faster rises in T_c—a second ominous positive feedback loop. Eventually, BF_{sk} as well as sweat secretion fall, and heat dissipation fails.

The pathological features of heatstroke are similar no matter what the cause of the heat illness. They are manifested by (1) swelling and degeneration of tissue and cell structures, and (2) widespread microscopic to massive hemorrhages.[61] The organs are congested, with increased weights and swollen cells.

Kidney

During moderate hyperthermia and normovolemia, the "excess" plasma K^+ released from the cells is excreted in the kidneys, thus maintaining normokalemia. In response to moderate hyperthermia and gradually decreasing blood volumes, blood flow to the kid-

neys is reduced, leading to reduced filtration and reduced urinary flow. Nevertheless, K^+ excretion persists and plasma K^+ is maintained near normal levels until blood pressure has fallen significantly. Eventually, as T_c rises above approximately 42°C and mean arterial pressure falls, renal blood flow is greatly reduced, and kidney function fails.[44] At this point, the K^+ released from cells in response to hyperthermia is no longer excreted; it accumulates in the plasma, leading to frank hyperkalemia. Plasma K^+ concentration may rise as high as 8 mmol, approximately double baseline levels. Eight millimoles of potassium in the blood implies the presence of 16 mmol K^+ in extracellular fluid in the tissues, a value high enough to depolarize some excitable tissues almost to threshold.

When T_c has risen so high that mean arterial pressure (MAP) falls, the O_2 content of arterial blood also falls.[44] At approximately the same time, renal blood flow drops still further and may be reduced to such low levels that O_2 delivery is below the minimum required for survival, and tissue destruction follows. Renal failure is an often-reported consequence of heatstroke.

At postmortem examination, the kidneys are found congested with macroscopic hemorrhages in 20% of cases.[61(p288)] Pigmented casts were present in the distal convoluted tubules when heatstroke victims survived more than 24 hours before dying.[61]

Circulation: Electrolyte Imbalance

In experimental studies using isolated cells, hyperthermia leads to a rise in $[Na^+]_i$ and a fall in $[K^+]_i$, but the results are far from clear in patients in the clinical setting. On admission to a hospital, victims of heat illnesses may have elevated, normal, or reduced concentrations of serum Na^+ or K^+. The interpretation of these results has generated controversy. However, on the basis of recent studies, the results may be explained as follows[44]:

1. Hyperthermia leads to a primary loss of K^+ from tissues into the blood circulation.
2. In a victim of heatstroke, the kidney would excrete this "excess" K^+ into the urine, thus maintaining normal or near-normal serum K^+.
3. When the combination of elevated T_c and dehydration is sufficiently severe, renal blood flow, filtration, and urine output all fall, with a consequent rise in serum K^+.
4. However, if the hyperkalemic victim is infused with liters of crystalloid in the field, thus raising systemic blood pressure, then normal renal function may return, causing a rapid excretion of the elevated plasma K^+ into the urine.
5. Cooling of the victim to near 37°C would terminate loss of K^+ from the tissues and cause the reuptake of K^+ by the cells from extracellular fluid. The K-Cl exchanger becomes *in*activated by cooler temperatures, while the Na^+/K^+ ATPase pump continues to pump K^+ inward from interstitial fluid and plasma.
6. As a result, by the time the victim reaches a hospital, serum K^+ may be reduced to normokalemia or even *hypo*kalemia.

Prior conditions, such as intense training in the heat over a period of several days, tend to lower body potassium, thus worsening hypokalemia. Similarly, acute intense hyperthermia could mask preexisting hypokalemia by acutely raising plasma levels. On treatment, potassium levels would return to normal ranges, effectively producing misleading clinical indications. Thus, to arrive at a better diagnosis and prognosis, it is important for the medical officer to know the thermal exposure and nutritional history of the soldier before collapse. Hyperkalemia is usually a grave clinical sign.

Studies of sodium concentration are less clear and represent an equally complex diagnostic situation because there is only a small absolute rise in $[Na^+]_i$, and this loss from the circulation represents a small percentage of the background serum sodium. Elevations in serum sodium are often secondary to depletion of body water.

Within certain temperature limits, normal thermoregulatory mechanisms are capable of restoring T_c to 37°C from either hyperthermia or hypothermia. However, if T_c rises to approximately 42.5°C, then metabolic pathways may be so affected that inappropriate physiological responses occur. Vascular collapse, shock, and death can follow unless countermeasures such as cooling and therapy to increase plasma volume are initiated. It is not certain at present whether there is a *single* critical intracellular derangement occurring at 42.5°C that ultimately leads to the activation of many harmful metabolic pathways and heatstroke death, or if *many* harmful pathways become independently established at about the same time in response to the given temperature. Probably it is the latter. In any case, the *beneficial impact of rapid cooling* on the underlying causes of energy depleting reactions *cannot be overstated,* and correlates well with reduced injury and improved recovery.

If a soldier is expending considerable metabolic energy and hydrolyzing ATP at a high rate during severe exercise, then he or she may develop the form of heatstroke called *exertional heatstroke* at a lower temperature than if the soldier had been at rest. In exertional heatstroke, metabolic heat is produced faster than the body's normal ability to dissipate it, a situation that is made worse by a high solar heat load, high ambient temperature, or both. This is in contrast to classic heatstroke, in which the heat-dissipation mechanisms are depressed. This differential mortality and morbidity, with exercise-related factors clearly demonstrated in animal research and certain series of human data, speaks to the existence of other causative parameters such as O_2 availability, energy status, and pH effects rather than direct thermal effects per se. Clearly, the local effect of exercise-induced ischemia and acidosis on certain tissues, and their reaction to heat, on the ultimate outcome of exertional heatstroke makes prediction and prognosis based entirely on thermal history alone very unlikely or exceedingly complex. If a substantial fraction of available high-energy phosphate stores (creatine phosphate plus ATP) within a cell is consumed by exercise, then less remains available for normal cell metabolism, for activating cooling mechanisms (eg, increased cardiac output), and for the repair of damage caused by elevated temperature.

Gut

Postmortem examination of heatstroke victims often shows engorged intestinal vessels, and the gastrointestinal tract may show massive ulcerations and hemorrhages.[61] The gut is an important focus in any discussion of heat illness for two important reasons:

1. its function determines whether ingested fluid and solutes are delivered to the systemic circulation to correct losses and thereby attenuate hyperthermia, dehydration, reductions in splanchnic blood flow, and gut distress; and
2. heatstroke may result from or be exacerbated by gastrointestinal dysfunction, leading to endotoxemia and circulatory collapse.

Current research indicates excellent parity between the rehydration demand and the capacity of the stomach to deliver ingested fluids (gastric emptying under optimal conditions can provide 1.8 L/h) and the intestines' capacity to absorb it (1.4–2.2 L/h). This degree of rehydration capacity should accommodate the average sweating rate of most endurance athletes, given that reductions in splanchnic blood flow (up to 80% with maximal exercise intensity) could not be maintained for long periods before other factors such as fatigue or hyperthermia intervened.

Intense and prolonged running is a common cause of gastrointestinal bleeding, and estimates as high as 85% of ultramarathoners demonstrate guaiac-positive stools from a 100-km race.[62] This bleeding varies in intensity from runner to runner and is due to gut ischemia, trauma to the gut wall, and the use of nonsteroidal antiinflammatory drugs. Exercise-induced gastrointestinal bleeding is most often mild but can be serious, and the serious cases speak to the more important issue of periodic bouts of decreased gut barrier function, especially when combined with nausea, diarrhea, and abdominal cramps. Nonsteroidal antiinflammatory drugs are widely used for training and to treat competition injuries and are known to enhance intestinal permeability and bleeding susceptibility.[63] The gastrointestinal tract has been dubbed the "canary of the body," reinforcing the concept that the presence of signs and symptoms in the gastrointestinal tract suggest an underlying disorder likely to be aggravated by exercise.[64]

The lumens of the small and large intestines contain considerable quantities of Gram-negative bacteria and their cell-wall component, highly toxic (10^{-12} mol is lethal) lipopolysaccharide (LPS, also called endotoxin). The combination of high temperature and consequent reduced intestinal blood flow injure the intestinal wall, compromising its ability to prevent LPS and other bacterial toxins from leaking out into the systemic circulation via the portal vein and intraperitoneal space.[65] If the plasma LPS concentration is high enough to overcome all the safeguards that normally inactivate it, then some LPS is complexed with a blood component, LPS-binding protein (LBP), and is bound to the cluster of differentiation 14 (CD14) receptor of macrophages and other cell types. In turn, it induces the inflammatory cytokines, tumor necrosis factor (TNF), and interleukin-1 (IL-1). These, in turn, cause the formation of oxygen free radicals and activate omega-6 fatty acid metabolism, leading to the formation of toxic prostaglandins (PGs), leukotrienes (LTs), and thromboxanes (TXs). Collectively, these agents directly damage cells and reduce blood flow to the tissues, exacerbating the pathophysiology induced by the heat.

LPS causes a second effect mediated by a completely different pathway. LPS binds to the Hageman

factor of blood, activating it, and leads to disseminated intravascular coagulation (DIC), a common complication of heatstroke. As a result of reduced blood clotting, conjunctival hemorrhage; melena; purpura; bloody diarrhea; and lung, renal, or myocardial bleeding frequently occur.[61] It is interesting that the effect of altering these pathways through enrichment of omega-3 fatty acid metabolism could provide future research avenues of investigation. (Interested readers can see Gaffin and Hubbard's 1996 article in *Wilderness and Environmental Medicine*[66] for further information on this topic.)

Liver

Hyperthermia reduces blood flow to the liver at the same time it reduces blood flow to the intestines. Therefore, delivery of O_2 and nutrients to the hepatocytes and Kupffer cells falls as T_c rises. The combination of thermal injury and local ischemia depresses liver function, which may persist even after heatstroke has been resolved. Postmortem examination of a heatstroke victim who died 30 hours after admission to a medical treatment facility showed centrolobular necrosis and, in biopsy specimens, hepatocellular degeneration around the widened centrolobular veins as well as swelling, cholestasis, and leukocytic cholangitis.[67]

Lungs and Respiratory Function

As T_c rises, tidal volume, respiratory rate, heart rate, and, to a lesser extent, stroke volume, also rise to meet the increased metabolic demands. In humans, there is a closely related rise in minute volume and heart rate. Ethical considerations usually limit studies on hyperthermic volunteers to a T_c of 39.5°C or lower. However, the temperatures reached in actual heatstroke may be several Centigrade degrees higher. In animal studies performed at those higher temperatures, respiration increases much faster than cardiac output, and the respiration rate may reach such high levels that the CO_2 is driven off too fast, resulting in respiratory alkalosis. Consistent with this, respiratory alkalosis is common in soldiers suffering from exertional heatstroke or exertional heat exhaustion with syncope and cramps.

When T_c rises sufficiently, the minute ventilation reaches a maximum and then rapidly declines to low values and may cease altogether.[44] As a result, blood becomes hypercapnic and acidotic and, if not rapidly treated, can lead to death with final pH approaching 6.9 to 6.8. In other words, heatstroke is first characterized by a respiratory alkalosis, and then is followed by a metabolic and respiratory acidosis.

Central Venous Pressure and Baroreceptors

In addition to the maintenance of heart function, proper function of the central nervous system (CNS) is probably most critical for survival during heatstroke. During early hyperthermia, arterial blood pressure remains approximately constant even though central venous pressure (CVP) progressively falls. This lowered CVP helps maintain adequate blood perfusion through the CNS by increasing the driving pressure, reducing the CNS vascular resistance by means of local vasodilation, or both. The unloading of baroreceptors in the great veins and atria is the stimulus for maintaining or raising CNS blood flow. When central blood volume was experimentally reduced in steps, arterioles in the forearm constricted first, then flow to the periphery was reduced, and the volume in the peripheral compliance vessels was reduced.[68] When the central blood volume was sufficiently reduced, and with CVP and MAP sufficiently low, then baroreceptor responses caused the forearm veins to contract to aid in the central mobilization of blood volume to resist decompensation.[69–71]

At moderate hyperthermia, thermoreceptors acting through the hypothalamus cause a dominant drive within the body toward vasodilation, leading to increasingly elevated BF_{sk} and secretion of sweat, resulting in a reduced plasma volume and reduced CVP.[72,73] However, once a certain T_c is exceeded[74,75] there is an altered sensitivity of BF_{sk} to increasing T_c. The central venous baroreceptors now initiate vasoconstrictor drives, which "override" the vasodilator drives from the thermoreceptors. At that T_c, the reduced CVP unloaded baroreceptors located in the great veins and atria. This initiates the changes that are critical to precipitation of heatstroke, such as the reduction in BF_{sk}.[76] Possible interaction between baroreflexes and thermal reflexes is an important consideration.[77] The thermoreceptor system appears somewhat more potent than the baroreceptor system.[78] Normally, CVP is lowered as a result of the high BF_{sk}. That is, at this early stage, BF_{sk} determines CVP, whereas at the final stage of severe heat stress, CVP controls BF_{sk}.[77–79]

To maximize heat loss from the skin, hyperthermic blood should pass only slowly through the cutaneous circulation. Vasodilation and venodilation of the skin provide a highly compliant circuit in the skin, which, owing to the large volume of blood that can be stored in skin, reduces venous return and lowers CVP during heat stress.[72,73] Excessively low CVP, however, leads to reduced cardiac filling, re-

duced stroke volume, and reduced cardiac output. Experimental maintenance of the central blood volume during heat stress increases stroke volume and cardiac output.[80,81] This observation indicates that the defense of CVP, acting via the low-pressure baroreceptors in the thoracic region, causes the late reduction in both skin blood flow and skin blood volume during severe heat stress.

To provide adequate skin perfusion and maintain heat tolerance, it is necessary to sustain elevated cardiac output, and, hence, stroke volume.[72,82–84] Classic heatstroke and exertional heatstroke (discussed later) may differ in this regard, among others (Table 5-2): in exertional heatstroke, stroke volume increases with acute heat stress and exercise, whereas in chronic heat stress (ie, classic heatstroke), stroke volume is initially reduced. Interested readers can consult the 1986 article by L. C. Senay, Jr., in the *Yale Journal of Biology and Medicine*[85] for further information on classic heatstroke.

This discussion describes the physiology of humans and most animals. However, because of their frequent use in experimental studies, it should be mentioned that in rats, CVP is not the critical determinant of heat tolerance.[86] The reason for this is not known.

Stress Hormones

During the Archeozoic period, organisms developed an immune system that destroys microorganisms. This nonspecific immunity is basic to all phyla today. In the original immune mechanism, the

TABLE 5-2

COMPARISONS BETWEEN CLASSIC AND EXERTIONAL HEATSTROKE

Patient Characeteristics	Heatstroke	
	Classic	**Exertional**
Age group	Elderly	Men (15–45 y)
Health status	Chronically ill	Healthy
Concurrent activity	Sedentary	Strenuous exercise
Drug use	Diuretics, antidepressants, antihypertensives, anticholinergics, antipsychotics	Usually none
Sweating	May be absent	Usually present
Lactic acidosis	Usually absent, poor prognosis if present	Common
Hyperkalemia	Usually absent	Often present
Hypocalcemia	Uncommon	Frequent
Creatine phosphokinase/aldolase	Mildly elevated	Markedly elevated
Rhabdomyolysis	Unusual	Frequently severe
Hyperuricemia	Mild	Severe
Acute renal failure	< 5% of patients	25%–30% of patients
Disseminated intravascular coagulation	Mild	Marked; poor prognosis
Mechanism of heatstroke	Poor dissipation of environmental heat	Excessive endogenous heat production and overwhelming of heat-loss mechanisms

Adapted with permission from Knochel JP, Reed G. Disorders of heat regulation. In: Kleeman CR, Maxwell MH, Narin RG, eds. *Clinical Disorders of Fluid and Electrolyte Metabolism.* New York, NY: McGraw Hill; 1987: 1212.

invader's cytoplasm was chemically destroyed by active oxygen species, including free radicals, produced by the host. During evolution over geological time, a rich variety of defense mechanisms arose with great variation in use and importance of particular mechanisms, and in which specific antibodies play no part.[41] In modern mammalian species, specialized inflammatory cells such as macrophages and natural killer (NK) cells are especially enriched in the enzymes and chemical pathways that produce the toxic free radicals; they also contain additional pathways that allow these inflammatory cells to recognize invaders and penetrate tight epithelial junctions, so the invaders can be easily reached and destroyed. The immune cells are activated by means of circulating and locally produced TNF and IL-1 as part of a stress reaction mediated by the hypothalamus. Natural selection generated a common stress reaction in vertebrates that is activated by stresses other than infections, such as hyperthermia, and activates pathways that produce toxic species, which may now be inappropriate and even toxic to the host. Interested readers can find further information in S. L. Gaffin's chapter in *Adaptation Biology and Medicine* (1999),[42] and M. J. Kluger's 1991 article in *Physiological Reviews*.[43]

The hypothalamus is ordinarily programmed to defend a T_c of approximately 37°C by initiating conventional thermoregulatory vasomotor effector responses to the skin for moderate hypothermia. The presence of circulating pyrogens raises this set point, resulting in fever, which is the defense of an elevated T_c, and not hyperthermia, which is a consequence of excess heat load or insufficient cooling capacity. When the hypothalamus receives thermal information that it interprets as severe hyperthermia, then it initiates a generalized programmed response. Within the anterior pituitary of an unstressed person are normally produced up-regulators of protein and hormone synthesis. These include prolactin, growth hormone (GH), and gonadotropin-releasing hormone (GRH). GRH induces follicle stimulating hormone, luteinizing hormone, and testosterone. Severe stress causes the hypothalamus to secrete corticotropin-releasing factor (CRF), which circulates to the anterior pituitary and down-regulates the synthesis of GH, GRH, and prolactin. At the same time, CRF up-regulates the immunosuppressors ß-endorphin, melanocyte-stimulating hormone, IL-1, TNF, and adrenocorticotropic hormone (ACTH). ACTH, in turn, circulates to the adrenal gland and up-regulates the secretion of the immunosuppressor, cortisol. IL-1 and TNF are part of a positive feedback loop, which causes further secretion of CRF.

Overall, hyperthermic stress initiates pathways that lead to the secretion of immunosuppressors, which can reduce overall resistance to infections. The same pathways are also activated in response to other severe stresses such as exercise, sleep deprivation, or infection and cause further secretion of CRF, lowering overall resistance to heat stress, and increasing the incidence of heat illnesses in general. Simultaneous severe stressors, such as those that occur during combat, become approximately additive in their immunosuppressive effects. (For a review of the effects of psychological factors on the immune system, interested readers should see S. Cohen and T. B. Herbert's 1996 article in the *Annual Review of Psychology*.[87]) Consistent with the general effect of stressors on the immune system, during World War II and the Korean War, the incidence of diseases increased with the intensity of combat.[88]

Both IL-1 and TNF are involved in the regulation of sleep; they are somnogenic, in addition to their role in inflammation. IL-10 inhibits the synthesis of these cytokines and reduces the amount of rapid eye movement sleep in mice. Therefore, rises in IL-10 by stress may alter sleep pattern and times, ultimately increasing the risk for heat illnesses.[89]

Strenuous exercise by athletes increases IL-1, TNF, and IL-6, and decreases interferon-γ (IFN-γ).[90] Changes in cytokine concentrations from exercise may persist for hours to days, and render a soldier at risk to heat the day *after* severe exercise.

Arachidonic Acid–Induced Dysfunctions

TNF and IL-1 exert their toxicity through the production of highly toxic phospholipase A_2 (PLA_2). The binding of TNF and IL-1 to their specific membrane receptors activates G-proteins, which increases the intracellular concentration of cyclic adenosine monophosphate (cAMP), which in turn, stimulates the formation of PLA_2 phosphatase (PLAP). This enzyme then activates the membrane toxin, PLA_2, which hydrolyzes membrane phospholipids, forming small lesions in plasma membranes. Some of those membrane phospholipids contain omega-6 fatty acid bases, producing AA on hydrolysis. AA is a *key metabolite,* which may be acted on by either of two enzymes, lipoxygenase or cyclo-oxygenase, leading to the production of toxic products through two main pathways (Figure 5-3). The lipoxygenase pathway leads to the production of the toxic leukotrienes B_4 (LTB_4) and D_4 (LTD_4), and the cyclo-oxygenase pathway to the production of

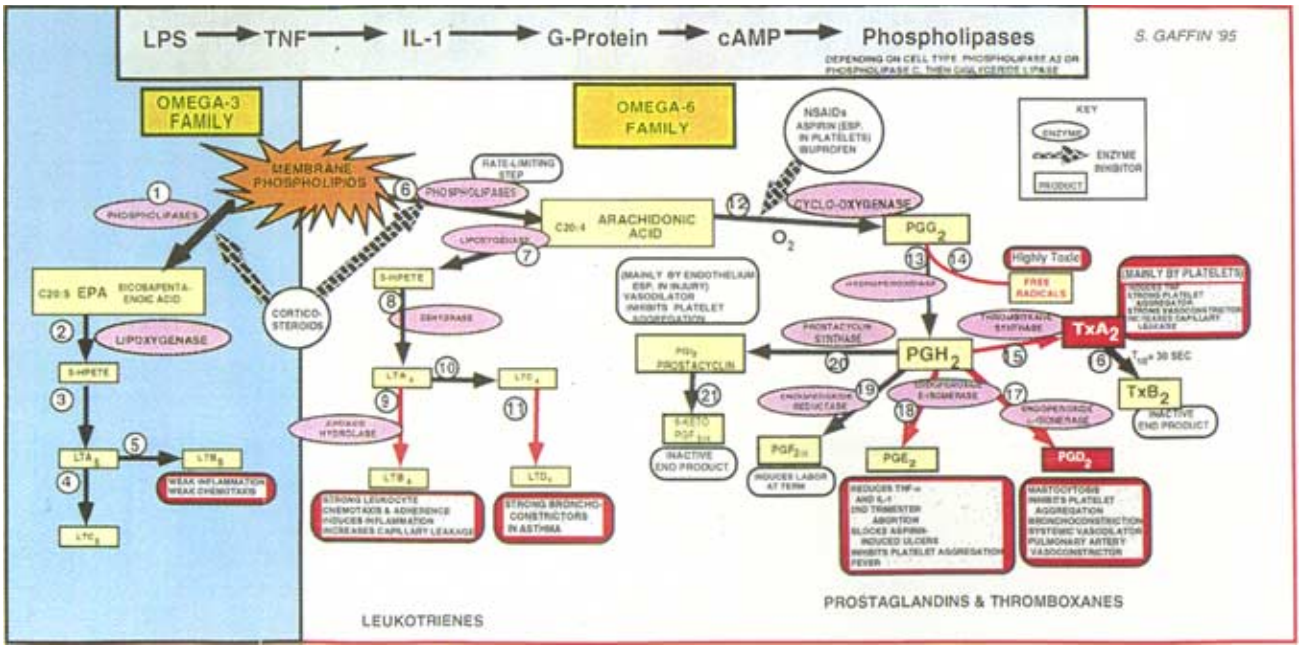

Fig. 5-3. Eicosanoid pathways; metabolism of omega-3 and omega-6 fatty acids induced by lipopolysaccharide (LPS) or cytokines. LPS binds to the CD14 receptor on macrophages, leading to the induction of tumor necrosis factor (TNF) and interleukin 1 (IL-1). These lead to the activation of membrane-associated phospholipase A_2, a critical step in the pathophysiology.

Omega-3 Family. Membrane phospholipids of the omega-3 family are (1) hydrolyzed by phospholipase A_2 into eicosapentaenoic acid (EPA), which is rapidly converted (2–4) into the benign leukotriene C_5 (LTC_5) or (5) weakly inflammatory leukotriene B_5 (LTB_5).

Omega-6 Family. Those phospholipids of the omega-6 family are (6) hydrolyzed by phospholipase A_2, into arachidonic acid, which may be converted by (7) lipoxygenase and (8) dehydrase into the powerful and toxic leukotrienes (9) LTB_4 and (10, 11) LTD_4. Arachidonic acid may also be converted by (12) oxygen and cyclo-oxygenase into prostaglandin G_2 (PGG_2). This is converted with (13) hyperperoxidase into the pivotal PGH_2, producing (14) toxic free radicals. PGH_2 may be converted by (15) thromboxane synthase into the highly toxic, but (16) short-lived thromboxane (TXA_2), or by (17) endoperoxide a-isomerase into the highly toxic PGD_2. Other prostaglandins formed vary (18–21) from mildly toxic to beneficial.

Adapted with permission from Hubbard RW, Gaffin SL, Squire DL. Heat-related illnesses. In: Auerbach PS, ed. *Wilderness Medicine: Management of Wilderness and Environmental Emergencies*. St. Louis, Mo: Mosby; 1995: 182.

toxic free radicals, thromboxane A_2 (TXA_2), and the prostaglandins D_2 (PGD_2) and E_2 (PGE_2).[91] Artificially raising the concentration of the intermediates PLAP or AA increased the plasma concentration of the cytokines, IL-1 and TNF. Therefore, not only can PLA_2 and AA synthesis be stimulated by cytokines, but cytokine concentrations can also be up-regulated by PLAP and AA in an inflammatory response.

LTs and PGs produced from AA cause the following toxic effects:

- LTB_4 and LTD_4 cause leukocyte adherence; induce inflammation and increase capillary leakage, thus reducing plasma volume; and cause the strong bronchoconstriction of asthma.[92,93]
- PGD_2 and PGE_2 cause mastocytosis, bronchoconstriction, vasoconstriction of the pulmonary artery, fever, abortion, and inhibit platelet aggregation.
- TxA_2 induces TNF, increases capillary leakage, and is a strong vasoconstrictor.
- The oxygen free radicals produced in the cyclo-oxygenase pathway damage cellular DNA and may cause cell death.

To a person in shock or with other circulatory disturbances, such agents could convert a serious but treatable condition into a lethal one. For more complete discussions of these pathways, see the 1988

articles in the *New England Journal of Medicine* by J. A. Oates and colleagues[94,95] and the 1992 article by G. Bottoms and R. Adams in the *Journal of the American Veterinary Medical Association*.[96]

The production of the key compound, AA, depends on the activation of PLAs and the presence of omega-6 fatty acids in plasma membranes.[97,98] The PLAs break down phospholipid esters of fatty acids, including the omega-6 fatty acids, which predominate in cell membranes of an individual on a normal Western diet.[99,100]

Fever and Infections

Normal T_c is maintained by a variety of homeostatic pathways. When there is a large rise in metabolism or in absorption of heat from the environment relative to heat-dissipating mechanisms, the rise in T_c is known as hyperthermia. Fever is different. Fever occurs when the temperature set point of the hypothalamus is reset by the actions of pyrogens released by bacteria or viruses,[101] which provoke the secretion of cytokines IL-1, TNF,[102,103] IL-2, or IFN-γ.[104] These secreted cytokines, in turn, alter homeostatic pathways to defend a new, higher temperature, or thermal set point.

A number of disease states lead to the induction of cytokines, which alter a variety of cellular enzymatic paths and functions. Physiologically, cytokines cause nausea, vomiting, diarrhea, fever, and at least one cytokine, IL-1, causes the feeling of tiredness and somnogenesis during many diseases. Several observers have noted that persons suffering from intercurrent illnesses, even very minor ones, are at much greater risk of heat illnesses.[105] Neutralizing antibodies to IL-1 and TNF are present in the sera of normal and sick individuals and may play a role in the regulation of those cytokines and of fever.[106]

Aspirin has long been known to reduce fever. Aspirin-like compounds inhibit cyclo-oxygenase (which synthesizes PGs from AA) and, by so doing, interfere with the fever induced by IL-1.[107] Circulating pyrogens eventually reach the thermoregulatory control center in the anterior hypothalamus of the brain, and induce the synthesis of PGs.[108,109] At the onset of a fever, patients often feel chilled and shiver (which increases metabolic rate), show reduced BF_{sk} (which reduces cooling), and may wrap themselves with blankets (which improves their insulation by behavior) to establish a new, elevated, and *preferred* T_c.[110] Once a new set point temperature is established, the thermoregulatory center uses all available homeostatic mechanisms to maintain it. Therefore, attempting to lower the elevated T_c *of fever* by active cooling measures causes sensations of extreme discomfort and violent shivering. *If attempts at cooling cause chills and violent shivering in a patient with suspected heat illness, a coexistent infection or disease should be suspected.*

The set point temperature mediated by PGs is responsible for fever, pathological elevations in temperature, and temperature elevations related to stress; and it contributes to normal circadian variations in temperature, at least in nonhuman animals.[111–114] Treatment for fever should be directed at agents that block the action of the pyrogen at the hypothalamic receptor sites (although some pyrogens act independently of PGs).[115,116] These include aspirin, acetaminophen, indomethacin, ibuprofen, and other newer nonsteroidal antiinflammatory compounds.[117]

Should antipyretic therapy be routine during an episode of fever? Because normal febrile response is generally self-limited in both magnitude and duration, there is no urgent need for active pharmacological measures.[118] Fever has long been recognized both as a manifestation of disease and potentially a serious problem in itself.[119] However, it is both illogical[120] and usually ineffective[121] to actively cool a patient with true fever, and antipyretic therapy should not be routinely instituted for every febrile episode.[122,123] Moderate (but not extreme) fever aids in host defense by promoting phagocytic engulfment of microorganisms and chemotaxis *up to approximately 40°C (104°F)*.[124,125] Routine antipyretic therapy for moderate fever may be counterproductive.[126] Rather, treatment should be based on the relative risks in individual cases,[126–128] particularly in those patients whose high T_c is not due to exercise, and should be reevaluated if expected benefits are not achieved.[120]

In simple cases of mild heat stress or hyperthermia, when exercise ceases and environmental heat is no longer absorbed, then body temperature will spontaneously fall toward normal levels.[102] However, observations in experimental animals suggest that in extreme hyperthermia (> 40°C) administration of vasopressin or melanotropin or their analogues may prove to be beneficial, by acting centrally to suppress temperature elevation.[129,130]

Lipopolysaccharides and Cytokines

There appears to be a relationship between hyperthermia, reduced splanchnic blood flow, and lethal heatstroke that mimics sepsis. To appreciate this relationship, it is necessary to consider the contents of the intestinal lumen and the likely results

of its leaking into the systemic circulation.[131] In healthy individuals, the intestinal lumen from the jejunum to the sigmoid contains large amounts of Gram-negative bacteria and LPS, the highly toxic endotoxin coat that sloughs from its walls.[132] LPS can cause death at plasma concentrations as low as 1 ng/mL. Whereas LPS remains within the intestines, no toxicity occurs; however, when it enters the blood, then pathology similar to sepsis ensues.[133] LPS is not a contact poison, but instead, induces in a variety of cell types excessive amounts of toxic inflammatory agents, including TNF and IL-1. These two can themselves produce most of the symptoms of septic shock (except DIC, which is caused directly by the activation of a clotting factor by LPS). At low concentrations, LPS alone, or in combination with TNF and IL-1, causes fever, somnogenesis, nausea, vomiting, diarrhea, and headache, but at high concentrations can cause vascular collapse, shock, and death.[134,135] At the onset of heat illnesses, there is probably a specific etiology for each case, but one that is unrelated to LPS. However, at a certain combination of elevated temperature, hydration status, and time, splanchnic blood flow is reduced so severely as to cause ischemic damage to the gut wall, which is followed by translocation of LPS from the gut into the circulation. The patient then becomes endotoxic as well as hyperthermic.[65,66]

Besides altering AA pathways and forming active oxygen species, IL-1 causes cachexia. IL-1 causes muscle proteolysis by inducing branched-chain α-keto acid dehydrogenase, a rate-limiting enzyme for the oxidation of amino acids in skeletal muscle. As this enzyme increases in concentration, amino acids are progressively oxidized, leading to the breakdown of muscle proteins. TNF induces IL-1 and also depolarizes the plasma membrane in skeletal muscles.[136] Consequently, alterations in physical performance are expected when TNF is present.

There is a reciprocal relationship between the brain and the immune system. Cytokines such as IL-1_β that are produced by immune cells in the periphery also alter neural activity.[137] IL-1_β is a chemical signal between immune cells during infection and injury, and is also a critical mediator of immune-to-brain communication. IL-1_β can activate sensory nerves to trigger sickness responses by the brain including fever, reduced food and water intake, increased sleep, exaggerated pain, and the like. IL-1_β in the periphery can increase IL-1_β within the CNS, which in turn, initiates classic sickness responses.[138] Furthermore, the integrity of the blood–brain barrier is normally compromised in several small areas of the brain, especially in the hypothalamus.[137,139–143] Thus, it is possible that cytokines produced elsewhere may circulate, cross the deficient blood–brain barrier in those regions, bind to specific cytokine receptors present in hypothalamic neurons, and alter CNS function.[144,145] Research related to the function of barrier systems within the body during heat and exercise appears clearly warranted.

Septicemia has been characterized by fever, vascular collapse, DIC, shock, and death. Fine[65] and others[133] noted almost identical symptoms in a heatstroke victim and suggested that part of the pathophysiology of heatstroke involved the same mechanisms as those of septic shock. Because most of the symptoms of Gram-negative bacteremia are produced by LPS,[134,135] they suggest that LPS participates in the pathophysiology of heatstroke.[65] Experiments in nonhuman primates suggest that LPS becomes increasingly important as a pathological agent as T_{re} approaches 43.5°C, but above this temperature direct thermal damage to brain tissue is probably most important.[146]

The intestinal walls are rendered reversibly permeable to LPS by reducing the intestinal blood flow to below approximately 50% of normal. Hyperthermia leads to a reduced splanchnic blood flow, and when severe enough, LPS leaks out of the gut lumen at a high rate and principally enters the portal vein. LPS may be removed from the circulation by the liver, or it may bind to a number of protective plasma proteins such as LBP, anti-LPS antibodies (anti-LPS), or soluble CD14, a fragment of the LPS binding ligand present on macrophages. When macrophage CD14 is activated by LPS, the production of TNF and IL-1 is induced, causing symptoms. Although many cell types produce cytokines in response to LPS challenge, bound macrophages within the liver may be the major source of the cytokines in circulation during endotoxemia.[147]

Maintenance of health requires adequate barrier function of the intestinal wall. Virtually any significant damage of the gut wall by ionizing radiation, trauma, viral scouring, bacterial overgrowth, and parasites permits LPS to leak into the systemic circulation. Elevated LPS leakage is also caused by major blocks of the splanchnic arteries (eg, occlusion of the superior mesenteric artery, severe hemorrhage or hypotension, and even temporary reductions in splanchnic blood flow caused by the reflex sympathetic activation from the breathing of a hypoxic gas mixture).[148] Probably, most stimuli leading to the activation of the sympathetic nervous system, including excitement, fear, and infection, can reduce splanchnic blood flow and may, especially in concert

with additional stressors, lead to endotoxemia. Cytokines may be produced by mechanisms other than LPS activity. IL-1 is also produced as a result of sleep deprivation, and may, in principle, contribute to endotoxicity.[149]

Heatstroke in experimental animals leads to an endotoxemia at 42°C to 43°C, and probably at a lower T_c in exercising humans, which probably results from a combination of ischemic injury and direct thermal damage to the gut wall.[150] The temperature at which heatstroke becomes irreversible depends on a complex relationship among T_c, exercise intensity, time, original state of hydration, and health. At temperatures below 42°C, heatstroke probably involves classical pathways not involving LPS, but at 43°C and higher, for a person at rest, clinical endotoxemia may be a complication.

Runners who collapsed during or at the end of an 89.5-km ultramarathon run on a warm day, all appeared superficially similar. However, based on their plasma LPS levels, they could be classified into two groups.[150] Most (80%) showed elevated levels of LPS, including two in the 1 ng/mL lethal range. (NB: For short periods the body can tolerate much higher LPS concentrations. The widely reported lethal concentration of 1 ng/mL refers to a long-term plasma level after all host defenses are activated.[132,151]) The second group, with lower, normal levels of LPS, showed better performance (ie, faster times to the finish line), had higher levels of natural anti-LPS immunoglobulin G (IgG; almost everyone has some measurable anti-LPS IgG in their plasma[152]), and lower morbidity indexes (combined scores of nausea, vomiting, diarrhea, and headache). In other words,[150]

- those with normal low levels of LPS, who usually had high plasma levels of anti-LPS IgG, recovered within 3 hours, and
- those with elevated levels of LPS, who usually had low levels of anti-LPS IgG, required up to 3 days to fully recover.

In a pilot study, the plasma of surviving heatstroke patients had been cleaned by 3 to 5 days of venovenous hemofiltration with a polyacrylonitrile hemofilter that nonspecifically binds to LPS, and exchanged with 40 units of fresh frozen plasma, in addition to conventional therapy. Those treated with conventional therapy alone died.[153] The exchanged plasma may have contained sufficient endogenous anti-LPS antibodies to neutralize any LPS remaining in the blood. Overall, the anti-LPS antibodies appeared protective.

The question is, Who has high levels of anti-LPS? A study of triathletes suggested that very hard training increased levels of anti-LPS, because those who had the highest combined miles of running, bicycling, and swimming 3 weeks before the race had the highest levels of anti-LPS.[154] Untrained thoroughbred horses had low levels of anti-LPS, which rose during the training period and fell immediately after a race.[155] It may be that a part of the benefit of physical training is the increase in levels of natural anti-LPS antibodies. This possibility is currently under active investigation.

Classic Heatstroke and Cytokines

Several studies of heatstroke victims during the Hajj in Saudi Arabia indicate that cytokine levels become elevated during heatstroke. However, these patients are mainly elderly, classic heatstroke victims and not the much younger, exertional heatstroke victims seen during combat and training in hot weather. Eight of 17 victims admitted to a hospital within 2 hours from the onset of heatstroke, suffering from delirium, confusion, and coma, had elevated levels of plasma LPS, TNF, and IL-1.[132,156–158] Those cytokines probably induced PGs, which exacerbated the hyperthermia of heatstroke, because IL-1, in particular, is known to cause fever.[159]

The rapidity of cooling and entry to a hospital intensive care unit is important in determining survival of heatstroke patients.[59,60] Heatstroke mortality is related to the total heat stress (ie, during heating *and* cooling). This speed may be important because of the time required for the production of cytokines, which is in the range of minutes to hours.

On the battlefield in summer, soldiers expend energy at a high rate, leading to rises in T_c despite substantial sweat losses. In addition to the usual condition of moderate hypovolemia, a number of other factors capable of reducing BF_{sk} interact (eg, fear, excitement, and sleep deprivation). These factors may be exacerbated from any additional LPS entering the circulation as a result of mild or subclinical salmonellosis or shigellosis from drinking contaminated water.[160]

The presence of circulating LPS, whether translocated from the gut or from mild infection, can alter the activities of normal heat dissipation mechanisms and exacerbate the pathophysiology that simple elevated T_c causes. Injection of LPS into healthy subjects at elevated ambient temperature caused a PG-mediated complete cessation of sweating from 1 to 1.5 hours after the injection, lasting from 7 to 60 minutes.[161] It is not known whether this

cessation of sweating is a direct effect or mediated via other mechanisms such as baroreceptor override of peripheral circulation and vasodilation. The subjects also showed the symptoms of fever, headache, fatigue, nausea, skin vasoconstriction with "gooseflesh" appearance, sensation of chill, and hypotension.

Exercise and Cytokines

It is possible for circulating cytokines to increase with exercise and independent of any rise in LPS. Strenuous exercise leads to mild increases in plasma IL-1, TNFα, IL-6, IFN, and soluble IL-2 receptor.[90] Eccentric exercise, which usually damages skeletal muscle, causes a rise in IL-1.[162]

In general, during severe exercise, B and T lymphocytes and subpopulations of NK cells are recruited into the blood from lymph nodes. Both the number and the activity of NK cells—a heterogeneous group—are enhanced.[163] The NK cell subsets that increased in number the most were those most responsive to IL-2 activity from 2 to 4 hours after exercise. Prostaglandins released by monocytes during severe exercise suppress NK activity for several hours. Afterward, NK activity returns to baseline. During that several-hour period of immunodepression, some studies suggest that there is an elevated susceptibility to viral or bacterial agents.[163] Because aspirin is PG-mediated, its administration would possibly prevent this temporary immunosuppression.

Monocytes produced in the bone marrow are released into the circulation in response to interleukins and LPS.[164] They are phagocytic and produce cytokines. Nevertheless, circulating monocytes are actually immature cells and have half-lives of only 2 to 3 days in transit to tissues. Once they have reached their tissue sites, they mature into the larger and more capable macrophages, with half-lives measured in months. Macrophages exist in different functional states, depending on local signaling such as the ranges of local concentrations of cytokines and stress hormones. Macrophages may have low functional activities, be up-regulated and primed for further activation as in inflammation, or may be fully activated.

As described earlier, acute, moderate exercise causes a transient increase in monocytes, which lasts minutes to hours, but exercise training does not increase the monocyte count in resting subjects.[164,165] On the contrary, exhaustive exercise for 7 consecutive days decreased resting monocyte counts. However, over a period of days or weeks, physical training alters metabolic parameters of macrophages, such as increased insulin-mediated glucose uptake and O_2 consumption[164,166] and an increased affinity of insulin receptors.[167]

Overtraining may be very harmful. Quantitative laboratory determinations of blood parameters will, hopefully, eventually be able to show at what point any benefit from exercise training becomes less important than the disadvantages of immunosuppression, and indicate, therefore, when exercise should be curtailed.[168]

HEAT ILLNESSES

Heat illnesses and heat-related illnesses may be induced by hyperthermia, dehydration, salt depletion (from sweat loss or inadequate diet), exercise, and hyperventilation, in any combination. Before 1950, the mortality rate of heatstroke was 40% to 75%, with long-term survival directly related to the speed with which cooling and volume therapy were instituted. Because hyperthermia leads to subjective feelings of weakness and exhaustion but is not actually painful, highly motivated soldiers may persist exercising in the heat even when they feel exhausted. As a result, they may develop a wide range of clinical illnesses, from fatigue to heat exhaustion to heatstroke. The distinction between various clinical diagnoses is somewhat artificial, and a differential diagnosis may be difficult to establish in the field or even in a hospital (Table 5-3). Heat exhaustion and heatstroke are two extremes of a continuum of disorders, and they probably share many common pathways and factors. The boundary between heat exhaustion and heatstroke is usually arbitrarily defined as a T_c of 41°C plus alterations in sensoria. However, the seriousness of the illness is an *individual* matter for each patient, and if a person collapses during or after exercise with a T_{re} higher than 39°C, the physician should consider possible heatstroke, institute cooling procedures immediately, and transport the patient to a hospital. Moreover, during the period of transporting an undiagnosed patient to a hospital, T_{re} may have fallen to 39°C or even less, which might render doubtful a hospital diagnosis of heatstroke. Typical symptoms of heatstroke include belligerence toward friends and authority, a vacant stare, confusion, babbling, and aimless running or crashing into objects.

Until relatively recently, cessation of sweating was considered critical to the diagnosis of heatstroke; today, however, it is recognized that sweating may persist until late in heatstroke. Documentation of

TABLE 5-3

SIGNS AND SYMPTOMS OF SALT- AND WATER-DEPLETION HEAT EXHAUSTION

Signs and Symptoms	Salt-Depletion Heat Exhaustion	Water-Depletion Heat Exhaustion	Dilutional Hyponatremia
Recent weight gain	No	No	Yes
Thirst	Not prominent	Yes	Sometimes
Muscle cramps	In most cases	No	Sometimes
Nausea	Yes	Yes	Usually
Vomiting	In most cases	No	Usually
Muscle fatigue or weakness	Yes	Yes	No
Loss of skin turgor	Yes	Yes	No
Mental dullness, apathy	Yes	Yes	Yes
Orthostatic rise in pulse rate	Yes	Yes	No
Tachycardia	Yes	Yes	No
Dry mucous membranes	Yes	Yes	No
Increased rectal temperature	Yes	In most cases	No
Urine Na^+/Cl^-	Negligible	Normal	Low
Plasma Na^+/Cl^-	Below average	Above average	Below average

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only mild elevation in T_c should not preclude the diagnosis of heatstroke because T_c may have fallen before measurement. Unless an alternative etiology is obvious, a previously healthy soldier who collapses after physical exertion in hot weather should be diagnosed with exertional heatstroke, even if body temperature was not found to be markedly elevated several hours after collapse.

The early symptoms of heat illness are often unrecognized, and casualties may present to a medical treatment facility with nausea and visual disturbances that mimic the prodrome of a migraine headache. Failure to attend to these symptoms puts an individual at great risk for thermal injury. Individuals who anticipate exposure to hot environmental conditions should be thoroughly versed in the manifestations of heat illness.

Heat Exhaustion

Heat exhaustion is the most common clinical syndrome resulting from heat stress and exercise. It tends to develop over several days of exposure, thus providing ample opportunity for electrolyte and water imbalance to occur. However, under conditions of rapid sweating (high temperature, humidity, or work rates), heat exhaustion can occur in hours rather than days. Three forms of heat exhaustion are recognized: (1) water-depletion heat exhaustion, better known as dehydration; (2) salt-depletion heat exhaustion; and (3) the combination of salt depletion and dehydration. The form of heat exhaustion that manifests is determined by the relative and absolute losses of water or salt in sweat. Victims usually show common symptoms, including intense thirst (although not necessarily in salt-depletion heat exhaustion), fatigue, weakness, anxiety, restlessness, mental confusion, and poor muscle coordination. In salt-depletion heat exhaustion, the body temperature may remain normal or even subnormal. But when victims stand up, blood pressure falls and they may faint.

In general, the loss of plasma volume is more severe in relatively unacclimated individuals because their sweat contains relatively high concentrations of salt. On the other hand, in those who are relatively more acclimated and are secreting a more dilute sweat (approaching a water deficit), there is a greater rise in plasma osmolality and sodium, and

thirst is greater. For further information, see Chapter 8 in *Human Performance Physiology and Environmental Medicine at Terrestrial Extremes*.[169]

Water-Depletion Heat Exhaustion

The symptoms of water-depletion heat exhaustion include hyperthermia, thirst, hyperventilation, tachycardia, fatigue, weakness, discomfort, and some impairment of mental state such as confusion, poor judgment, disorientation, paraesthesia, and muscular incoordination. Delirium and coma occur in advanced cases. A patient may collapse with either a normal or an elevated temperature (in severe cases, around 40°C). Spontaneous cooling is normal if the patient is sweating. Oliguria is common and urinary contents of sodium and urea may reflect normal renal conservation mechanisms. Clinical evaluation is necessary, as *serum sodium is always elevated* and may approach 170 mEq/L in severe dehydration. If left untreated, the dehydration could lead to heatstroke. Particular caution must accompany the lowering of serum sodium levels to avoid the serious risk of cerebral edema. The cautious administration of 1 to 2 liters of normal saline over 3 to 6 hours is followed by the judicious administration of 5% dextrose. *Under no circumstances should serum sodium be permitted to fall more rapidly than 2 mEq/h.*[170]

Salt-Depletion Heat Exhaustion

The hyponatremia and hypochloremia of salt-depletion heat exhaustion usually occur in nonacclimatized individuals who have not fully developed salt-conserving mechanisms. Therefore, it may even occur in temperate weather, such as in spring; or a cold environment, such as Alaska even while one is encapsulated in heavy clothing, when extraordinary work periods cause large sweating losses of salt and water. Even prolonged insensible sweat (and electrolyte) losses that are unreplaced, such as waiting in the sun for delayed transportation, predispose to salt-depletion heat exhaustion if cumulative salt losses are significant. In contrast, predominantly *water*-depletion heat exhaustion, or dehydration, tends to occur when water intake is inadequate owing to voluntary dehydration or the discredited, misinformed concept of deliberate restriction, "water discipline." Among 44 summertime hikers who requested medical help in Grand Canyon National Park in June through September 1993, and whose serum samples were analyzed, 7 had frank hyponatremia with serum sodium levels lower than 130 mmol/L, and had clinically significant symptoms: 3 had grand mal seizures, 2 had other major CNS disorders, and 2 had minor neurological symptoms.[171]

Casualties with salt-depletion heat exhaustion present with hyponatremia and hypochloremia. Symptoms include profound weakness, giddiness, nausea, vomiting, diarrhea, and skeletal muscle cramps in a high percentage of cases (50%–70%). *These patients are much sicker* than those with simple muscle cramps. The skin is pallid and clammy, and the T_c may be normal or even subnormal. Orthostatic hypotension, tachycardia, and syncope are common. Owing to dehydration, laboratory values reflect volume depletion and hemoconcentration. Mild cases of hyponatremic heat exhaustion are generally well managed with the administration of salt and water. Patients who are confused, disoriented, orthostatic, febrile, or vomiting require laboratory evaluations and should be seen by a medical officer.

Salt-Depletion Dehydration

In hot weather and when water supplies are adequate but food is being rationed, an insidious form of dehydration occurs. Over a prolonged period, the body's salt content is gradually depleted from sweating. The salt lost in sweat is not replaced, owing to inadequate dietary replacement. This condition is worsened by both the anorexia accompanying mild dehydration and any diarrheal disorder. Each would shorten the onset and increase the severity of this disorder, which is called *salt-depletion dehydration*. This disorder often contributes to the physiological strain seen in unacclimatized troops who are suddenly exposed to heat and exertion. Salt-depletion dehydration could be used as a weapon, by forcing the enemy to move during daylight hours while his food supplies are limited. For further information, consult Chapter 8 in *Human Performance Physiology and Environmental Medicine at Terrestrial Extremes*.[169]

Heat Cramps

Heat cramps are a frequent complication of heat exhaustion and occur in about 60% of casualties with heat exhaustion, but a preexhaustion period of exercise is also always required. Heat cramps are characterized by brief or intermittent, often excruciating, contractions of voluntary skeletal muscles of the legs, arms, and abdomen, and usually occur during or after prolonged work in the heat. The cramp consists of a painful, localized contraction that sometimes appears to wander over the affected muscle as adjacent muscle bundles contract. Cramps

of the rectus abdominus may cause frank abdominal rigidity. In general, cramps usually occur later in the day, sometimes while showering, and occasionally in the evening. The incidence has been estimated at about 1% of foundry workers exposed to a hot work environment. For further information, see Chapter 8 in *Human Performance Physiology and Environmental Medicine at Terrestrial Extremes*.[169]

The exact mechanism of heat cramps and other similar maladies, such as exercise-induced muscle cramps, nocturnal cramps, or even writer's cramp, is unknown. Heat cramps sometimes occur as the only complaint, with minimal systemic symptoms. Factors common to most reports of cramps are (1) a prior period of several hours of sustained effort, (2) heavy sweating in a hot environment, and (3) the ingestion of large volumes of water. Their appearance while showering suggests that muscle cooling may be involved. The consumption of large amounts of fluid with inadequate intake of salt, or in the presence of inadequate salt-conserving mechanisms (eg, lack of heat acclimatization), may explain the clinical findings of hyponatremia and hypochloremia, and reduced levels of sodium and chloride in the urine, which is indicative of negative salt balance. Both hyponatremia and hypochloremia disturb calcium regulation (by means of the Na^+/Ca^{2+} exchanger) within muscle cells, resulting in spontaneous contractions of the skeletal muscle, nausea, and vomiting.

Mild muscle cramps respond to a 0.1% NaCl solution taken by mouth (two crushed salt tablets in a liter of water) and, in severe cases, to intravenous (IV) administration of saline solutions (10–15 mL/kg body weight). Heat cramps tend to be rare in individuals who are fully acclimatized to their thermal and working environments and are almost nonexistent in the armies of Israel and India. It is not known why the incidence of heat cramps is only 50% to 70% as great as salt-depletion heat exhaustion. Patients with heat exhaustion are very sick, as opposed to those with heat cramps, in which a combination of heavy work and the drinking of large volumes of pure water tends toward dilutional hyponatremia and cramping.

Heat-Induced Tetany. Heat-induced tetany *at rest* is caused by hyperventilation in extremely hot environments, with consequent alterations in CO_2 concentrations and pH. Deliberate overbreathing can also induce this condition. The onset of symptoms varies from slight tingling sensations in the hands and feet to more severe carpopedal spasms. Symptoms are more related to the *rate* of change in CO_2, PCO_2, pH, and T_{re} rather than the absolute change. Classic heat cramps are distinguished from hyperventilation tetany because they (1) generally involve voluntary skeletal muscle subjected to prior exertion and (2) usually only affect a few muscle bundles at a time, persisting from 1 to 3 minutes, and with excruciating pain in severe cases.

The Syndrome of Cramps, Syncope, and Respiratory Alkalosis. There is a rarely described but not uncommon form of nonclassic heat exhaustion seen in military training settings obtained by running or speed marching in the heat (Table 5-4). Patients are characterized by hyperventilation, moderate-to-marked respiratory alkalosis, and syncope. Nearly all casualties have abdominal or extremity muscle cramps, and nearly 50% experience tetany with carpopedal spasm. The majority of these patients are not depleted of either water or salt. Hyperventilation with its resulting decrease in cerebral blood flow could account for a significant number of cases of exercise-induced syncope.

Recumbency, rest, cooling, and oral replacement of potential fluid and electrolyte deficits are usually recommended. If rebreathing of expired air is initiated to elevate arterial blood CO_2, it should be done with extreme caution because of its hypoxemic effect. Classic syncope is usually associated with postural hypotension, whereas heat exhaustion and heat cramps are not. The latter two are usually associated with water and electrolyte imbalance.

Syncope

Hyperventilation dizziness is a result of slight but prolonged increase in respiratory rate or tidal volume. It can accompany an increase in anxiety and represent some degree of generalized cerebrovascular vasoconstriction.

Vasovagal syncope is the cause of about 3% of emergency department visits and 6% of hospital admissions throughout a typical year. Syncope resulting from diminished venous return due to the pooling of blood in the peripheral circulation is caused not only by heat, but also by (1) psychological disturbances activating an autonomic vasodilation response; (2) reflexes initiated by heavy coughing, micturition, or pressure on an irritable carotid sinus; or (3) reduced vasomotor tone induced by hypotensive drugs or alcohol.

Heat syncope that is characterized by the transient or temporary loss of consciousness has its origins primarily in the cardiovascular system. In an upright and stationary person, blood is displaced into dependent limbs by gravity, which if combined with the filling of capacious peripheral veins to support heat transfer of the skin, can temporarily compromise

TABLE 5-4

CLINICAL DATA ON 17 HEAT CASUALTIES, FORT POLK, LOUISIANA, 12–23 JULY 1970

Soldier[*] No.	Activity	Syncopy (Fainting)	Cramps	Temperature[†] (°F)	Respiration Rate[‡] (Breaths/min)	Blood[§] pH	Na^+	K^+	Cl^-	Lactate	Creatinine
1	Marching	Yes	Abdomen	99.6	24	—	142	4.5	100	—	1.15
2	Running a mile	Yes	Legs, abdomen	98.4	30	—	145	4.2	102	—	1.50
3	Rifle range	No	No	99.4	24	—	143	4.7	102	—	
4[¥]	Marching, running	Yes	Hands	100.4	22	7.47	162	4.3	116	0.75	1.05
5	Marching	No	Legs, abdomen	102.4	35	7.50	141	4.3	102	1.48	1.84
6[¥]	Marching	No	Legs	100.0	22	7.70	152	4.3	—	—	1.40
7	Rifle range	No	Mild	100.0	22	—	140	4.1	100	1.36	1.30
8	Marching	Yes	Legs, abdomen	100.8	30	7.52	145	3.8	102	0.86	0.95
9	Marching	No	Abdomen	101.4	24	7.69	—	—	—	0.62	1.20
10	Marching	Yes	Chest	100.8	18	7.56	140	4.0	100	0.62	—
11[¥]	Marching	Yes	Tetany	101.5	30	7.44	160	4.9	106	1.44	1.30
12	Marching	Yes	Severe	100.6	30	7.71	130	4.5	100	—	1.15
13	Marching	No	Mild	98.6	26	7.77	141	4.0	104	0.91	1.30
14	Marching	Yes	Legs, abdomen	100.7	30	7.76	145	4.8	102	0.49	1.05
15[¥]	Rifle range	Yes	Legs, abdomen	101.0	32	7.66	148	3.7	104	1.05	1.65
16	Marching	Yes	Chest, legs	101.2	28	7.78	148	4.3	105	1.25	1.15
17	Marching	Yes	Abdomen	101.6	22	7.53	146	5.1	102	0.67	1.05

[*]All heat casualties among military recruits during training in the field presenting to a heat ward with heat exhaustion, heat syncope, or heat cramps
[†]Core (rectal) temperature was elevated (> 100.0°F) in only 11 of 17 casualties
[‡]All casualties had increased respiratory rates on admission to the medical treatment facility
[§]Serum electrolytes reported in mEq/L; creatinine in mg%; lactate in mmol/L
[¥]Hemoconcentration was seen in patients 4, 6 ,11, and 15
Data source: Boyd AE, Beller GA. Acid base changes in heat exhaustion during basic training. *Army Science Conference Proceedings*. 1972;1:114–125.

venous return, cardiac output, and cerebral perfusion. Prodromal symptoms include restlessness, sighing, yawning, and dysphoria. The hypotension results predominantly from vasodilation and bradycardia. Fainting and the assumption of a horizontal position is usually self-limiting. Although startling to onlookers and the casualty, the effects appear readily reversible with improved venous return. The casualty should be allowed to rest in cooler, shadier surroundings and offered replacement fluids. Orthostatic pooling and predisposition to syncope is counteracted by avoiding protracted standing in hot environments and by repeatedly flexing leg muscles to promote venous return. Patients should be advised to sit or

lie down at the onset of prodromal symptoms.

The incidence of syncope falls rapidly with increasing number of days in the heat, suggesting the importance of water intake and salt retention in preventing the disorder. Individuals who take diuretics would be at increased risk, and hypokalemia could lower blood pressure and blunt cardiovascular responsiveness. For further information, see Chapter 8 in *Human Performance Physiology and Environmental Medicine at Terrestrial Extremes*.[169]

Rhabdomyolysis

Rhabdomyolysis (1) is a complication of exhaustive exercise even in well-trained athletes, (2) often occurs in association with exertional heatstroke, and (3) probably would affect everyone if the exercise were sufficiently severe.[172–174] Rhabdomyolysis most commonly occurs in athletes who force themselves to continue to run maximally despite cramping pain, disorientation, and confusion. Rhabdomyolysis occurs more often in runners with white-collar jobs, and rarely in those with blue-collar occupations.[172] In this devastating disease, the skeletal muscle plasma membrane becomes so severely injured (the mechanism is unknown but may be due to depletion of high-energy phosphate reserves) that cell contents leak out into the blood, as shown by rises in concentration of muscle enzymes (eg, creatine kinase-MM, aldolase) and leads to myoglobinuria. But more severe problems may develop over the next 24 hours, including potentially fatal hyperkalemia, metabolic acidosis, DIC, and adult respiratory disorder syndrome (ARDS). Conventional thinking attributes the sequelae of rhabdomyolysis to the release of the contents of damaged muscle cells. However, similar pathophysiology can occur if LPS is released from the lumen of intestines owing to ischemic damage from a reduced flow of blood to the intestines due to severe exercise.

The severity of symptoms (except for eventual DIC) can vary greatly, from an asymptomatic rise in skeletal muscle enzymes, to muscle tenderness and weakness, to muscle pain, myoglobinuria, and even acute renal failure. The usual sequence of events is a *long* race on a warm, but not necessarily hot, day. During the race the runner appears pale and disoriented, with profuse sweating and hyperventilation, but is not necessarily hyperthermic. Over the next 12 to 24 hours, the patient virtually always shows DIC and may exhibit renal failure, hypocalcemia, and possibly ARDS. The DIC is worst on the third to the fifth day, and spontaneous improvement may commence after 10 to 14 days. If cellular damage is extensive, tissue lysis syndrome may present, and lead to infection, especially pneumonia, shock, myocardial ischemia, and progressive renal failure.[175] Extreme care is required in caring for these patients because they may manifest only minimal clinical abnormalities, yet show severe metabolic dysfunctions.

Summary of Heat Exhaustion

Classic heat exhaustion usually develops over several days and primarily involves electrolyte and water imbalance. Classic heat exhaustion results from a prolonged cardiovascular strain in the attempt to maintain normothermia. It is well documented that patients with classic heat illness often show fluid and electrolyte parameters within normal ranges.[173] This suggests that it is the prolonged duration of heat stress per se, and its consequent cardiovascular strain, that is the predominant cause of classic heat illness. The symptoms of heat exhaustion include various combinations of headache, dizziness, fatigue, hyperirritability, anxiety, piloerection, chills, nausea, vomiting, heat cramps, as well as heat sensations in the head and upper torso. A patient may collapse with either normal or elevated T_c, usually with profuse sweating and tachycardia, hyperventilation, hypotension, and syncope. Spontaneous body cooling can occur with heat exhaustion. This is not prominent in severe heatstroke, thus the clinical determination of heat exhaustion is primarily a diagnosis of exclusion.

The alternate forms of heat exhaustion are characterized by the type of fluid deficit, electrolyte deficit (primarily pure water and/or salt deficiency), or both; their underlying causes (prolonged heat exposure vs intense, short-term exertion); the intensity of the hyperthermia; and the absence or form of CNS disturbance. Intercurrent illness should be suspected if external cooling does not rapidly lower T_c to normal, or, conversely, external cooling precipitates severe shivering. Anecdotal experience suggests that approximately 20% of suspected heat exhaustion cases have some form of viral or bacterial gastroenteritis, especially if nonchlorinated water or ice has been consumed. The term "heat cramps" is a misnomer because the cramps do not usually occur during exposure to heat. The condition is usually precipitated by exhaustive work, ingestion of copious fluids, and cooling of the muscles.

Exertional Heatstroke

Severe exercise appears to cause local disruption of tissues, with the sloughing of tissue fragments into the blood. These fragments circulate, and acti-

vate complement factors of the blood clotting system, forming microscopic polymers that may be filtered out by the kidney and clog glomerular pores. Furthermore, complement activation primes monocytes (ie, renders them responsive to much lower than normal concentrations of activator) for further activation by LPS, or by fragments of tissue subsequently damaged, ultimately leading to DIC. Intense exercise can damage renal function so severely that the excretion rate of proteins rises by 100-fold and can even lead to a depletion of circulating antibodies.[176,177]

Bouchama and colleagues[158,178] further studied the immune systems of 11 patients with classic heatstroke. The responses were not uniform. Nine of the 11 heatstroke victims showed (1) a marked rise in leukocyte numbers that increased with increasing T_c, due to a large increase in the number of T suppressor/cytotoxic cells (CD8) and NK cells, and (2) substantial decreases in the number of T helper cells (CD4) and B cells. Catecholamines also rise during heatstroke; and because epinephrine administration causes leukocytosis with increased NK and CD8 cells, the rise in catecholamines induced by heat stress may have caused some of the changes in lymphocyte subpopulations seen in most heatstroke victims. In a comparison of at least 30 different assays of immune activity, the best marker for immune status was the determination of CD4, CD8, and their ratio.[179] In a study of 14 victims with classic heatstroke and heat exhaustion, the percentage of CD4 cells fell from 43% in controls to 31% in heat exhaustion to 15% in heatstroke; at the same time, CD8 rose from 28% to 42% to 46%, respectively; and the CD4/CD8 ratio fell from 1.54 to 0.738 to 0.326, respectively, indicating that heatstroke is associated with *a large relative rise in T cytotoxic/suppressor cell activity.*[178]

However, in the study by Bouchama and colleagues[158] mentioned above, 2 of those 11 heatstroke patients had a *decreased* number of lymphocytes. As previously described, hyperthermia increases cortisol,[180–182] and cortisol causes lymphocytopenia, the opposite effect of catecholamines.[157] To account for this reduction in lymphocytes in some patients, the effects of cortisol, rather than of catecholamines, were considered to be dominant. Overall, changes in concentrations of subpopulations of lymphocytes in heatstroke may depend, on an individual basis, on the relative rises in concentrations of catecholamines and cortisol, and individual sensitivities to them.

Classic Versus Exertional Heatstroke

Exposure to extremely high ambient temperatures caused a mean of 381 deaths per year in the United States from 1979 to 1996.[183] Nowadays, classic heatstroke is manifested in waves, for example, during the Hajj in Saudi Arabia or in some 500 deaths in Chicago in the 1995 heat wave. Victims of the heat among the Hajji usually collapsed while circling the shrine in Mecca. Following collapse they were usually rapidly cooled nearby and then taken to a local hospital, with T_{re} recorded as high as 47°C. At those high temperatures, survivors usually suffered neurological damage, with the extent of damage related to the duration of elevated T_{re}.[184]

As described by Dill,[185] a heat wave in Cincinnati, Ohio, in July 1936 resulted in hospital admissions of 44 heatstroke victims. Between 8 and 15 July the environmental temperature exceeded 38.3°C (101°F) every day and reached as high as 40.6°C. During that period the daily admission rates were 0, 0, 0, 4, 0, 8, 9, and 14.[186] The increasing number of admissions over time suggests that there was a progressive deterioration of the body with prolonged hot weather. This may be related to elevated cytokine levels. In a different heat wave in the region of Dallas, Texas, lasting from 24 June 1978 through 19 July 1978, half the cases (14 of 28) occurred from 13 to 15 July, but the first case occurred on 3 July and the last on 29 July.[173] Age was a factor, with a mean age of 70.5 years in the patients in Dallas; in a separate heat wave in Boulder City, Nevada, the victims had a mean age of 59 years. Furthermore, 5 of 28 patients in Dallas were older than 80 years, as were 3 of 44 patients in Boulder City. Alcoholism and degenerative diseases were contributing factors in both studies because they were present out of proportion to their numbers. The patients characteristically had high rectal temperatures and dry skin, and half of the patients in Boulder City and 24 of the 28 patients in Dallas were comatose. Twenty-three of the patients in Boulder City showed a fiery red skin rash over the body, particularly over the chest, abdomen, and back.[185] The most common presentation of the Dallas patients was that of respiratory alkalosis, often accompanied by metabolic acidosis.[73] All Dallas patients whose blood lactate was greater than 3.3 mmol/L suffered a poor outcome, whereas all those with initial lactate less than 3 mmol/L did well. That is, what would appear to be only *modest* elevations in blood lactate in exercise studies, become adverse prognostic indicators in classic heatstroke. Furthermore, 9 of 28 classic heatstroke patients arriving with normal serum potassium subsequently became hypokalemic, and all patients were hypokalemic at some point in their course.[173]

Classic heatstroke tends to be a disease of infants, the elderly, the alcoholic, and the infirm. Exertional

heatstroke is different; it typically affects young, healthy, and even euhydrated men and women during exercise, and is a syndrome involving hyperventilation and respiratory alkalosis.[187] The respiratory rate may reach 30 per minute, with a plasma pH as high as 7.78 and elevated arterial lactate.[187] Nevertheless, alcohol may be an indirect factor even in exertional heatstroke. In one incident, a football player became intoxicated the night before practice, and the coach punished him with 50 wind sprints. The athlete completed the exercises, walked off the field, went to his room, and was found dead 3 hours later.[188] Punitive exercises for an exhausted soldier should not be tolerated because the poor performance is probably due to heat exhaustion or impending heatstroke.

Risk Factors

Military Training

A 10-year retrospective study was published in 1996 of heat illnesses among US Marine Corps recruits at Parris Island, South Carolina.[189] A total of 1,454 cases were reported, 89% among men and 11% among women. Heat illnesses occurred during every month of the year, commencing with wet bulb globe temperatures as low as 18.3°C (65°F). In a different study in the British army, heat illness even occurred at an air temperature as low as 10.2°C (50.4°F).[190] Eighty-eight percent of the Parris Island cases occurred during late spring through fall, May through September. In the British army too, most cases occurred during the hot months, with the highest rates found in soldiers stationed in Hong Kong and Cyprus.[191]

At Parris Island, most heat illnesses occurred during the cooler early morning hours, with 60% occurring between 0700 and 0900 hours.[189] This is somewhat surprising, given that early morning is the time for strenuous exercises. That is, endogenous heat produced by exercise was more injurious than environmental heat. It is significant to note that the incidence of heat illnesses did not depend only on the immediate local ambient temperature but was strongly related to the peak temperature the previous day. That is, high environmental temperature caused some unknown biochemical or physiological changes, or both, in the soldiers that persisted for 24 hours and rendered them susceptible to heat illnesses. It is suspected, but not proved, that heat-induced, long-lasting cytokines or inappropriate apoptosis is responsible.

There was a gender difference in heat illness rates among the Marine recruits. Rates for women were higher during the early hot season (May) and rates for men were higher than those for women in the late hot season (September). Furthermore, when considering combined rates, there was a higher overall rate in May even though May was cooler than September. This is probably due to lack of acclimatization in May.

The day of the week also had an effect in the Parris Island study and might affect future allocation of medical resources. Very few heat casualties (1.1%) occurred on Sundays because physical training was limited on weekends. Slightly fewer women developed heat injuries on Mondays and there were fewer cases in men on Tuesdays, both of which may be due to consistent daily differences in their training schedules.[189]

Fitness

A sedentary lifestyle leads to both decreased muscle mass and increased nonmuscle tissue. As a result, for any given amount of exercise, muscles require more energy per gram of body mass. That is, more heat is produced per gram of body mass as overall efficiency declines and the relative metabolic heat load increases.

Physical training improves tolerance to heat not only by improving the efficiency of the cardiovascular system and reducing the amount of excess body fat, but also by reducing the threshold T_c for initiating cooling mechanisms. Whereas physical training increases heat tolerance, a sedentary lifestyle decreases it.[192] Most striking has been the demonstration of a much higher rate of heat-induced mortality in sedentary than in trained rats (Figure 5-4). The key factors of "training" include not only increased efficiency of muscle movement but also increased extracellular volume and better thermoregulatory reactions. Although there are many close similarities with heat acclimation, the maximal O_2 utilization capacity (often defined as relative fitness) of an individual is rivaled only by anthropometric characteristics (eg, body fat, the ratio of surface area to mass) as the principal correlate with reactions to heat stress.[193] The critical determinant of fitness for heat tolerance is probably not O_2 intake capacity per se, because associated physiological adaptations such as changes in organ and cellular or molecular state are very important also. Nevertheless, Gisolfi[194] has warned that because endurance athletes have a greater capacity to sustain circulatory stability at the expense of increasing T_c, they may ultimately be at greater risk of heat injury. Finally, a high level of fitness will slow the loss of heat acclimation and expedite its return if heat exposure is interrupted.[195]

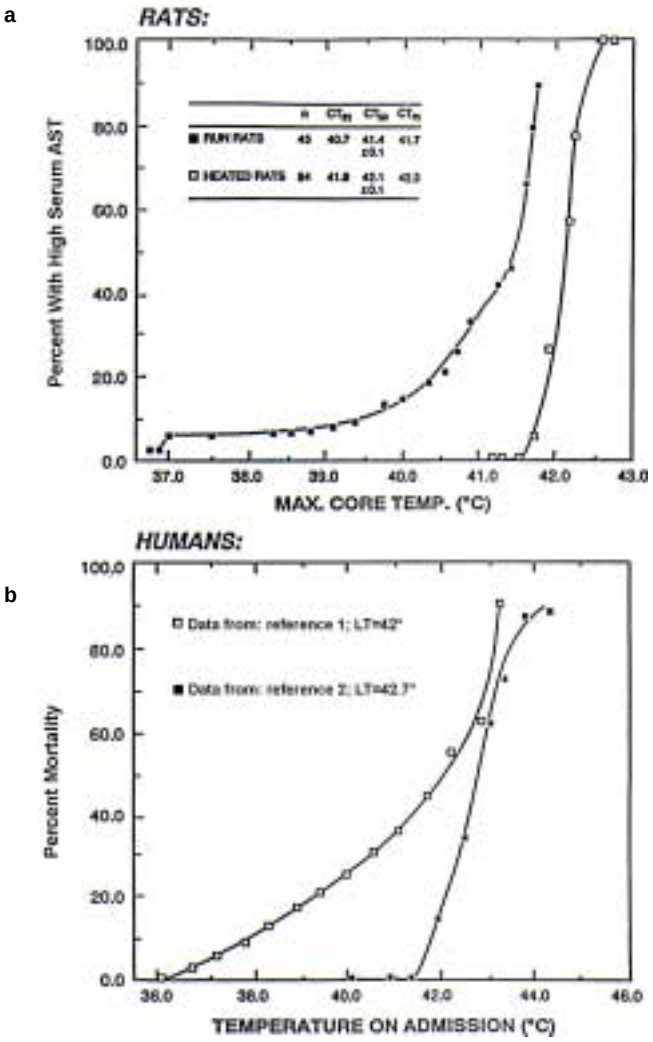

Fig. 5-4. Effect of temperatures on liver damage in rats and mortality in humans. (**a**) Dose-response curve of percentage of surviving rats with serum aspartate aminotransferase (AST, formerly called SGOT) levels in excess of 1,000 IU/L, versus maximum core temperatures of run–exhausted or restrained–heated rats. Values in the insert represent mean ± SE of core temperature at indicated percentages. CT_{50} for run rats was significantly different from CT_{50} for heated rats ($P < 0.025$). Note the increased morbidity (enzyme release) in exercising rats at equivalent core temperatures. (**b**) Dose-response curve of percentage mortality versus temperature was based on hospital records of patients with heatstroke. Note the similarity to mortality data in exertional versus classical heatstroke in humans. Data points in graph b are recalculated from original data in (1) Gauss H, Meyer KA. Heat stroke: Report of one hundred and fifty-eight cases from Cook County Hospital, Chicago. *Am J Med Sci.* 1917;154:554–564 and (2) Ferris EB, Blankenhorn MA, Robinson HW, Cullen GE. Heat stroke: Clinical and chemical observations on 44 cases. *J Clin Invest*. 1938;17:249–262.
Reprinted with permission from Hubbard RW, Matthew WT, Criss REL, et al. Role of physical effort in the etiology of rat heatstroke injury and mortality. *J Appl Physiol*. 1978;45:(graph a) 466, (graph b) 467.

PROPHYLAXIS AND THERAPY

Acclimatization to heat and to physical training is very important in resisting heat illnesses. Hypohydration leads to reduced muscle strength, reduced endurance during exercise, and elevated rates of heating.[196] In response to 1- to 2-hour periods of heat stress per day, over several days, a soldier develops elevated levels of aldosterone, and increased numbers of Na^+/K^+ ATPase plasma membrane pumps in his or her cells. One effect is that the extracellular volume is enlarged and responds to heat stress with a reduced fall in CVP.[86,197,198] Whereas complete acclimatization requires 7 to 10 days, there is significant improvement in response to heat even after 2 days. For a review of cellular adaptations to heat, see the review by Horowitz.[199] Ingestion of fluids enhances heat tolerance by minimizing the decline in central plasma volume from elevated BF_{sk} and sweat loss.[200]

Hydration and Rehydration

"Water discipline," meaning fluid deprivation, is a long-practiced attempt at reducing the body's water requirements during activities in the desert or jungle. However, it is an outdated, incorrect, and dangerous concept that implies that proof of manhood and esprit de corps can overcome the principles of physiology. That concept of voluntarily or involuntarily withholding of water from soldiers in the heat, despite severe thirst, leads to unnecessary deaths and permanent neurological damage in the survivors of heatstroke.[201]

If a soldier is *hypohydrated* when commencing strenuous physical exercise or combat in the heat, he will be at a disadvantage compared with a euhydrated soldier. He will overheat earlier, his physical and mental performance will deteriorate sooner, and he will

be more susceptible to hemorrhage or other trauma. Soldiers should be taught that the "Cost of Work in the Heat = Sweat = Water." Water can be seen as a "tactical weapon" that enhances and extends performance and resistance to heat illness.[202] Water is better carried in the body than unused in a canteen.

Clearly, a soldier should be well-hydrated, but not excessively overhydrated—which is just as debilitating—before beginning physical activity in the heat. Soldiers who are dehydrated for any reason should be prevented from exertion while heat-stressed, and they should drink 8 ounces (1 cup) of water or appropriate fluid-replacement beverage 10 to 15 minutes before starting physical activity. A soldier should be forced by command to drink 8 to 12 ounces of fluid every 20 to 30 minutes during exercise. Reliance on voluntary intake to maintain adequate fluid balance will result in dehydration at high ambient temperatures. The traditional rules of some sports (such as field hockey, soccer, and rugby) unintentionally limit opportunities for hydration by failing to provide for adequate time-outs and maintaining very brief half-times. During extremely hot–humid weather, team physicians, trainers, coaches, and officials should work together to incorporate additional breaks (quarters rather than halves) and provide unlimited access to fluids at the sidelines. For additional information see the 1990 *Report of a Workshop Committee of Military Nutrition*, by R. W. Hubbard, P. C. Szlyc, and L. E. Armstrong.[203]

Nude weights taken before and after exercise can guide the requirements for intake of additional fluids after exercise and before the next trial. For every pound of weight lost during activity, a soldier should consume a pint (2 cups) of liquid. Fluid loss should be replaced before return to activity in the heat; if a weight loss of more than 2% persists, the individual should be withheld from activity. Prehydration will forestall dehydration and enhance long-term performance. Commanders who fail to comply with these standards should be held accountable for any resulting heat injury.[1]

Because most heat illnesses in the field involve dehydration, volume expanders such as Ringer's lactate or normal saline should be administered intravenously immediately after commencement of both intubation, if necessary, and cooling. These solutions expand the intravascular volume without effects on hyponatremia.

The current (year 2000) protocol for treating suspected exertional heatstroke victims among Marine recruits at Parris Island is described in Exhibit 5-2.[204]

EXHIBIT 5-2

PARRIS ISLAND PROTOCOL FOR TREATING SUSPECTED EXERTIONAL HEATSTROKE

1. During physical training, the clinic routinely maintains a dedicated room with two bathtubs full of cold water and ice. In the field, the blouse and pants are removed from a collapsed suspected heatstroke patient; the shorts and T-shirt remain on. Rectal temperature is measured, ice is packed around the groin and axillary areas, and the patient is immediately transported to the clinic on a stretcher. On arrival, the stretcher is placed on top of the iced bathtub above the water and ice, with the carrying handles sticking out at both ends. Mental status and other vital signs are assessed, and blood is drawn for laboratory analyses.
2. One liter of normal saline is administered intravenously, *as a bolus.*
3. Sheets are dipped into the tub's icy water and are used to cover and drench the patient. Copious ice is added to the top of the sheet to cool still further, and the skin is massaged to improve skin blood flow. The sheets are frequently rewetted with the icy water. Concurrently, the head is constantly irrigated with more ice water and a fan is directed at the patient.
4. If rectal temperature is not lowered sufficiently, then the patient is immersed directly into the ice and water. With this procedure rectal temperature usually falls to 102.5°F (39.5°C) within 15 to 20 minutes, and the patient is removed from the stretcher, rinsed, placed on a gurney, and intravenous fluids and laboratory studies are reviewed.

   Supplemental potassium should not be administered until serum electrolytes have been determined. Once they are known, then the choice of additional fluids should be based on the electrolyte status and cardiac and renal functions.

Source: Gaffin SL, Gardner JW, Flinn DS. Cooling method for exertional heatstroke. *Ann Intern Med*. 2000;132:678.

(NB: These victims are young men and women who are otherwise healthy. Victims of classic heatstroke are usually elderly and with concurrent diseases, and those factors must be taken into consideration.)

Fluid Replacement Beverages

One cannot rely on the thirst reflex to prevent dehydration. Simply providing water or other fluids during training or combat or even resting (especially in sunshine) may not be sufficient. Required are (1) breaks in activity during training and (2) drinking on command every 20 to 30 minutes, depending on the degree of heat stress.

What should be the composition of the ideal beverage, given that both electrolytes and water are lost during sweating, and that mainly carbohydrates are used as a fuel source during physical activity? Water and nutrients are absorbed in the upper part of the small intestine. The rate at which fluid is emptied from the stomach or absorbed in the intestines determines the rate at which it can be of value in rehydration. The rate of gastric emptying depends on osmolality and caloric content. Which factor predominates depends on physical activity and the temperature and volume of the beverage. When normal performance is the criterion for the maintenance of plasma volume, some studies suggest that there is no need to add carbohydrates and electrolytes to water.[205] A number of commercial and experimental carbohydrate–electrolyte drinks were tested for their ability to prevent hyponatremia during exercise or to improve performance. Most of the solutions were about equally effective in maintaining water and mineral balance. Furthermore, despite early disagreements, there is little difference in emptying time between beverages that contain 2.5% and those that contain 7% carbohydrate. During exercise, both 5% glucose polymer solutions and water show similar gastric emptying rates. Probably the major benefit of commercially available sports drinks was in their enhanced palatability, which reduced hypohydration through a voluntary increase in fluid intake.[206–212]

Although it is widely believed that drinking cold water causes stomach cramps and inhibits emptying, this is not the case.[213] On the contrary, drinking cold water increases the activity of the smooth muscle in the gastric wall, thereby increasing motility and emptying the stomach more rapidly than drinking warm beverages.

Transport of sodium is the major determinant of water absorption in the proximal small bowel. The active, coupled transport of sodium and glucose creates an osmotic gradient that pulls water from the lumen into the epithelial cells. A frequent argument for including sodium in fluid replacement beverages is enhancement of intestinal absorption. Nevertheless, solutions of carbohydrates and electrolytes are not absorbed more rapidly than pure water.[210]

On the other hand, *feeding* carbohydrates during prolonged exercise *enhances* exercise performance, whether assessed by exercise time-to-exhaustion or by time to complete a predetermined exercise task.[214,215] To do so, a sports drink needs to contain 5% to 10% carbohydrate in the form of glucose or sucrose.[216] However, drinking a solution more concentrated than 10% glucose causes athletes to suffer cramps, nausea, and diarrhea. But glucose can be polymerized, so that a sport drink that is isocaloric to native glucose has only one-fifth the osmotic pressure. With this lower osmolality, one can increase the carbohydrate content without risking the gastrointestinal side effects of a high-osmolar drink. Several commercial polymer solutions are currently available. Glucose polymer solutions given before and during a soccer game resulted in sustained blood glucose and improved performance.[217] Athletes who might benefit are those involved in soccer, field hockey, rugby, and tennis, because the paucity of rest periods and substitutions makes these sports similar to sustained operations in the military. Whether the use of these beverages spares muscle glycogen is a matter of current debate.

The use of carbohydrate solutions is not completely without disadvantages, however. First, these beverages are expensive, and second, the presence of such drinks may attract bees and hornets into the vicinity of the athletes, placing them at risk for sting-induced allergic or anaphylactic reactions. Furthermore, once a carbohydrate has been placed into a canteen, then health risks from potential pathogens growing in the canteen may be more serious than the potential benefit of the carbohydrates, which could probably be better administered in the form of candy bars.

Under usual conditions, electrolyte- and carbohydrate-containing beverages offer no advantage over water in maintaining plasma volume, or electrolyte concentration, or in improving intestinal absorption. Consumption of an electrolyte-containing beverage may be indicated under conditions of caloric restriction or repeated days of sustained sweat losses. For these athletes, use of glucose polymer solutions may be considered. For the vast majority of individuals, however, the primary advantage of electrolyte- or carbohydrate-containing drinks appears to be that they enhance voluntary consumption. This factor should not be considered unimportant if regulated intake is impossible.

Adequacy of Hydration: Urine Test

Because dehydration usually precedes heatstroke, a simple test for hydration status that is easily carried out in the field would be of considerable benefit. In response to dehydration the normal kidney conserves water by excreting small volumes of osmotically concentrated urine, leading to long periods between urinations. Because the bile pigments that give urine its color become more concentrated, urine color darkens to orange or brown. If a soldier is overhydrated (a rare event in the summer) and urinates frequently, then urine color will be faintly yellow or even water-clear. A practical color chart for urine has been developed (Figure 5-5), which shows that for moderate degrees of hypohydration, the color of the urine is a more sensitive index of hypohydration than are blood measurements.[218–220] In short, soldiers should pay attention to the color of their urine. If urine is strongly yellow-colored, they are dehydrated and must drink more water. If it is clear, they are adequately hydrated.

Acclimatization

Acclimatization to heat has a profound relevance to real life problems in the armed forces.[221] Prior heat exposure enhances heat tolerance by (1) expanding circulating plasma volume, (2) increasing the maximum capacity of cutaneous vasodilatation and sweating, and (3) reducing the temperature threshold for increased BF_{sk} and sweating.[204,222] That is, acclimatization is easily shown by the presence of a lower T_c, skin temperature (T_{sk}), and heart rate in response to a standard heat stress. A further important benefit of heat acclimation is reduced sodium loss (both urinary and sweat) and, therefore, a reduced likelihood of salt depletion from high sweat losses.

Because most studies on acclimatization combined heat with exercise, it has been difficult to separate the effects of heat from those of exercise. However, it appears that heat exposure in its own right can markedly improve the tolerance of combined exercise and heat, due to increased thermoregulatory and cardiovascular capacity.[223] On a cellular basis,

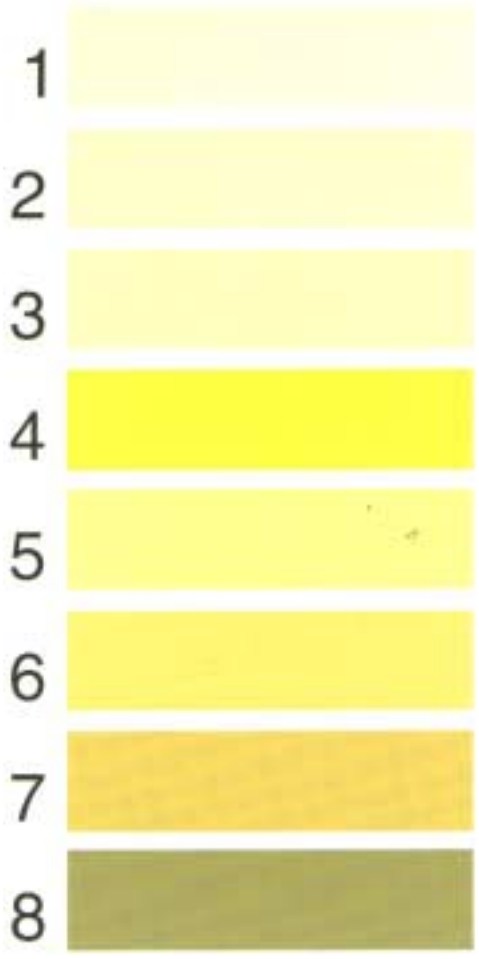

Fig. 5-5. In the presence of normal renal and hepatic function and the absence of significant hemolysis, a soldier's level of dehydration is indicated by the color of the urine. The urine color is matched closest to one in this chart. If the urine sample matches #1, #2, or #3, then the soldier is well hydrated. If the urine sample matches or is darker than #7, then the soldier is substantially dehydrated and should consume fluids.
This chart has been scientifically validated[1,2] but is not at this time officially mandated by the Department of Defense as doctrine. The chart is provided here as an aid to medical officers to consider as one of several possible indicators of hydration status of troops in training or in the field. (1) Armstrong LE, Maresh CM, Castellani JW, et al. Urinary indices of hydration status. *Int J Sport Nutr.* 1994;4:265–279. (2) Armstrong LE, Herrera Soto JA, Hacker FT Jr, Casa DJ, Kavouras SA, Maresh CM. Urinary indices during dehydration, exercise, and rehydration. *Int J Sport Nutr.* 1998;8:345–355. Copyright Lawrence E. Armstrong, 2000. Reprinted with permission from Armstrong LE. *Performing in Extreme Environments*. Champaign, Ill: Human Kinetics Publishers; 2000: 345.

heat exposure leads to a blunted rise in $[Ca^{2+}]_i$ induced by heat. Thus, maximum benefit is derived from exercise combined with heat stress, presumably because only under these conditions are there maximal drives for the required functional and anatomical changes.[194]

Heat Shock Proteins

Almost all cell types in all species can produce proteins to help repair damage caused by stressors. One such group is collectively known as heat shock proteins (HSPs) because they are induced when exposed to moderately high temperatures.[224] Once produced, these HSPs render the cell more tolerant to heat (ie, these cells can survive subsequent temperatures that were previously lethal). HSPs also prevent heat-induced cell death caused by the DNA fragmentation in apoptosis.[225] HSPs are named according to their approximate molecular weights; for example, those with molecular weights around 70 kd are in the HSP-70 family. HSPs are produced intracellularly in response to the stress over a period of minutes to hours. However, even at normal temperatures, many HSPs can be induced by other stresses such as the presence of molecules that alter or denature protein conformation, including increasing concentrations of hydrogen ions, hypoxia, urea, or nonionic detergents and calcium ions,[226] as well as toxic levels of ethanol, arsenite, and heavy metal ions.[227]

The HSPs act as "chaperones," helping translocate important proteins through cell and organelle membranes. However, their protective function in heat stress probably depends on their ability to prevent aggregation of partially denatured proteins, and their ability to help "refold" protein tertiary and quaternary structures that have been partially denatured by the stress.[228,229]

The presence of HSP-70 family members would be expected to be protective against heatstroke in mammals and appear to be involved in the process of acclimatization.[230] Experiments are underway to induce or passively administer HSPs and determine protective effects. Such studies are difficult to carry out because the HSPs are present almost entirely intracellularly, and not in the plasma.

Emergency Medical Treatment and Cooling Modalities

Heatstroke is a medical emergency, with survival depending primarily on the duration and magnitude of the elevated T_c. Therefore, the main therapeutic effort should be directed toward lowering T_c as rapidly as possible.[204,231,232] Nevertheless, it is important to follow the ABCs (airway, breathing, circulation) of stabilization while cooling efforts are initiated.

If a casualty is comatose, a cuffed endotracheal tube should be used to control the airway. Administration of supplemental O_2, if available, may help meet the increased metabolic demands and treat the hypoxia commonly associated with aspiration, pulmonary hemorrhage, pulmonary infarction, pneumonitis, and/or pulmonary edema.[100,233] If hypoxia persists despite the administration of supplemental O_2, then positive pressure ventilation should be applied.

Monitoring and recording rectal temperature on site may be important in the accurate diagnosis of heatstroke. Vital signs should be monitored, with attention to blood pressure and pulse. Although normotension should not be taken as a reassuring sign, hypotension should be recognized for the ominous sign it always is.

After removing the soldier from the heat, loosening clothing, and initiating cooling, a wide-gauge intravenous catheter should be inserted to establish access to the circulation. Intravenous fluids, saline or Ringer's lactate, should be administered as soon as possible. Recommendations regarding the rate of administration of fluids vary widely in the literature.[234] The current (year 2000) procedure at Parris Island for treating exertional heatstroke in Marine recruits is to administer an IV bolus of at least 1,000 mL.[204] The rapidly infused bolus may be more risky in elderly and infirm patients than in a youthful military victim. *Because vigorous fluid resuscitation may precipitate development of pulmonary edema, careful monitoring is indicated. Supplemental potassium should be withheld until serum electrolyte levels are known.* Future choice of fluids should reflect the individual's electrolyte status and cardiac and renal functions.[235]

Although cooling measures should be initiated immediately, cooling techniques are much less effective when the patient is actively seizing. In such cases, convulsions should be controlled by intravenous administration of 5 to 10 mg of diazepam as necessary. Following cooling, the victim should be rapidly evacuated to an emergency medical facility.

Because morbidity is directly related to the duration of the elevated T_c, the efficiency of a given method (how rapidly body temperature is lowered) is most important. In addition, there is the need for unimpeded access to the patient for continuous monitoring. Several methods for cooling heatstroke victims have been described, and there has been

controversy regarding the best approach, including administration of cold intravenous fluids, gastric lavage with cold fluids, cooling the inhaled air, and covering with cooling blankets. Although these therapies may cause lowering of T_c, they are much less effective than ice water immersion or evaporative cooling.[236–240] Ice water immersion provides a very high heat-transfer rate from the skin to the water, and the overall rate of cooling by this method is highest.[204,241] Use of cold water resulted in a rate of cooling similar to that of ice water and is less uncomfortable for the patient than immersion in iced water.[238]

In victims of extreme hyperthermia or exertional heatstroke, the ice water procedure was approximately twice as rapid in lowering T_c as the evaporative spray method (0.20°C/min vs 0.11°C/min).[242] In patients with exertional heatstroke with T_{re} as high as 43.3°C (110°F), cold water or ice water treatment in the clinic reduced T_{re} of Marine victims of heat illnesses to lower than 39°C in 10 to 40 minutes, with *no deaths or renal failure observed in more than 200 cases*.[236] On the other hand, when the evaporative air spray method was used to cool patients with classic heatstroke, 26 to 300 minutes were required to lower T_c to 38°C *and 2 of 18 patients died*.[243]

The following are the most commonly offered criticisms of cooling by ice water immersion[244]:

1. Exposure to severely cold temperatures may cause peripheral vasoconstriction with shunting of the blood away from the skin, resulting in paradoxical rise in body temperature.
2. Induction of shivering (in response to the cold) may cause additional elevation in temperature.
3. Exposure to ice water causes marked patient discomfort.
4. Working in ice water is uncomfortable for medical attendants.
5. Physical access to the patient for monitoring vital signs or administration of cardiopulmonary resuscitation is more difficult.
6. Maintaining sanitary conditions is difficult, should the patient develop vomiting or diarrhea.

While the first two criticisms may appear to be physiologically reasonable, there have been *no* reports of a rise in body temperature following ice water immersion. In fact, decreased vascular resistance has been shown to persist during ice bath cooling to normothermia.[234] Other authors who used ice water immersion for treatment of heatstroke did not find shivering problematic.[241] This is not an unexpected observation; as the hypothalamic set point for temperature regulation is not raised during heatstroke (unlike during febrile illness), the shivering response should occur only if the T_c is allowed to fall below normal. When shivering occurred, IV administration of chlorpromazine (25–50 mg) was effective.[245]

In case cardiopulmonary resuscitation becomes necessary, instead of completely immersing the victim in ice and water, it is usually preferable to place the victim on a stretcher that is placed on top of the tub, with the stretcher handles protruding at each end.[204] The patient is then conveniently drenched with sheets frequently dipped into the ice water, covering the sheets with more ice, massaging the skin, and wetting the head with ice water. The massaging may improve the flow of blood through the skin. In three series of exertional heatstroke victims in a military population (66 patients), there were no fatalities or permanent sequelae after treatment with ice water immersion.[241,246,247] In a second report of 252 cases of heatstroke in Marines, all were successfully treated with ice water immersion.[236] While other cooling methods reduce the rate of mortality, none has been as successful as ice water immersion.

Victims of heatstroke rarely require cardiopulmonary resuscitation, so this concern should not preclude use of ice baths to treat heatstroke. The documented efficacy of ice water immersion in the rapid reduction of body temperature, morbidity, and mortality overrides any consideration of transient personal discomfort for the patient or medical attendants.

An additional benefit of cooling strategies involving water immersion is the physiological shifting of fluid from the periphery to the central region, thus supporting circulation. This is particularly relevant in a tactical situation where intravenous fluids are not available, but access to a poncho-lined hole dug into desert sand and filled with 15 gallons of water is possible.[244]

The most important alternative to ice water immersion is a body cooling unit developed by Khogali and associates,[248] which maximizes evaporative cooling by suspending the patient on a net, spraying him or her from all sides with water at 15°C (59°F), and blowing warm air (45°C–48°C; 113°F–118.4°F) over the victim. Cooling rates of 0.06°C/min have been obtained. Although this method has been widely recommended as the treatment of choice, its rate of cooling is much less

EXHIBIT 5-3

FEATURES THAT HEAT ILLNESSES AND SEPSIS HAVE IN COMMON

Clinical

- Elevated core temperature[1,2–4]
- Neurological symptoms (fatigue, weakness, lethargy, confusion, delirium, stupor, coma, dizziness, paralysis, amnesia, staggering, spasm, paralysis, somnolence, lack of coordination)[1,4–8]
- Hyperventilation[6,9,10]
- Tachycardia[3,8]
- Hypotension[1,3,4]
- Renal failure[11–14]
- Organ failure[6,15]
- Shock[11,12,16,17]
- Edema[8,17,18]
- Hematocrit elevated[6,15]
- Nausea[1,3–7,19]
- Vomiting[5,8,16]
- Diarrhea[3,8,18,20]
- Headache[1,3,4,19,21]
- Myalgia[3,5,6,19,22]

Laboratory

- Leukocytosis or neutropenia[2,8]
- Hypofibrinogenemia, with fibrin degradation products elevated[19]
- Respiratory alkalosis[2,6,10]
- Metabolic acidosis[3,6]
- Decreased systemic vascular resistance[2,23]
- Increased cardiac output[2,24]
- Metabolic acidosis[2,6]
- Ischemia of the bowel, with hemorrhagic necrosis[3,8,25]
- Disseminated intravascular coagulation[17,18,26,27]
- Lactate elevated[6,28]
- Hepatic dysfunction[17,18]
- Cytokines elevated[2,5,29]
- Lipopolysaccharide elevated[29,30]

Sources: (1) Bannister RG. Anhidrosis following intravenous bacterial pyrogen. *Lancet.* 1960;2:118–122. (2) van Deventer SJH. *Endotoxins in the Pathogenesis of Gram-Negative Septicemia* [PhD dissertation]. Amsterdam, The Netherlands: University of Amsterdam; 1988. (3) Franzoni G, Leech J, Jensen G, Brotman S. Tumor necrosis factor alpha: What role in sepsis and organ failure? *J Crit Illnesses*. 1991;6:796–805. (4) Genzyme Corporation. Genzyme: Tumor necrosis factor. In: *1994 Cytokine Research Products*. Cambridge, Mass: Genzyme Corporation; 1994: 207–209. (5) Armstrong LE, Hubbard RW, Kraemer WJ, Deluca JP, Christensen EL. Signs and symptoms of heat exhaustion during strenuous exercise. *Ann Sports Med.* 1987;3:182–189. (6) Howorth PJN. The biochemistry of heat illness. *J R Army Med Corps.* 1995;141:40–41. (7) Axelrod BN, Woodard JL. Neuropsychological sequelae of heatstroke. *Int J Neurosci.* 1993;70:223–232. (8) Johannsen U. Experimental studies on the pathogenesis of Coli-enterotoxemia in swine, IV: Effect of lipopolysaccharide endotoxin on weaned piglets following parenteral administration [in German]. *Arch Exp Veterinärmed*. 1977;31:191–202. (9) Boyd AE, Beller GA. Acid–base changes in heat exhaustion during basic training. *Proc Army Science Conf*. 1972;1:114–125. (10) Boyd AE, Beller GA. Heat exhaustion and respiratory alkalosis. *Ann Intern Med.* 1975;83:835. (11) Shibolet S, Lancaster MC, Danon Y. Heatstroke: A review. *Aviat Space Environ Med.* 1976;47:280–301. (12) Shibolet S, Coll R, Gilat T, Sohar E. Heatstroke: Its clinical picture and mechanism in 36 cases. *Q J Med.* 1967;(New Series)36:525–548. (13) Gitin EL, Demos MA. Acute exertional rhabdomyolysis: A syndrome of increasing importance to the military physician. *Mil Med.* 1974;139:33–36. (14) Harman E, Frykman P, Palmer C, Lammi E, Reynolds K, Backus V. *Effects of a Specifically Designed Physical Conditioning Program on the Load Carriage and Lifting Performance of Female Soldiers.* Natick, Mass: US Army Research Institute of Environmental Medicine; November 1997. USARIEM Technical Report T98-1. (15) Hansbrough J, Moore E, Eiseman B. Shock and multiple organ failure. In: Hardaway RM III, ed. *Shock: The Reversible Step Toward Death.* Littleton, Mass: PSG Publishing Co; 1988: 435–441. (16) Haseeb MA, Amin F. Fatal effects of heat on man. *J Trop Med Hyg*. 1958;61:280–281. (17) Zhi-cheng M, Yi-tang W. Analysis of 411 cases of severe heat stroke in Nanjing. *Chin Med J (Engl).* 1991;104:256–258. (18) Southwick FS, Dalglish PH Jr. Recovery after prolonged asystolic cardiac arrest in profound hypothermia. *JAMA.* 1980;243:1250–1253. (19) Suffredini AF, Harpel PC, Parrillo JE. Promotion and subsequent inhibition of plasminogen activation after administration of intravenous endotoxin to normal subjects. *N Engl J Med.* 1989;320:1165–1172. (20) Fogoros RN. Runner's trots. *JAMA.* 1980;243:1743–1744. (21) Skidmore R, Gutierrez JA, Guerriero V, Kregel KC. Hsp70 induction during exercise and heat stress in rats: Role of internal temperature. *Am J Physiol*. 1995;268:R92–R97. (22) Knochel JP. Management of heat conditions. *Athletic Ther Today.* 1996;2:30–34. (23) Gisolfi CV, Matthes RD, Kregel KC, Oppliger R. Splanchnic sympathetic nerve activity and circulating catecholamines in the hyperthermic rat. *J Appl Physiol*. 1991;70:1821–1826. (24) Koroxenidis GT, Shepherd JT, Marshall RJ. Cardiovascular response to acute heat stress. *J Appl Physiol*. 1961;16:869–872. (25) Baska RS, Moses FM, Graeber G, Kearney G. Gastrointestinal bleeding during an ultramarathon. *Dig Dis Sci*. 1990;35:276–279. (26) Caridis DT, Reinhold RB, Woodruff WH, Fine J. Endotoxaemia in man. *Lancet*. 1972;1:1381–1386. (27) Rosenthal T, Shapiro Y, Seligsohn U, Ramot B. Disseminated intravascular coagulation in experimental heatstroke. *Thromb Diath Haemorrh.* 1971;26:417–425. (28) Boyd AE, Beller GA. Acid base changes in heat exhaustion during basic training. *Proc Army Science Conf.* 1972;1:114–125. (29) Bouchama A, Parhar RS, Er-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;70:2640–2644. (30) Gathiram P, Wells MT, Brock-Utne JG, Gaffin SL. Portal and systemic arterial plasma lipopolysaccharide concentrations in heat stressed primates. *Circ Shock.* 1988;25:223–230.

than that seen with ice water immersion and should be employed only as an alternative when a bath of cold or ice water is unavailable. For further discussion see B. Yarbrough and R. W. Hubbard's chapter in *Management of Wilderness and Environmental Emergencies*.[249]

If other cooling methods are used initially, any patient whose T_c does not fall to 38.9°C within 30 minutes should be placed in an ice water bath. A rapidly falling T_c may not be accurately reflected by measured T_{re}. Therefore, no matter what technique is used, active cooling should be discontinued when T_{re} falls below 39°C (102.2°F) to prevent inducing hypothermia.

Use of antipyretics is generally inappropriate and potentially harmful in heatstroke victims unless T_c is very high. Aspirin and acetaminophen lower temperature by normalizing the elevated hypothalamic set point caused by pyrogens. Furthermore, acetaminophen could cause hepatic damage, and aspirin could aggravate bleeding tendencies. Alcohol sponge baths are inappropriate under any circumstances because absorption of alcohol may lead to poisoning and coma, particularly in a patient with heatstroke who has residual liver injury from the heat and reduced splanchnic blood flow.

In heatstroke, the set point is usually normal, with the temperature elevation reflecting failure of the normal cooling mechanisms. This failure is indicated by successes of external therapeutic cooling procedures. However, elevated levels of LPS and cytokines such as IL-1 have been reported in the plasma of heatstroke victims and in experimental heatstroke models.[156,250] In those particular cases, the thermoregulatory set point may have been altered, and they may benefit from antipyretics. But this has not been proved. To facilitate future research on the underlying mechanisms of heatstroke and sepsis, and to further elucidate many overlapping areas that share common mechanisms and pathways, we offer the comparative summary in Exhibit 5-3.

SUMMARY

Heat illnesses may vary in intensity from a sense of fatigue to severe symptoms, shock, and death. These disorders are always medical emergencies requiring immediate recognition and rapid initiation of therapy. Heatstroke typically appears in two completely different types of patients:

1. Classic heatstroke: the victim is older; debilitated, often with liver failure; does not exercise; and develops the disease over a few days during a heat wave.
2. Exertional heatstroke: the victim is usually in his teens to thirties, in otherwise good health, and collapsed during a few minutes to a few hours of exercise in a cool-to-warm environmental temperature.

Other heat illnesses, such as heat cramps and heat exhaustion, depend on alterations in circulating volume and electrolytes due to relatively unequal sweat losses or inappropriate ingestion of water and salts.

In most medical schools, heatstroke and other heat illnesses have usually been taught as a straightforward series of well-described pathophysiological conditions characterized by various levels of core temperature, extent of dehydration in various body compartments, reduced CVP, depression of sweat gland function, and alterations of intracellular and plasma ions and pH. These physiological mechanisms, however, do not explain why classic heatstroke victims are different from exertional heatstroke victims, nor do they explain why a number of heatstroke symptoms are similar to those of septic shock, such as DIC, nausea, vomiting, diarrhea, intestinal bleeding, and so forth. Furthermore, classic physiological theory does not explain why concurrent physical activity lowers the threshold core temperature.

Recent advances in basic science provide new information that can help explain the underlying cellular, subcellular, and chemical pathophysiology of heat illnesses, and can lead to new therapy and prophylaxes. Specifically, heatstroke patients usually have altered immune systems with elevated and probably inappropriate levels of circulating inflammatory cytokines, Gram-negative bacterial lipopolysaccharides, and corticotropin-releasing hormone; show a programmed generalized response to stressors; and have depressed stores of intracellular ATP.

In addition to providing support for the classic mechanisms for the pathophysiology and diagnoses of heatstroke and other heat illnesses, and their limitations, we presented new information about these other factors: how they may participate in the pathophysiology of heat illness, with a view to using these newer pathways in designing future therapy and prophylaxis. Also included are current (year 2000) protocols for cooling and rehydrating patients with heatstroke.

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